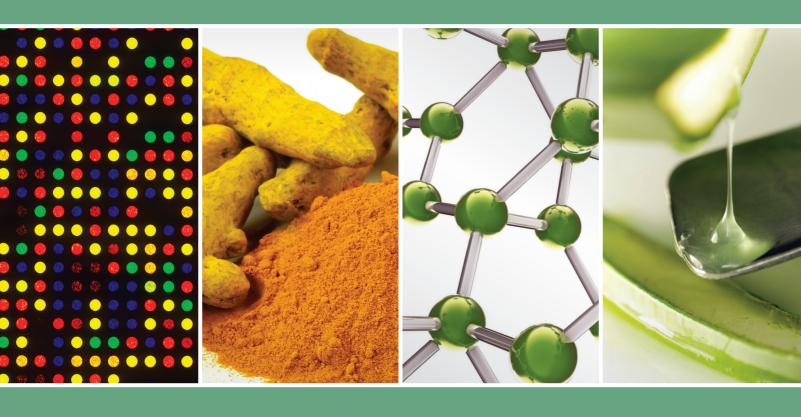


High-Tech Acupuncture and Integrative Laser Medicine 2014

Guest Editors: Gerhard Litscher, Xin-Yan Gao, Lu Wang, and Bing Zhu



High-Tech Acupuncture and Integrative Laser Medicine 2014

High-Tech Acupuncture and Integrative Laser Medicine 2014

Guest Editors: Gerhard Litscher, Xin-Yan Gao, Lu Wang, and Bing Zhu



Editorial Board

Mona Abdel-Tawab, Germany Jon Adams, Australia Gabriel A. Agbor, Cameroon Ulysses P. Albuquerque, Brazil Samir Lutf Aleryani, USA Ather Ali, USA Gianni Allais, Italy Terje Alraek, Norway Shrikant Anant, USA Isabel Andújar, Spain Letizia Angiolella, Italy Virginia A. Aparicio, Spain Makoto Arai, Japan Hyunsu Bae, Republic of Korea Giacinto Bagetta, Italy Onesmo B. Balemba, USA Winfried Banzer, Germany Panos Barlas, UK Vernon A. Barnes, USA Samra Bashir, Pakistan Purusotam Basnet, Norway Jairo Kennup Bastos, Brazil Sujit Basu, USA Arpita Basu, USA George David Baxter, New Zealand André-Michael Beer, Germany Alvin I. Beitz, USA Louise Bennett, Australia Maria Camilla Bergonzi, Italy Anna R. Bilia, Italy Yong C. Boo, Republic of Korea Monica Borgatti, Italy Francesca Borrelli, Italy Gloria Brusotti, Italy Arndt Büssing, Germany Rainer W. Bussmann, USA Andrew J. Butler, USA Gioacchino Calapai, Italy Giuseppe Caminiti, Italy Raffaele Capasso, Italy Francesco Cardini, Italy Opher Caspi, Israel Subrata Chakrabarti, Canada Pierre Champy, France

Shun-Wan Chan, Hong Kong

Il-Moo Chang, Republic of Korea Chun-Tao Che, USA Kevin Chen, USA Evan P. Cherniack, USA Salvatore Chirumbolo, Italy Jae Youl Cho, Korea K. B. Christensen, Denmark Shuang-En Chuang, Taiwan Y. Clement, Trinidad And Tobago Paolo Coghi, Italy Marisa Colone, Italy Lisa A. Conboy, USA Kieran Cooley, Canada Edwin L. Cooper, USA Olivia Corcoran, UK Muriel Cuendet, Switzerland Roberto K. N. Cuman, Brazil Vincenzo De Feo, Italy Rocío De la Puerta, Spain Laura De Martino, Italy Nunziatina De Tommasi, Italy Alexandra Deters, Germany Farzad Deyhim, USA Manuela Di Franco, Italy Claudia Di Giacomo, Italy Antonella Di Sotto, Italy M.-G. Dijoux-Franca, France Luciana Dini, Italy Tieraona L. Dog, USA Caigan Du, Canada Jeng-Ren Duann, USA Nativ Dudai, Israel Thomas Efferth, Germany Abir El-Alfy, USA Tobias Esch, USA Giuseppe Esposito, Italy Keturah R. Faurot, USA Yibin Feng, Hong Kong Nianping Feng, China Patricia D. Fernandes, Brazil Josue Fernandez-Carnero, Spain Antonella Fioravanti, Italy Fabio Firenzuoli, Italy Peter Fisher, UK Filippo Fratini, Italy

Maria pia Fuggetta, Italy Joel J. Gagnier, Canada Siew Hua Gan, Malaysia Jian-Li Gao, China Mary K. Garcia, USA Susana Garcia de Arriba, Germany Dolores García Giménez, Spain Gabino Garrido, Chile Ipek Goktepe, Qatar Michael Goldstein, USA Yuewen Gong, Canada Settimio Grimaldi, Italy Gloria Gronowicz, USA Maruti Ram Gudavalli, USA Alessandra Guerrini, Italy Narcis Gusi, Spain Svein Haavik, Norway Solomon Habtemariam, UK Abid Hamid, India Michael G. Hammes, Germany Kuzhuvelil B. Harikumar, India Cory S. Harris, Canada Jan Hartvigsen, Denmark Thierry Hennebelle, France Lise Hestback, Denmark Eleanor Holroyd, Australia Markus Horneber, Germany Ching-Liang Hsieh, Taiwan Benny T. K. Huat, Singapore Roman Huber, Germany Helmut Hugel, Australia Ciara Hughes, UK Attila Hunyadi, Hungary Sumiko Hyuga, Japan H. Stephen Injeyan, Canada Chie Ishikawa, Japan Angelo A. Izzo, Italy Chris J. Branford-White, UK Suresh Jadhav, India G. K. Jayaprakasha, USA Stefanie Joos, Germany Zeev L Kain, USA Osamu Kanauchi, Japan M. Ali-Shtayeh, Palestinian Authority

Brett Froeliger, USA

Wenyi Kang, China Shao-Hsuan Kao, Taiwan Juntra Karbwang, Japan Kenji Kawakita, Japan Deborah A. Kennedy, Canada Cheorl-Ho Kim, Republic of Korea Youn C. Kim, Republic of Korea Yoshiyuki Kimura, Japan Toshiaki Kogure, Japan Jian Kong, USA Tetsuya Konishi, Japan Karin Kraft, Germany Omer Kucuk, USA Victor Kuete, Cameroon Yiu W. Kwan, Hong Kong Kuang C. Lai, Taiwan Ilaria Lampronti, Italy Lixing Lao, Hong Kong Christian Lehmann, Canada Marco Leonti, Italy Lawrence Leung, Canada Shahar Lev-ari, Israel Min Li, China Xiu-Min Li, USA Chun G. Li, Australia Bi-Fong Lin, Taiwan Ho Lin, Taiwan Christopher G. Lis, USA Gerhard Litscher, Austria I-Min Liu, Taiwan Yijun Liu, USA Víctor López, Spain Thomas Lundeberg, Sweden Filippo Maggi, Italy Valentina Maggini, Italy Gail B. Mahady, USA Jamal Mahajna, Israel Juraj Majtan, Slovakia Francesca Mancianti, Italy Carmen Mannucci, Italy Arroyo-Morales Manuel, Spain Fulvio Marzatico, Italy Marta Marzotto, Italy James H. McAuley, Australia Kristine McGrath, Australia James S. McLay, UK Lewis Mehl-Madrona, USA

Peter Meiser, Germany

Karin Meissner, Germany Albert S Mellick, Australia A. Guy Mensah-Nyagan, France Andreas Michalsen, Germany Oliver Micke, Germany Roberto Miniero, Italy Giovanni Mirabella, Italy David Mischoulon, USA Francesca Mondello, Italy Albert Moraska, USA Giuseppe Morgia, Italy Mark Moss, UK Yoshiharu Motoo, Japan Kamal D. Moudgil, USA Yoshiki Mukudai, Japan Frauke Musial, Germany MinKyun Na, Republic of Korea Hajime Nakae, Japan Srinivas Nammi, Australia Krishnadas Nandakumar, India Vitaly Napadow, USA Michele Navarra, Italy Isabella Neri, Italy Pratibha V. Nerurkar, USA Karen Nieber, Germany Menachem Oberbaum, Israel Martin Offenbaecher, Germany Junetsu Ogasawara, Japan Ki-Wan Oh, Republic of Korea Yoshiji Ohta, Japan Olumayokun A. Olajide, UK Thomas Ostermann, Germany Siyaram Pandey, Canada Bhushan Patwardhan, India Berit S. Paulsen, Norway Philip Peplow, New Zealand Florian Pfab, Germany Sonia Piacente, Italy Andrea Pieroni, Italy Richard Pietras, USA Andrew Pipingas, Australia Jose M. Prieto, UK Haifa Qiao, USA Waris Qidwai, Pakistan Xiangin Qu, Australia E. Ferreira Queiroz, Switzerland

Roja Rahimi, Iran

Khalid Rahman, UK

Cheppail Ramachandran, USA Elia Ranzato, Italy Ke Ren, USA Man-Hee Rhee, Republic of Korea Luigi Ricciardiello, Italy Daniela Rigano, Italy José L. Ríos, Spain Paolo Roberti di Sarsina, Italy Mariangela Rondanelli, Italy Omar Said, Israel Avni Sali, Australia Mohd Z. Salleh, Malaysia Andreas Sandner-Kiesling, Austria Manel Santafe, Spain Tadaaki Satou, Japan Michael A. Savka, USA Claudia Scherr, Switzerland Guillermo Schmeda-Hirschmann, Chile Andrew Scholey, Australia Roland Schoop, Switzerland Sven Schröder, Germany Herbert Schwabl, Switzerland Veronique Seidel, UK Senthamil Selvan, USA Felice Senatore, Italy Hongcai Shang, China Karen J. Sherman, USA Ronald Sherman, USA Kuniyoshi Shimizu, Japan Kan Shimpo, Japan Yukihiro Shoyama, Japan Morry Silberstein, Australia Kuttulebbai N. S. Sirajudeen, Malaysia Graeme Smith, UK Chang-Gue Son, Korea Rachid Soulimani, France Didier Stien, France Con Stough, Australia Annarita Stringaro, Italy Shan-Yu Su, Taiwan Barbara Swanson, USA Giuseppe Tagarelli, Italy Orazio Taglialatela-Scafati, Italy Takashi Takeda, Japan Ghee T. Tan, USA Hirofumi Tanaka, USA Lay Kek Teh, Malaysia

Norman Temple, Canada

Mayank Thakur, Germany
Menaka C. Thounaojam, USA
Evelin Tiralongo, Australia
Stephanie Tjen-A-Looi, USA
Michał Tomczyk, Poland
Loren Toussaint, USA
Yew-Min Tzeng, Taiwan
Dawn M. Upchurch, USA
Konrad Urech, Switzerland
Takuhiro Uto, Japan
Sandy van Vuuren, South Africa
Alfredo Vannacci, Italy
Subramanyam Vemulpad, Australia
Carlo Ventura, Italy

Giuseppe Venturella, Italy Pradeep Visen, Canada Aristo Vojdani, USA Dawn Wallerstedt, USA Shu-Ming Wang, USA Chong-Zhi Wang, USA Yong Wang, USA Jonathan L. Wardle, Australia Kenji Watanabe, Japan J. Wattanathorn, Thailand Michael Weber, Germany Silvia Wein, Germany Janelle Wheat, Australia Jenny M. Wilkinson, Australia Darren R. Williams, Republic of Korea Christopher Worsnop, Australia Haruki Yamada, Japan Nobuo Yamaguchi, Japan Junqing Yang, China Ling Yang, China Eun J. Yang, Republic of Korea Ken Yasukawa, Japan Albert S. Yeung, USA Armando Zarrelli, Italy Christopher Zaslawski, Australia Ruixin Zhang, USA

Contents

High-Tech Acupuncture and Integrative Laser Medicine 2014, Gerhard Litscher, Xin-Yan Gao, Lu Wang, and Bing Zhu

Volume 2015, Article ID 878620, 3 pages

Systematic Review of Adverse Effects: A Further Step towards Modernization of Acupuncture in China, Junyi Wu, Yanmei Hu, Yin Zhu, Ping Yin, Gerhard Litscher, and Shifen Xu Volume 2015, Article ID 432467, 19 pages

Neuroimaging and Neuromonitoring Effects of Electro and Manual Acupuncture on the Central Nervous System: A Literature Review and Analysis, Brigitte Elisabeth Scheffold, Ching-Liang Hsieh, and Gerhard Litscher

Volume 2015, Article ID 641742, 29 pages

Auricular Acupressure Can Modulate Pain Threshold, Antonietta Santoro, Stefania Lucia Nori, Letizia Lorusso, Carmine Secondulfo, Marcellino Monda, and Andrea Viggiano Volume 2015, Article ID 457390, 7 pages

Bioceramic Resonance Effect on Meridian Channels: A Pilot Study, Ting-Kai Leung, Wing P. Chan, Chen-Jei Tai, Ting-Pin Cho, Jen-Chang Yang, and Po-Tsung Lee Volume 2015, Article ID 769546, 9 pages

Effects of Jae-Seng Acupuncture Treatment on the Improvement of Nasolabial Folds and Eye Wrinkles, Jin Hyong Cho, Ho Jin Lee, Kyu Jin Chung, Byung Chun Park, Mun Seog Chang, and Seong Kyu Park Volume 2015, Article ID 273909, 7 pages

Effects of GUASHA on Heart Rate Variability in Healthy Male Volunteers under Normal Condition and Weightlifters after Weightlifting Training Sessions, Xingze Wang, Uraiwan Chatchawan, Saowanee Nakmareong, Atit Silsirivanit, Yingying Wang, Dongbei Xie, Jinsheng Yang, and Wichai Eungpinichpong Volume 2015, Article ID 268471, 6 pages

A Pilot Study: Warm Stimulation on Guangming (GB37) to Relief Asthenopia, Tao Huang Volume 2015, Article ID 641792, 4 pages

The Effects of Acupuncture at Real or Sham Acupoints on the Intrinsic Brain Activity in Mild Cognitive Impairment Patients, Baohui Jia, Zhishun Liu, Baoquan Min, Zhenchang Wang, Aihong Zhou, Yong Li, Haifa Qiao, and Jianping Jia
Volume 2015, Article ID 529675, 9 pages

Therapeutic Effects of Oligonol, Acupuncture, and Quantum Light Therapy in Chronic Nonbacterial Prostatitis, İlhan Öztekin, Hakan Akdere, Nuray Can, Tevfik Aktoz, Ersan Arda, and Fatma Nesrin Turan Volume 2015, Article ID 687196, 8 pages

Efficacy and Cost Effectiveness of the Acupuncture Treatment Using a New Skin Stimulus Tool Called M-Test Which Is a Measure Based on Symptoms Accompanied with Body Movements: A Pragmatic RCT Targeting Hemodialysis Patients, Shuji Ono and Yoshito Mukaino Volume 2015, Article ID 802846, 8 pages

Inhibiting Effect of Electroacupuncture at Zusanli on Early Inflammatory Factor Levels Formed by Postoperative Abdominal Adhesions, Lijian Zhang, Huizhen Wang, Zhenjun Huang, Xian Shi, Sen Hu, Ingrid Gaischek, Daniela Litscher, Lu Wang, and Gerhard Litscher Volume 2014, Article ID 950326, 5 pages

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 878620, 3 pages http://dx.doi.org/10.1155/2015/878620

Editorial

High-Tech Acupuncture and Integrative Laser Medicine 2014

Gerhard Litscher,^{1,2} Xin-Yan Gao,² Lu Wang,¹ and Bing Zhu²

¹Research Unit for Complementary and Integrative Laser Medicine, Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, TCM Research Center Graz, Medical University of Graz, 8036 Graz, Austria

Correspondence should be addressed to Gerhard Litscher; gerhard.litscher@medunigraz.at

Received 10 March 2015; Accepted 10 March 2015

Copyright © 2015 Gerhard Litscher et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The special issue focuses on the latest innovative aspects of high-tech acupuncture, including related research topics. In this year, the accepted papers deal with the following interesting aspects.

L. Zhang et al. investigated the inhibiting effect of electroacupuncture (EA) at Zusanli on early inflammatory factor levels formed by postoperative abdominal adhesions in a rat model, to find out the relationship between EA and the cholinergic anti-inflammatory pathway. Sixty-four male Wistar rats were divided into 8 groups. The α -bungarotoxin (α -BGT) was injected into the abdominal cavity after surgery, and the bilateral celiac vagotomy was done during the surgery. Three days later, the levels of inflammatory mediators in tissues were evaluated. The abdominal adhesion groups developed obvious edema. It was found that EA lowered the elevated levels of inflammatory mediators significantly; EA plus α -BGT and vagotomy showed less anti-inflammatory effects. The authors concluded that the activation of the cholinergic anti-inflammatory pathway might be one of the mechanisms of EA at Zusanli points to exert the antiinflammatory effects.

Effects of Guasha on heart rate variability (HRV) were investigated by X. Wang et al. in ten healthy male volunteers and 15 weightlifters. These test persons were divided into two groups and underwent 20-minute Guasha therapy. Electrocardiography was recorded before and immediately after Guasha. HRV was calculated in both the time domain and frequency domain. The different evaluated HRV parameters reacted differently to the Guasha therapy. In conclusion, Guasha therapy facilitates the parasympathetic nervous activity and modulates the balance between parasympathetic and

sympathetic activities in both healthy men under normal conditions and weightlifters after training sessions. Although the changes of the HRV parameters were similar in both groups, the responsiveness was more pronounced in healthy men than in male weightlifters.

I. Oztekin et al. conducted a study aimed to compare antiinflammatory effects of oligonol, acupuncture, and quantum light therapy in rat models of estrogen-induced prostatitis. Ninety adult male Wistar albino rats were divided into nine different experimental groups. Chronic prostatitis (CP) was induced by the administration of 17-beta-estradiol (E2) and dihydrotestosterone. Oligonol was given for 6 weeks. Acupuncture needles were inserted at CV 3/4 and bilaterally B 32/35 points. Quantum therapy was administered three times weekly for 6 weeks. Lateral lobes of prostates were dissected for histopathologic evaluation. All treatment modalities tested in this study showed anti-inflammatory effects in the treatment of CP. The authors found a synergistic effect for oligonol plus quantum light combination, whereas monotherapy with oligonol showed a superior antiinflammatory efficacy as compared to quantum light and acupuncture monotherapies.

J. Wu et al. performed a systematic review of adverse effects of acupuncture in China as a further step towards the modernization of acupuncture. This review took note of the frequency and severity of adverse complications and events in acupuncture treatment reported in China from 1980 to 2013. Over the 33 years, 182 incidents were identified in 133 relevant papers. Internal organ, tissue, or nerve injury was found to be the main complications of acupuncture especially for pneumothorax and central nervous system injury. Adverse

²Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing 100700, China

effects also included syncope, infections, hemorrhage, allergy, burn, aphonia, hysteria, cough, thirst, fever, somnolence, and broken needles. Therefore, the authors concluded that qualifying training of acupuncturists should be systemized and the clinical acupuncture operations should be standardized in order to effectively prevent the occurrence of acupuncture accidents.

A literature review and analysis of neuroimaging and neuromonitoring effects of electro- and manual acupuncture on the central nervous system was performed by B. E. Scheffold et al. The PubMed Database was searched from 1/1/2000 until 1/6/2014 with restriction on human studies in English language. Only studies comparing manual or electroacupuncture with sham acupuncture were eligible. In 29 out of 33 studies, verum acupuncture results were found to present either more or different modulation effects on neurological components measured by neuroimaging and neuromonitoring methods than sham acupuncture. Only four studies reported no effects of verum in comparison to sham acupuncture. Evaluation of the very heterogeneous results showed evidence that verum acupuncture elicits more modulation effects on neurological components than sham acupuncture.

A pilot study by T. K. Leung et al. investigated the effects of bioceramic (BC) irradiation and resonant sound waves on meridian channels. BC is a material which emits nonionizing radiation and luminescence induced by visible light. It also facilitates the break-up of large clusters of water molecules by weakening hydrogen bonds, which is one of the key mechanisms underlying the effects of BC. In their study, the authors used sound to amplify the effect of BC. Thirteen patients severely affected in their sleep patterns and life quality were enrolled in a trial of BC resonance (i.e., rhythmic 100-dB sound waves with frequency set at 10 Hz) applied to the skin surface of the anterior chest. According to the preliminary data, a "propagated sensation along meridians" was experienced in all BC resonance-treated patients but not in any of the nine control patients. The authors believe that the device enhances microcirculation through a series of biomolecular and physiological processes and subjects the specific meridian channels of traditional Chinese medicine to coherent vibration. They conclude that this noninvasive technique may offer an alternative to needle acupuncture.

B. Jia et al. investigated the effects of acupuncture at real or sham acupoints on the intrinsic brain activity in mild cognitive impairment (MCI, a transitional phase between normal function and Alzheimer disease (AD)) patients. Previous studies established that acupuncture at different acupoints could exert different modulatory effects on the brain network. However, based on the pathology characteristics of MCI and AD, whether acupuncture at real or sham acupoints can produce different effects on the brain network in MCI or AD patients remains unclear. The authors used resting state fMRI and reported that acupuncture at Taixi (KI3) induced amplitude of low frequency fluctuation (ALFF) change of different brain regions in MCI patients from those shown in the healthy controls. In resting state, acupuncture at the sham acupoint in MCI patients activated brain regions different from those in healthy controls. Therefore, the authors

concluded that, in MCI patients, acupuncture at KI3 and sham acupoint improved the neuronal activities of certain cognitive-related regions.

The objective of the study by A. Santoro et al. was to investigate if auriculotherapy (AT) can modulate pain threshold. Two groups of healthy volunteers were enrolled in the study. AT consisted of placing vaccaria seeds over the "fingers point" of one ear, and sham treatment consisted of a puncture/massage above the skin of the neck. Each subject was asked to perform an autoalgometric test on three occasions (before, 1 hour after, and 24 hours after AT), until a minimum pain sensation or a maximally tolerable pain sensation. The results showed a significantly higher pain threshold in the maximal test at 24 hours after AT compared to sham treatment. This result indicated for the first time that AT can increase pain tolerability, rather than affecting the minimal pain threshold.

J. H. Cho et al. explored effects of Jae-Seng acupuncture treatment, a newly attempted bloodletting therapy, on the improvement of nasolabial folds and eye wrinkles. The microneedle therapy system, a mechanical method involving making multiple minute holes in the skin, reportedly improves skin condition. According to the authors, Jae-Seng acupuncture has several advantages over traditional mechanical punching methods because it allows the practitioner to regulate the depth and direction of needle stimulations. The nasolabial folds and eye wrinkles of 107 patients were subjected to a digital skin image analyzer, before the treatment and one month after treatment. Additionally, stimulation of some meridians was performed to improve the function of these vessels. Analyses of the images indicated that Jae-Seng acupuncture improved eye wrinkles, suggesting that this technique is a safe and effective method for the improvement of facial skin conditions.

Within a pilot study, T. Huang applied electrothermal Bian-stone stimulation to Guangming (GB37) to relieve asthenopia in 15 female patients. The results of this controlled pilot study showed significant increases in the eyes' temperature. At the same time, no changes were found following stimulation at the control points. Furthermore, after warm stimulation on Guangming, the clinical symptoms were getting better than using the control points. The symptoms score also decreased significantly. The author states that it was demonstrated that there is some relationship between the Guangming (GB37) acupoint and the eyes and that warm stimulation on Guangming could relieve the uncomfortableness of asthenopia.

S. Ono and Y. Mukaino tested the efficacy and cost effectiveness of an acupuncture treatment using a new skin stimulus tool called *M*-Test which is a measure based on symptoms accompanied with body movements within a pragmatic randomized controlled trial targeting hemodialysis patients. The authors stated that *M*-Test can simultaneously reduce hemodialysis patients' diverse symptoms. Its diagnosis and treatment are based on simple movements that can be performed by anyone and allow determining which meridians have problems by analyzing symptoms accompanied with movement. It also enables conducting a safe and effective treatment with use of microcorn which is a noninvasive

treatment tool. This time they conducted microcorn intervention on hemodialysis patients based on the diagnosis of M-Test. As a result, almost all of dialysis patients' complaints were relieved while the score of health-related quality of life increased. According to the authors' calculation of cost effectiveness, it was confirmed to be very cost-effective.

Acknowledgments

We would like to thank the authors for their excellent contributions and patience in assisting us. We would also like to express our sincere gratitude to all the reviewers involved; without their valuable comments, the improvements in these papers could not have been achieved. Some publications of this special issue and the editorial were supported by the Austrian Federal Ministries of Science, Research and Economy and of Health (Project title: Evidence-Based High-Tech Acupuncture and Integrative Laser Medicine for Prevention and Early Intervention of Chronic Diseases).

Gerhard Litscher Xin-Yan Gao Lu Wang Bing Zhu Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 432467, 19 pages http://dx.doi.org/10.1155/2015/432467

Review Article

Systematic Review of Adverse Effects: A Further Step towards Modernization of Acupuncture in China

Junyi Wu, 1 Yanmei Hu, 1 Yin Zhu, 2 Ping Yin, 1 Gerhard Litscher, 3 and Shifen Xu1

Correspondence should be addressed to Shifen Xu; xu_teacher2006@126.com

Received 8 July 2014; Accepted 30 July 2014

Academic Editor: Lu Wang

Copyright © 2015 Junyi Wu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

As a further step towards the modernization of acupuncture, the objective of this review was to figure out the frequency and severity of adverse complications and events in acupuncture treatment reported from 1980 to 2013 in China. All first-hand case reports of acupuncture-related complications and adverse events that could be identified in the scientific literature were reviewed and classified according to the type of complication and adverse event, circumstance of the event, and long-term patient outcome. The selected case reports were published between 1980 and 2013 in 3 databases. Relevant papers were collected and analyzed by 2 reviewers. Over the 33 years, 182 incidents were identified in 133 relevant papers. Internal organ, tissue, or nerve injury is the main complications of acupuncture especially for pneumothorax and central nervous system injury. Adverse effects also included syncope, infections, hemorrhage, allergy, burn, aphonia, hysteria, cough, thirst, fever, somnolence, and broken needles. Qualifying training of acupuncturists should be systemized and the clinical acupuncture operations should be standardized in order to effectively prevent the occurrence of acupuncture accidents, enhance the influence of acupuncture, and further popularize acupuncture to the rest of the world.

1. Introduction

Complications and adverse effects in medical practice are always of concern to the public and the medical profession. While being widely used in current medical treatment, especially in the area of intertrochanteric hip fractures, the cephalomedullary devices (CMN), however, led to a considerably high complication rate of 41.9% according to Pui et al. [1]. Faunø et al. [2] conducted a study on the medical records of 997 patients who were suffering from stoma closure, which revealed 131 cases of early complications and 187 late ones, accounting for 13.1% and 18.8% of the total subject pool, respectively. Umuroglu et al. [3] identified that the nuss procedure showed an overall complication rate of 18.7% through a retrospective analysis. Fortunately, with the increasing attention from the society on medical care safety and the further standardization of doctor's qualifications,

such medical incidents have been decreasing. As acupuncture and moxibustion (A&M) are increasingly used in world, their widening acceptance necessitates continual safety assessment. This review, a sequel to two previous reviews from our team [4, 5], is an evaluation of the frequency and severity of adverse events (AEs) for acupuncture reported between 1980 and 2013 in China. These two reviews reported the AEs of A&M in the West, reported from 1965 to 1999 and from 2000 to 2011, respectively. In the first review, the main source of infection was found to be hepatitis caused by reused needles. In the second review, the majority of infections were bacterial, caused by skin contact at acupoint sites, without cases of hepatitis. For these two reviews, we just searched English articles, without Chinese reports, so it is unclear which AE happens in China. Since acupuncture is widely used in China, it is necessary to make sure what is happening about AE. In this review, we found internal organ, tissue, or

¹Acupuncture Department, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai 200071, China

²Huadong Hospital Affiliated to Fudan University, Shanghai 200040, China

³Research Unit for Complementary and Integrative Laser Medicine, Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, and TCM Research Center Graz, Medical University of Graz, 8036 Graz, Austria

nerve injuries were the main complications of acupuncture in China from 1980 to 2013. Clearly, guidelines must be followed in order to minimize acupuncture-related AEs and to modernize acupuncture and make it safer to apply.

2. Materials and Methods

2.1. Inclusion Criteria. All case reports concerning acupuncture-related complications or AEs in China published from 1980 to 2013 were identified. Only firsthand reports were included to avoid multiple reports of the same event. Thus, reviews, comments, or case-control studies were excluded from this review.

Complications, defined as "an added difficulty: a complex state, a disease, or an accident superimposed upon another without specific relation," include infections, internal organ or tissue injuries, and other severe consequences. AEs and adverse reactions were defined as "development of an undesired side effect or toxicity" and include less severe consequences, such as contact dermatitis. Side effects, defined as "the action or effect other than that desired," are included within the discussion of AEs [4, 5].

- 2.2. Search Strategy. The following databases were searched for case reports published from 1980 to 2013: VIP science and technology periodical database (CQVIP), China National Knowledge Infrastructure (CNKI), and Wanfang Database (WF). Search terms included "acupuncture, electro-acupuncture, acupuncture points, ear acupuncture, needling." These terms were combined with "safe, safety, adverse event, adverse reaction, side effects, side events, complications, and risk."
- 2.3. Data Extraction. A total of 739 papers were found; 133 were relevant (Figure 1). Information pertaining to the author, year of publication, number of patients, patient's age, sex, original treatment, the punctured site, circumstances of the complication or AE, and long-term patient outcome when available was extracted from each case. These data were then organized according to the type of complication or AE.

3. Results

A total of 133 papers published from 1980 to 2013 were reviewed, and 182 cases of complications or AEs were identified to be associated with pneumothorax (n=30), central nervous system injury (37), peripheral nerve injury (8), organ injury (22), other tissue injury (18), syncope (18), infections (17), hemorrhage (10), complications caused by broken needles (7), and others (15). Pneumothorax and central nervous system injury were the major complications.

3.1. Complications of Acupuncture: Internal Organ, Tissue, or Nerve Injury. A total of 115 cases of internal organ, tissue, or nerve injuries were reported, including pneumothorax (n = 30), central nervous system injury (37), peripheral nerve injury (8), organ injury (22), and other tissue injury (18).

3.2. Pneumothorax (Table 1). Between 1980 and 2013, pneumothorax was the most common complication of acupuncture treatment, as 30 cases in 27 papers were noted to be possibly associated with acupuncture (Table 1). Among the 30 cases presented, 25 recovered through thoracocentesis, thoracic closed drainage, anti-infection treatment, and clinical observation; 2 patients died; and the outcomes of the other 3 cases were not stated or unknown. More than half of them were reported by doctors in emergency rooms or departments of internal medicine, but the practitioner's training background was not reported. The punctured sites were mostly in the chest, supraclavicular fossa, and the back. The patients' major complaints were chest stuffy, chest pain, and dyspnea. One pneumothorax patient did not receive timely treatment and died [6]. Another case died because of a tension pneumothorax after acupuncture treatment [7].

3.3. Central Nervous System Injury (Table 2). There were 37 cases of central nervous system injury associated with acupuncture (Table 2). The 37 patients suffered subarachnoid hemorrhage (n=27), subdural hematoma (2), spinal cord injury (2), cerebral hemorrhage reformulation (2), cervical spinal epidural hematoma (1), medulla oblongata hemorrhage (1), cisterna magna hemorrhage (1), and leukemia acute intracerebral hemorrhage (1). The causes were acupuncture of cervical acupoints (n=31), acupoints between the second and third thoracic spinal process [8], acupoints KI01 (Yongquan) [9] and BL37 (Yinmen) [10], waist acupoint [11] (each n=1), and body acupuncture (n=2) [12, 13]. Among the 37 cases, 26 recovered and 11 died.

Because of insufficient compliance and protected observation, accidents occurred in 3 schizophrenia patients, of whom 2 died and 1 recovered [14]. Two cerebral hemorrhage patients after receiving body acupuncture died from recurrence, and the authors speculated the reason might be that acupuncture had irritated the parasympathetic nerve, causing vascular contraction and increasing blood pressure and thus cerebral hemorrhage recurred before the original cerebrovascular fracture could be fully restored [9, 12]. Two patients suffered from dizziness and vomiting during treatment, but the acupuncturists did not pay high attention; the symptoms did not improve significantly after treatment, but the acupuncturists did not realize the severity and even allowed the patients to go home. One patient was treated the next day after onset and was diagnosed as subarachnoid hemorrhage; he recovered and left hospital [11]. The other patient died the next day [13].

3.4. Peripheral Nerve Injury (Table 3). There were 8 cases of acupuncture-induced peripheral nerve injury (Table 3). They include aggravated facial paralysis [15], mistakenly hitting the vagus [16], phrenic nerve injury [17], optic atrophy [18], oculomotorius injury [19], right trigeminal nerve injury [20], sciatic nerve injury [10], and peroneus nerve injury [21], respectively. The patient with optic atrophy lost sight [18], the patient with right trigeminal anchor injury improved after 3 days [20], the patient with sciatic nerve injury did not recover [10], and the other 5 patients recovered.

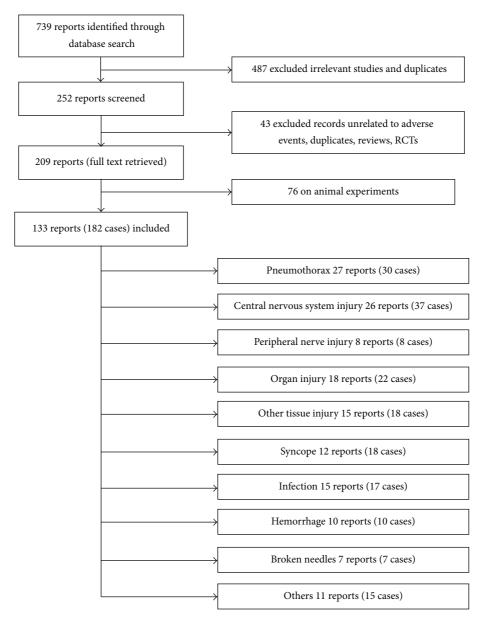


FIGURE 1: Flow chart of the screening process.

3.5. Organ Injury (Table 4). Twenty-two cases were reported to have organ injury associated with acupuncture treatment (Table 4). There was cardiovascular injury (n=7) [14, 22–27], thoracic duct injury (1) [28], peritonitis induced by abdominal system (9) [29–33], gastric perforation (3) [34–36], intestinal obstruction (1) [37], and multiple organ injury (1) [38]. Of them, 14 recovered, 7 died, and 1 did not recover. Most of them were caused by too deep puncture and incorrect acupoint location.

One patient received treatment following gastric abscess induced by gastric ulcer. He was treated by electroacupuncture (EA) at ST36 (Zusanli) and the acupoint was located without violation, but the state of illness was not relieved and gastric perforation occurred. The doctor was puzzled and put forward this case for discussion [35]. One patient with

a history of stomach bleeding received treatment following knee pains induced by rheumatoid arthritis and took antiinflammatory analgesic drugs for a long time. The lower limb acupoint was selected, but the excessive EA irritation during treatment caused an irritable gastric ulcer and then hemorrhagic shock and the patient recovered after timely rescue [36].

3.6. Other Tissue Injuries (Table 5). In addition to injuries of the organs in thorax and abdomen, 18 cases of other tissue injuries were reported (Table 5), including cervical common carotid aneurysm [39], shock [38, 40], asphyxia [41], dyspnea [42], eye injury [18, 43, 44], and the locomotor system injury [10, 44–50]. Among the 18 cases, 12 recovered, 2 improved, 2 did not recover, 1 died, and the outcome of 1 was not stated.

Table 1: Pneumothorax associated with acupuncture.

Author/year (reference)	Cases	Age/sex	Disease treated	Punctured site	Practitioner	Follow-up
Jiang, 1980 [117]	1	54/F	Gastroptosis	RN15	Not specified	Recovered
Cai and Wang, 1982 [118]	1	41/M	Numbness and pain of shoulders and chest	Shoulder and back	Not specified	Recovered (1 mo)
Zheng and Pang, 1983 [119]	1	21/M	Stiff neck	GB21	Not specified	Recovered after surgery (1 mo)
Gao, 1984 [120]	1	50/F	Chest and back pain	Back	Factory doctor	Recovered (12 d)
Duan and Wang, 1984 [29]	2	26/F	Bronchitis	GB21, BL13, EX-B2	Not specified	Recovered (3 d)
, and the second		50/F	Bronchitis	GB21, BL13	Not specified	Recovered (7 d)
Chang, 1984 [121]	1	33/M	Back pain	Back	Country doctor	Recovered (19 d)
Yan, 1985 [122]	1	55/F	Chronic bronchitis	RN22	Health center	Recovered (16 d)
Hu, 1986 [123]	1	58/F	Pulmonary heart disease	BL13	Not specified	Recovered (13 d)
Zhang, 1986 [124]	1	52/M	Cervical pain	Left shoulder	Factory doctor	Recovered (20 d)
Yang, 1986 [6]	1	57/F	Chronic asthmatic disease	BL12	Not specified	Dead
Jin, 1987 [125]	1	26/F	Shoulder pain	SI13	Acupuncturist	Recovered (9 d)
Song and Xu, 1987 [126]	1	60/F	Shoulder pain	GB21	Not specified	Not specified
Ruan et al., 1992 [127]	1	35/F	Hysteria	Supraclavicular fossa	Acupuncturist	Recovered (10 d)
Thong et al. 1002 [29]		53/F	Chronic bronchitis and emphysema	BL18		Recovered (1 wk)
Zhang et al., 1992 [38]	3	65/F	Cough	RN22	Not specified	Recovered (1 mo)
		21/M	Spasmodic torticollis	LI17		Recovered (2 wk)
Lu, 1993 [128]	1	60/M	Cough, chest, and back pain	Back	Acupuncturist	Recovered (1 wk)
Xia, 1993 [129]	1	60/M	Back pain caused by hyperplastic spondylitis	BL18, BL23	Acupuncturist	Recovered (10 d)
Li and Chen, 1997 [130]	1	65/F	Shoulder pain	Scapular region	Clinic	Recovered (5 d)
Ma and Zhang, 1997 [131]	1	48/M	Neck and shoulder pain	Shoulder and back	Clinic	Recovered (1 wk)
Wang, 1999 [7]	1	47/F	Shoulder and leg pain	LI17	Not specified	Dead
Song and Wu, 2001 [9]	1	45/F	Scapulohumeral periarthritis	GB21, SI11	Hospital	Recovered (1 wk)
Qin and Ao, 2003 [132]	1	55/M	Intercostal neuralgia	The sixth intercostal space on the anterior axillary line	Factory doctor	Recovered (2 wk)
Zha, 2006 [133]	1	32/M	Chronic hepatitis B	Chest and back	Itinerant doctor	Recovered (14 d)
Gan et al., 2006 [134]	1	30/M	Neck and back pain	Back	Individual clinic	Not specified
Huo et al., 2007 [135]	1	39/M	Chest and back pain	Not specified	Not specified	Recovered after surgery (7 d)
Liu, 2007 [136]	1	50/M	Cervical and back pain	Back	Individual clinic	Not specified
Ma, 2007 [137]	1	35/F	Shoulder pain	Not specified	Individual clinic	Recovered
Zhang and Zhao, 2012 [138]	1	65/F	Cervical spondylopathy	GB21	Acupuncturist	Recovered (10 d)

Table 2: Central nervous system injury associated with acupuncture.

Author/Year (reference)	Cases	Age/Sex	Disease treated	Punctured site	Complication	Onset after acupuncture	Follow-up
Liu, 1980 [139]	1	19/F	Impaired vision	GB20	Subarachnoid hemorrhage	1 h	Recovered (20 d)
		16/M		DU16	Subdural hematoma		
Liu, 1981 [14]	3	30/F	Schizophrenia	DU14	Cervical and thoracic cord injury	Immediately	Dead
		30/M		GB20	Subarachnoid hemorrhage	1 h	Recovered (47 d)
		30/F	Eyelid muscle twitch	GB20			Recovered (14 d)
Bao and Gao, 1983 [140]	3	27/M	Bulbar palsy	DU15	Subarachnoid hemorrhage	Immediately	Recovered (20 d)
		40/F	Headache	GB20			Recovered (19 d)
Chen and Wu, 1985 [141]	1	30/F	Hysteria	Ex-HN18	Subarachnoid hemorrhage and medulla oblongata hemorrhage	1 d	Dead
Yang et al., 1985 [8]	1	15/M	Chronic tracheitis	Between 2 and 3 thoracic spinous process	Subarachnoid hemorrhage	Immediately	Recovered (1 mo)
Chen and Huang, 1985 [142]	1	57/M	Facial Spasm	Neck	Subarachnoid hemorrhage	Immediately	Recovered (3 wk)
Su et al., 1985 [143]	1	11/F	Deaf-mute	DU15	Subarachnoid hemorrhage	At night	Recovered (1 wk)
		42/M	Psychosis	DU15	Subarachnoid	Several hours	Recovered (1 mo)
		4.5/M	Cerebral agenesis with aphasia	DU15		Immediately	Recovered (20 d)
Yu, 1986 [144]	7	29/M	Weakness of limbs	DU15, DU16		Minutes after treatment	Recovered (1 mo)
		22/M	Acid swells of the neck	Back neck	hemorrhage		Recovered (40 d)
		55/F	Aural vertigo	Back neck		Immediately	Recovered (20 d)
		24/F	Stuffy head	GB20			Recovered (1 mo)
		22/M	Facial paralysis	Ex-HN21			Recovered
Chen, 1987 [145]	1	37/F	Neck pain	DU15	Subarachnoid hemorrhage	1 min	Recovered (1 mo)
Jiang and Chen, 1987 [146]	1	77/F	Stiff neck	GB20	The cerebellopontine and subarachnoid hemorrhage	After treatment	Dead
Zhou, 1988 [147]	1	15/M	Cold	GB20	Subarachnoid hemorrhage	During the treatment	Dead
Mi et al., 1989 [148]	1	28/F	Neurosis	DU15	Subarachnoid hemorrhage	2 d	Recovered (27 d)
Wu and Xu, 1990 [149]	1	57/M	Stroke	Ashi points near C3	Subarachnoid hemorrhage	1 h	Dead (10 d)

Table 2: Continued.

						Onset after	
Author/Year (reference)	Cases	Age/Sex	Disease treated	Punctured site	Complication	acupuncture	Follow-up
Liu, 1992 [150]	1	28/M	Insomnia	GB20	Acute subdural hematoma	3 hours	Recovered after surgery
Mi, 1993 [12]	1	73/M	Cerebral hemorrhage	LI11, LI4, GB30, ST36, GB39, GB14, ST2	Cerebral hemorrhage reformulation	10 min	Dead
	2	45/M	Cervical	GB20	Subarachnoid	T 1: 4 1	Recovered (30 d)
Jiang et al., 1996 [151]	2	54/M	spondylopathy	Neck	hemorrhage	Immediately	Recovered (1 mo)
Liu et al., 1996 [152]	1	35/M	Ankylosing Spondylitis	DU16	Medulla oblongata hemorrhage	5 hours	Dead
Bian et al., 1997 [153]	1	29/F	Headache caused by pesticide poisoning	GB20	Subarachnoid hemorrhage	3 min	Recovered (1 mo)
Wang, 1999 [10]	1	54/M	Low back pain	BL37	Acute subarachnoid hemorrhage	Immediately	Recovered
Wang, 1999 [154]	1	39/F	Neurosis	GB20	Cervical cord injury	Immediately	Dead
Song and Wu, 2001 [9]	1	58/M	Hypertensive cerebral hemorrhage	KI01	Cerebral hemorrhage reformulation	Immediately	Dead
Li et al., 2003 [155]	1	55/M	Neck and back pain	Neck and back	Cervical spinal epidural hematoma	Immediately	Recovered
Niu and Zhang, 2006 [156]	1	42/M	Headache	Neck	Cisterna magna hemorrhage	Not specified	Recovered after surgery
Li et al., 2008 [157]	1	36/F	Migraine	DU16	Subarachnoid hemorrhage	At night	Recovered (3 wk)
Chen, 2009 [11]	1	43/F	Lumbago pain	Waist	Subarachnoid hemorrhage	Immediately	Recovered (1 mo)
Li et al., 2011 [13]	1	45/F	Toothache	RN16, RN10, RN9, RN4	Leukemia acute intracerebral hemorrhage	Immediately	Dead (2 d)

Table 3: Peripheral nerve injury.

Author/year (reference)	Cases	Age/sex	Disease treated	Punctured site	Complication	Practitioner	Follow-up
Tang and Fang, 1986 [15]	1	Not specified	Facial paralysis	Not specified	Aggravated facial paralysis	Not specified	Recovered
Nie and Zhou, 1990 [16]	1	26/M	Left eye pain	SJ17	Cardiac arrest	Acupuncturist	Recovered (1 min)
Yan, 1994 [17]	1	57/M	Cervical dislocation	Bitong point	Phrenic nerve injury	Acupuncturist	Recovered (1 wk)
Yang and Wang, 1996 [18]	1	62/M	Lateral rectus paralysis	Ex-HN07	Optic atrophy	Acupuncturist	Blind
Xu and Liu, 1997 [19]	1	48/M	Tinnitus and hearing loss	ST1, ST2, BL2, LI20, SJ21, SI19	Oculomotorius injury	Not specified	Recovered (17 d)
Huang and Wei, 1997 [20]	1	53/F	Trigeminal nerve pain	Around the mandible	Trigeminal nerve injury	Acupuncturist in the stomatological hospital	Improved (3 mo)
Wang, 1999 [10]	1	54/F	Lumbago	GB30	Sciatic nerve injury	Private practitioner	Unrecovered
Ruan et al., 2009 [21]	1	67/F	Lumbago	GB34	Peroneus nerve injury	Not specified	Recovered (3 wk)

Table 4: Organ injury associated with acupuncture.

				-		
Author/year (reference)	Cases	Age/sex	Disease treated	Punctured site	Complication	Follow-up
Liu, 1981 [14]	1	19/F	Schizophrenia	RN15	Cardiac tamponade	Dead
Zhu, 1990 [22]	1	64/M	Chest stiffness and rib pain	LR14	Aortoclasia	Dead
Shi, 1993 [23]	1	42/F	Witchcraft	Limbs, chest, abdomen, back	Aortoclasia	Dead
Xie and Lin, 2003 [24]	1	35/F	Intercostal neuralgia	Right breast	Cardiac trauma	Dead
Luo et al., 2006 [25]	1	40/M	Chronic esophagitis	RN15	Cardiac tamponade	Recovered
Zhang and Dong, 2006 [26]	1	37/M	Chest tightness, asthma	Chest and back	Cardiac tamponade	Dead
Zhu et al., 2008 [27]	1	44/F	Diabetes	Chest	Cardiac tamponade	Dead
Yang, 1991 [28]	1	21/M	Bad cold	BL13	Chylothorax	Recovered (2 wk)
71 171 1002 [20]	1	31/F	Stomachache	ST25, LR14, RN12	Gallbladder	Recovered after
Zheng and Zhao, 1983 [30]	1	59/M	Cervical spondylopathy	RN12, RN13, ST25	perforation and biliary peritonitis	surgery
Deng, 1985 [31]	1	45/F	Acute attack of chronic cholecystitis	ST21	Gallbladder perforation	Not specified
Bai, 1991 [32]	1	32/F	Paralytic ileus	Upper abdomen	Gallbladder perforation and biliary peritonitis	Recovered after surgery
Duan and Wang, 1984 [29]	1	42/M	Intestinal spasm	RN8, RN12, ST25	Intestinal perforation and suppurative peritonitis	Recovered after surgery (14 d)
		51/M	Paroxysmal abdominal pain Right lower		•	
Zhang, 1997 [33]	4	47/F	abdominal pain Abdominal pain,	Abdomen	Localized peritonitis	Recovered after surgery
		53/F 37/F	diarrhea Periumbilical pain			
Xiao, 1985 [34]	1	20/M	Abdominal discomfort	RN12	Gastric perforation	Recovered after surgery (11 d)
Huang, 1999 [35]	1	54/M	Gastric ulcer	ST36	Gastric ulcer with perforation	Recovered after surgery (10 d)
Tang et al., 2006 [36]	1	61/M	RA	ST34, ST40, SP6, SP10, GB33, GB34	Gastric stress ulcer and hemorrhagic shock	Recovered (2 mo)
Liu et al., 1992 [37]	1	2/M	Diarrhea	RN12, ST25, DU1	Complete intestinal obstruction	Recovered after surgery
Zhang et al., 1992 [38]	1	45/F	Chronic bronchitis, coronary disease	GB21, BL13, BL23	Multiple organ injury	Dead

One patient suffered from retinal detachment, and eyesight was corrected to 0.2 after treatment [43]. One patient lost eyesight because of traumatic cataract [18]. One patient experienced femoral neck fracture after strong stimulation to myospasm [45]. One patient suffered from subluxation in right wrist joint due to excessive EA intensity [48].

3.7. Syncope (Table 6). A total of 18 cases of acupuncture-associated syncope were reported (Table 6). Syncope occurred during the treatment in 9 cases, several minutes after the treatment in 5 cases, and several hours later in 4 patients. Two patients fainted after taking liquors [51, 52]. The positions were sitting (n = 5), lying (5), and not specified (8).

Table 5: Other tissue injury.

Author/year (reference)	Canan	A ma la ave	Diagramentad	Punctured	Commination	Duantitionou	Fallow
Author/year (reference)	Cases	Age/sex	Disease treated	site	Complication	Practitioner	Follow-up
Chen, 1980 [39]	1	33/F	Sore throat	Neck	Cervical common carotid aneurysm	Not specified	Recovered after surgery (3 mo)
Wang, 1987 [40]	1	42/F	Thyroid cancer (anaesthesia for thyroidectomy)	SJ17	Sinus caroticus syndrome, shock	Not specified	Recovered
Zhang et al., 1992 [38]	1	39/M	Asthma	BL13	Pleural shock	Not specified	Recovered (2 d)
Zhu, 1986 [41]	1	56/M	Chest distress	RN22	Asphyxia	Acupuncturist	Dead
Gao, 1989 [42]	1	73/M	Cough	LI18	Dyspnea	Not specified	Recovered (3 d)
Liu et al., 1988 [43]	1	53/M	Blepharospasm	The lateral upper eyelid	Retinal detachment	Health worker	Recovered after surgery
Yang and Wang, 1996 [18]	1	63/F	Left eye ptosis	Periocular	Traumatic cataract	Acupuncturist	Blind
Wang, 1982 [44]	2	20/M	Traumatic mydriasis	EX-HN5	The orbicularis oculi muscle tremor	Not specified	Recovered (3 d)
		35/F	Right migraine		Speech and swallowing difficulties		Recovered (2 h)
Li and Zhou, 1980 [45]	1	40/M	Schizophrenia	EX-HN5	Femoral neck fracture	Acupuncturist	Not specified
Liang and Song, 1984 [46]	1	23/M	Cramp	BL57	Flexor hallucis muscle and digitorum longus muscle scar contracture	Health worker	Recovered after surgery
Chen, 1992 [47]	1	17/F	Shortsightedness	GB20, EX-HN17	Nape spasm	Acupuncturist	Recovered (6 d)
Wang, 1994 [48]	1	65/F	Stroke	LI4, SJ5, LI15	Subluxation of wrist	Intern	Recovered (1 wk)
Chi and Char 1004 [40]	1	52/M	Facioplegia	LI11	Elbow pain	Acupuncturist	Recovered (2wk)
Shi and Chen, 1994 [49]	1	61/F	Scapulohumeral periarthritis	Not specified	Shoulder pain	T	Recovered (20 d)
Wang, 1999 [10]	1	53/M	Cough, epistaxis	LU6	Amyotrophy	Private practitioner	Unrecovered
Luo and Huang, 2006 [50]	2	42/M 63/M	Amyotrophic lateral sclerosis	Upper limb Upper limb	Fasciculation	Not specified	Improved Improved

Most patients recovered with rest and drinking sugar water, while 2 patients recovered after injection of metoclopramide via ST36 [53]. Two cases suffered from sudden cardiac arrest and were cured after first aid [54, 55]. One patient recovered after massaging an ear acupoint [56].

3.8. Infection (Table 7). A total of 17 cases were infections associated with acupuncture (Table 7). Among them, 10 recovered, 3 died, 2 improved after 3 days, 1 was disabled, and 1 was not stated. The infection was caused by tetanus bacillus (n = 6) [10, 57–61], hydatid (1) [62], Escherichia coli (1) [63], and Mycobacterium tuberculosis (3) [64]. One patient was infected after deep 3-degree burning [65] while others were not stated.

In one patient, the right epigastric mass due to acupunctured liver hydatid caused extensive metastasis in hydatid abdominal cavity; the patient recovered after operation [62]. One diabetic patient without controlling blood glucose suffered from diabetic feet because of infection and recovered after hypoglycemic and anti-infection treatments.

3.9. Hemorrhage (Table 8). Among 10 cases of acupuncture-induced local hemorrhage (Table 8), 8 patients recovered, 1 improved, but 1 died. The positions of hemorrhage included eyes (n = 2) [6, 66], extraperitoneal (1) [67], thyroid (1) [68], hypoglossus (2) [69, 70], suffocated death from hematoma compressed trachea (1) [71], hand (1) [72], 1 case of buttock

Table 6: Syncope associated with acupuncture.

Author/year (reference)	Cases	Age/sex	Disease treated	Punctured sites	Position	Start time	Causes	Practitioner	Follow-up
Yang, 1986 [6]	1	32/M	Facioplegia	GB14, ST6, ST4, SJ17, LI20, LI4	Sitting	5 min after inserting needle	Limosis	Acupuncturist	Recovered
Shao, 1989 [51]	1	53/M	Myotenositis of long head of biceps brachii	LI15, LI11, ashi	Not specified	After inserting needle	After drinking	Acupuncturist	Recovered (20 m)
Shi and Chen, 1994 [49]	1	57/F	Stomachache	LI3, ST36, PC6	Not specified	Finish needling	Limosis	Acupuncturist	Recovered (30 min)
Guo, 1995	2	65/F	Scapulohumeral periarthritis	Ex-UE01, GB21, LI14, LI11, SJ5, LI4		Finish needling	Weakness	Acupuncturist	Recovered
[158]	2	24/F	Waist sprain	BL40, ashi point and acupoint of bladder meridian	Clinostatism	Finish needling	Nervous	Acupuncturist	Recovered (10 min)
Wu et al., 2001 [56]	1	24/F	Insomnia	PC6, ST36, HT7	Not specified	At night	Not specified	Acupuncturist	Recovered (2 d)
		45/F	Lumbago pain	BL23, BL40, DU3, GB30, KI7	Not specified	Finish needling	After drinking	Acupuncturist	
Liu, 2001 [52]	3	34/F	Shoulder pain	LI11, LI14, LI15, SJ5, SJ14	Sitting	After inserting needle	Tiredness	Acupuncturist	Recovered
		56/F	Right thumb pain	LI4, LI5, LI11, ashi point	Not specified	On the way home	Limosis	Acupuncturist	
Ma, 2005 [54]	1	28/M	Prosopalgia	EX-HN5, LI4, ST6, SJ5	Sitting	5 min after inserting needle	Not specified	Acupuncturist	Recovered (30 s)
		72/M	Stroke	LI11, SJ5, ST36, SP6, EX-UE17, EX-LE11	Clinostatism	10 min after inserting needle	Nervous	Acupuncturist	Recovered (2 min)
Long et al., 2006 [55]	3	41/F	Cervical spondylopathy	BL10, GB20	Sitting	1 min after inserting needle	Not specified	Acupuncturist	Recovered (30 min)
		42/F	Lumbago pain	ST36	Clinostatism	After inserting needle	Heavy stimulus	Acupuncturist	Recovered (2 min)
Liu, 2007 [159]	1	42/F	Scapulohumeral periarthritis	Ex-UE01, LI14, Ashi point, SJ3	Sitting	10 min after inserting needle	Not specified	Acupuncturist	Recovered (30 min)
Chen, 2009 [11]	1	42/M	Acute lumbar sprain	EX-B5, BL40	Not specified	Finish needling	Not specified	Acupuncturist	Recovered (10 min)
Liao and Guo, 2009 [160]	1	57/F	Gouty arthritis	GB20	Clinostatism	After inserting needle	Limosis	Acupuncturist	Recovered (10 min)
I: at al. 2000		48/M	Cervical spondylopathy radiculaire	GB21, LI11, SJ5, Ex-B5		6 h after treatment	Not specified	Acupuncturist	Recovered after stop treatment
Li et al., 2009 [53]	2	68/F	Facial paralysis	GB14, ST2, ST4, ST6, SJ17, LI4, Ex-HN16	Not specified	12 h after treatment	Not specified	Acupuncturist	Recovered after stop treatment

Punctured Author/year (reference) Cases Disease treated Follow-up Age/sex Diagnosis Practitioner site Middle finger Zhang, 1980 [161] 1 5/F Ex-UE19 Infection Not specified Heat, cough disability Right upper Abdominal Recovered Xie and Zong, 1983 [62] 38/F abdominal mass Ashi points metastatic hepatic Local hospital after surgery and discomfort hydatid Third-degree burns Gao and Qi, 1989 [65] 1 54/M Right leg pain Local points Clinic Not specified with infection Head abscess. Health worker EX-HN5, Xu, 1990 [162] 1 19/M Migraine intracranial Recovered GB14, DU20 in the army infection Right cheek Recovered Xia, 1993 [129] 1 37/F Facioplegia ST5 hematoma with Not specified (1 wk) infection Recovered Chen and Gao, 1995 [63] 1 30/M Encephalopyosis Not specified Insomnia Head after surgery From 22 to **Tuberculous** Lumbar muscle Recovered Zhou, 1999 [64] 3 28/M (1); F Loin abscess on the Not specified (3-6 mo)strain body surface (2) EX-LE4, Rheumatic Individual clinic Recovered Song and Wu, 2001 [9] 1 38/M EX-LE5, Pyogenic arthritis arthritis in the country (2 wk) GB34, SP9 Scapulohumeral Remission Ding et al., 2008 [112] 1 60/F ST38 Diabetes foot Not specified periarthritis after 3 days Malnutritional Yang et al., 1990 [57] 1 2/F Ex-UE19 **Tetanus** Illegal treatment Dead stagnation Ex-HN05, Village Recovered Liu, 1991 [58] 1 52/F Headache DU20, GB20, **Tetanus** acupuncturist (2 wk) LI4 Private Recovered Liu, 1992 [59] 1 52/F Leg pain Not specified Tetanus practitioner (1 mo) Remission Sun and Hu, 1997 [60] 1 Facioplegia Not specified **Tetanus** Health-center 23/M after 3 days

Headache and

fever

RA

TABLE 7: Infection associated with acupuncture.

hematoma due to acquired hemophilia B which improved after treatment [73], and lower limb (1) [74].

1

60/M

62/F

Wang, 1999 [10]

Chen et al., 2008 [61]

3.10. Complications Caused by Broken Needles (Table 9). Seven cases of accidents due to broken or bent needles were identified (Table 9). Five recovered after the surgery [75-79], and 2 cases of bent needles were slowly pushed out by acupuncturists [6, 80].

3.11. Other Complications Associated with Acupuncture (Table 10). A total of 15 other complications associated with acu-puncture were reported (Table 10): aphonia [81], hoarseness [82], allergy to electroacupuncture [83] and metal [84], epilepsy [85, 86], fever [87], cough [88], thirst [88], infusion reaction [89], hyperventilation syndrome [90], and aggravation of fatigue [91]. Of them, 14 cases recovered completely and 1 improved.

One patient was not allergic after several acupuncture treatments, but systemic allergy occurred after EA treatment [65]. Among three patients with acupuncture-induced epilepsy, only one had a history of epilepsy [85, 86].

Not specified

Illegal treatment

Dead

Dead

Tetanus

Tetanus

4. Discussion

GB20, GB21,

SJ5

Knee

The studies about safety of acupuncture are gradually increasing. One study protocol of a randomized controlled trial is efficacy and safety of acupuncture for chronic dizziness [92]. This trial's aim is to get result that acupuncture has good efficacy and without adverse effect for chronic dizziness. We hope it is success.

Some studies that researched acupuncture as an alternative means for pediatric diseases found that it is safe, feasible, and acceptable [93-99]. One study explored acupuncture as an effective therapy of pain relief for children and adolescents after tonsillectomy [100]. Severe throat pain can result from

TABLE 8: Hemorrhage.

Author/year (reference)	Cases	Age/sex	Disease treated	Punctured site	Complication	Practitioner	Follow-up
Yang, 1986 [6]	1	28/F	Chronic conjunctivitis	BL1	Eye hematoma	Acupuncturist	Recovered (14 f)
Li, 1989 [67]	1	62/F	Teratoma of ovary	Hypogastrium	Extraperitoneal hematoma	Roving doctor	Recovered after surgery
Cai, 1991 [68]	1	47/M	Neck mass	Neck	Thyroid intracapsular hemorrhage with apnea	Not specified	Recovered after surgery (10 d)
Han, 1994 [69]	1	56/M	Stroke	RN23	Sublingual hematoma	Not specified	Recovered (1 wk)
Zeng and Liu, 1996 [71]	1	50/M	Cough	ST9	Hematoma compression tracheal cause apnea	Unauthorized acupuncturist	Dead
Wang, 1996 [70]	1	72/M	Cerebral infarction	Ex-HN20	Sublingual hematoma	Not specified	Recovered (2 d)
Gan, 2000 [66]	1	46/F	Cold headache	Ex-HN05	Orbital hemorrhage	Not specified	Recovered (1 mo)
Jiang, 2001 [72]	1	68/M	Hypertension, stroke	LI4	Hand hematoma	Acupuncturist	Recovered (7 d)
Duan, 2007 [73]	1	65/F	Neck, waist, and leg pain	Hip	Buttock hematoma	Not specified	Improved
H. Liu and X. H. Liu, 2007 [74]	1	61/M	Cerebral thrombosis	SP6	Lower extremity hematoma	Acupuncturist	Recovered (1 d)

Table 9: Complications caused by broken needles.

Author/year (reference)	Cases	Age/sex	Disease treated	Punctured site	Complication	Practitioner	Follow-up
Yang, 1986 [6]	1	45/M	Flaccid paralysis	ST36, LI11	Bent needle	Acupuncturist	Recovered
Lu and Teng, 1994 [75]	1	39/M	Scapulohumeral periarthritis	Supraclavicular fossa	Hemopneumothorax caused by broken needle	Country doctor	Recovered after surgery
Wang, 2000 [80]	1	54/M	The left upper limb dysfunction	Upperlimb	Sticking of needle	Not specified	Recovered
Geng, 2005 [76]	1	58/M	Chronic bronchitis and emphysema	LU1	Damage of arteria coronaria and cardiac tamponade caused by embedded needle	Self	Recovered after surgery
Quan, 2008 [77]	1	43/F	Gastric disease	Xiphoid	Palpitation and paroxysmal pricking pain caused by broken needle	Not specified	Recovered after surgery
Liu and Yu, 2010 [78]	1	45/F	Multiple injuries by traffic	RN23	Pulmonary bulla caused by embedded needle	Not specified	Recovered after surgery
Cheng, 2010 [79]	1	55/M	Lumbago	Lower limb	Broken needle	Not specified	Recovered after surgery

tonsillectomy and last up to 10 days in children. Codeine elixir has long been used for pain relief but has recently been banned by the Food and Drug Administration due to a recently recognized risk of death. This study suggested that acupuncture decreases perceived pain in children and adolescents after tonsillectomy. These data, combined with the cost

effectiveness, safety, and ease of administering acupuncture, suggest that further studies exploring the effectiveness of acupuncture in juveniles after tonsillectomy are merited.

One research evaluated the feasibility of delivering acupuncture in an emergency department (ED) to patients presenting with pain and/or nausea [101]. The acupuncture

Table 10: Other complications associated with acupuncture.

Author/year (reference)	Cases	Age/sex	Disease treated	Acupoint	Complication	Practitioner	Follow-up
Wang and Lan, 1980 [81]	2	46/F	Intercostal neuralgia	PC6	Aphonia	Not specified	Recovered (3 d)
		36/F	Obstinate hiccup				
Zhou et al., 2005 [82]	1	43/F	Neck pain	Ex-B05	Hoarseness	Acupuncturist	Recovered (10 min)
Peng, 1982 [83]	1	54/not specified	Scapulohumeral periarthritis	Ex-UE01, GB21, LI11, SJ5	Allergy to electroacupuncture	Acupuncturist	Recovered (10 min)
Gao and Zheng,		72/M	Nerve root cervical spondylopathy	EX-B2			Recovered (1 wk)
2008 [84]	2	49/F	Cervical type cervical spondylopathy	EX-B2	Allergy to metal	Not specified	Recovered (5 d)
Wang, 2004 [85]	1	35/M	Soft tissue injury	Ashi point	Epilepsy	Acupuncturist	Recovered
D.: 2012 [0]		45/M	Epilepsy				Recovered (2 min)
Dai, 2012 [86] 2	2	53/M	Cervical spondylosis	Not specified	Epilepsy	Acupuncturist	Recovered (1 min)
Li, 2000 [87]	1	52/M	Cerebral concussion	DU20, GB20, GB30, GB39, LI4, LI11, ST36	Fever	Acupuncturist	Recovered
Shang, 2006 [88]	2	65/F	Facial neuritis	GB14, BL2, ST2, SI18, RN24, LI4, ST36, LR3	Cough	Acupuncturist	Recovered (2 min)
		46/F	Obesity	ST25, ST36, SP15, RN6, LI11, SJ6, SP9, ST40	Thirsty	Acupuncturist	Recovered
Quan and Jiang, 2008 [89]	1	45/F	RA	Local points	Infusion reaction	Acupuncturist	Recovered (2 h)
Fang, 2010 [90]	1	35/F	Cervical pain	GB20, EX-B2	Hyperventilation syndrome	Acupuncturist	Recovered (15 min)
Wang, 2010 [91]	1	46/F	Nasopharyngeal carcinoma radiation sequela with fatigue	LI11, LI4, ST36, SP6, KI3; LU7, SI6, SJ3	Aggravation of fatigue	Acupuncturist	Improved

group comprised 200 patients who received usual medical care and acupuncture; the usual care group comprised 200 patients with retrospective data closely matched from ED electronic health records. The results confirmed that acupuncture in the ED appears safe and acceptable for patients with pain and/or nausea. Further high-quality, sufficiently powered randomized studies evaluating the cost-effectiveness and efficacy of the add-on effect of acupuncture are recommended.

Some reports confirmed that acupuncture for pregnant women is safe and effective [102–109]. For example, one reported a complete recovery from Bell's palsy (BP) of a 27-year-old woman, 27-week pregnant, after 2 weeks of acupuncture treatment. Prior to treatment, her House-Brackmann facial nerve grading system (HBS) was II, Nottingham facial

nerve grading system was 50.88%, and the Facial Disability Indexes (FDI) were 90. After 2 weeks, her symptoms had disappeared, her face was restored to normal, HBS was I, Nottingham was 96.46%, and FDIP was 100. These results suggest that acupuncture may be a safe, alternative treatment for BP in pregnancy [110]. Another study described patients' experience of acupuncture treatment in low back and pelvic pain during pregnancy. Women received acupuncture treatment from gestational week 20 or week 26, for a period of 6 weeks divided into eight sessions of 30 minutes each. The results of Pain-O-Meter and visual analogue scale (POM-VAS), Short-Form McGill Questionnaire (SF-MPQ), and Short-form-36 health survey (SF-36) showed a relief of pain. Telephone interviews confirmed that expectations of treatment were fulfilled. The authors suggested that it may be advantageous

to begin acupuncture therapy later in pregnancy to maximize pain relief [111].

However, complications and adverse effects in medical practice always concern the public and the medical profession. Acupuncture has been used for several thousand years in China. Although it has been deemed a safe and reliable therapy, the rare adverse effects and complications should arouse concerns. During the 33 years from 1980 to 2013, about 182 cases of acupuncture-associated complications and adverse effects were reported in China, including 25 fatal cases. The frequency of acupuncture associated complications reported in China appears to be steady over time (see Figure 2).

As indicated in Table 1, the most frequent complication of acupuncture treatment is internal organ, tissue, or nerve injury. Of the 115 reported cases involving internal organ, tissue, or nerve injury, 30 (26.08%) were pneumothorax, 37 concerned the central nervous system (32.17%), others included injury in peripheral nerve, organ, and other tissues. Based on our research, one major cause of direct thrusted injuries to organ, tissue, or nerve is the lack of knowledge about anatomy and other systems. In 1980s, the acupuncturists or individuals in many country grassroot regions performed acupuncture because of low cost and convenience, but the deficient knowledge on anatomy led to many cases of pneumothorax and subarachnoid hemorrhage, as well as injuries to abdomen organs, heart, and peripheral nerves. With the increasing requirement for acupuncturists, these accidents decreased from the 1990s. Particularly, the frequency of pneumothorax and central nervous system injury appears to be on the decline since the 2000s (see Figure 3). This may be because the government has demanded that the acupuncturists should have licenses and formal education background if they practice in clinic in recent years. They should also undergo short time training every year. All these make the acupuncture technique become more and more standardized so that the accidents of pneumothorax and central nervous system injury are reduced. However, there is a possibility that we lack the accident reporting system so that the incidences were underreported.

We put forward suggestions for the medical system in order to avoid more accidental injury on organ, such as enhancing training on anatomy for acupuncturists; setting up more continuation courses on the safety of acupuncture practice for acupuncturists; establishing a reporting system on the incidents of acupuncture adverse effect; and safety courses and certificates should be required in order to obtain the license of acupuncture in China.

The acupuncturists (1) should avoid important organs and tissues during selection of acupoints and reposition if the patient changes body position; (2) do not distract attention during treatment and do not move the patient after acupuncture so as to avoid accidents; for unconscious patients unable to cooperate, shallow needling or not retaining needle is preferred, and the process of treatment should be strictly monitored; (3) inquire detailed medical history and carefully determine the needling depth for patients with emphysema or hemorrhagic disease. Moreover, traditional medicine holds that acupuncture should be performed to bring about the

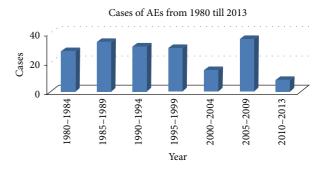


FIGURE 2: Distribution of cases of acupuncture-associated complications reported from 1980 to 2013.

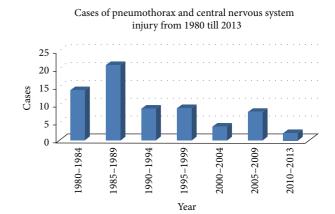


FIGURE 3: Distribution of cases of pneumothorax and central nervous system injury from 1980 to 2013.

desired sensations of "sour, numb, heavy, and swelling." Many acupuncturists and patients think that a stronger sensation of needling will bring about better therapeutic effects, but excessively violent operation will also cause accidents. The 2 cases of irritable stomach bleeding due to excessive irritation [35, 36] and the 1 case of femoral neck fracture due to myospasm [45] are typical examples and should alert clinicians. In case of suspected acupuncture-induced injury, the doctor should prolong the time of observation and warn for prompt treatment.

Syncope is also a common acupuncture-induced accident. The hungry, thirsty, drunken, or nervous patients should be asked to eat, drink, or rest for half an hour before treatment and calm down. They should be observed for a moment during and after treatment to avoid syncope. Once syncope occurs, needles should be pulled out immediately, sugar water should be provided, and the patient should lie down with head low; if the symptom becomes severe, take appropriate treatment. Two patients had severe adverse reaction like shock, with the clinical manifestation, including loss of consciousness, respiratory arrest, and carotid pulselessness. After doing CPR, both of them recovered [54, 55]. Reviewing medical history, one was found to have the similar experience several years ago [55]. Therefore, acupuncturists

are required to inquire patients' medical history carefully and learn to deal with emergencies.

Acupuncture infection usually occurs in rural grassroot health centers with low awareness of hygiene, but accidents will be largely controlled along with the use of disposable needles and the popularization of health knowledge. Moreover, tetanus is still an adverse event that should be strictly prevented, and once it occurs, it will cause a high mortality rate. Along with the increasing incidence of diabetes, for patients with poorly controlled blood glucose [112], careful operation is required to avoid infection due to disunion of acupuncture-caused wounds.

The acupuncture-induced bleeding and hematoma are unavoidable; thus to reduce their incidence rates, acupuncturists should (1) get familiar with the anatomy of acupoints and avoid blood vessels during needle manipulation; (2) avoid manipulation methods such as lifting and thrusting when acupuncturing intraorbital acupoints; (3) appropriately extend the time of compression for patients with hypertension, arteriosclerosis, or inclination to hemorrhage and for women during the menstrual period. The acupuncture-induced hematoma is usually cold compressed within 24 hours and hot compressed after 24 hours. H. Liu and X. H. Liu [74] suggested pressing the local hematoma site heavily for a long time, which could immediately disperse the swelling, without leaving bruises. This method is recommended for other acupuncturists.

With a long history in China, acupuncture has been widely accepted and applied in people's daily life due to its exceptional therapeutic effects and low side effects. As early as 1980, WHO unveiled 43 kinds of diseases that can be treated with acupuncture. The number had increased to 107 in 2002 [113], from which we can see that acupuncture has been recognized by an increasing number of people and more research in this field is being undertaken. In countries where acupuncture is widely used, it is inevitable to encounter the occurrence of some side reactions in acupuncture therapies. However, the accident rate in acupuncture is relatively low. Although existing reports in China show no statistical data about acupuncture accidents, some studies conducted in large subject pools in Germany reveal some relevant information. It has been reported that Endres et al. [114] conducted a study about accidents in acupuncture therapies on 190,924 patients. The study showed an occurrence of 14,449 acupuncture accidents, which accounted for 7.57% of the total subject pool. According to statistics conducted by Witt et al. [115] on 229,230 clinical acupuncture cases, there were 19,726 accidents, which occupied 8.6% of the total subject pool. Chinese literatures show that most of the acupuncture accidents are caused by acupuncturist's lack of corresponding techniques and nonstandard operations. Since 2005, the Chinese National Administration of Quality Supervision, Inspection and Quarantine and the Chinese National Standardization Management Committee have issued a total of 18 acupuncture technical operation specifications in two batches, including terms and definitions, operating procedures and requirements, operating methods, attentions, and contraindications. Among them, operating procedures and requirements specifically include

the selection of needles, acupuncture points and acupuncture positions, environmental requirements, the disinfection of needles, selected acupuncture points and acupuncturist's hands, specific operation techniques, and after-treatments of wounds [116]. The acupuncture technical operation specification series covers a wide area and contains comprehensive and specific contents, but it still shows some deficiency in the popularization and implementation of acupuncture.

In conclusion, we recommend that the qualifying training of acupuncturists should be systemized and the clinical acupuncture operations be standardized in order to effectively prevent the occurrence of acupuncture accidents, enhance the influence of acupuncture, and further popularize acupuncture to the rest of the world. All this would mean a huge step towards modernization of acupuncture.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported partially by Grant no. 81102636 from the National Natural Science Foundation (NSFC) in China. In Austria, the work was supported by the Federal Ministries of Science, Research and Economy and of Health (project title "Evidence-Based High-Tech Acupuncture and Integrative Laser Medicine for Prevention and Early Intervention of Chronic Diseases"). The authors would like to thank Ms Ingrid Gaischek, M.S. (Medical University of Graz) for her valuable help concerning this paper.

References

- [1] C. M. Pui, M. P. Bostrom, G. H. Westrich et al., "Increased complication rate following conversion total hip arthroplasty after cephalomedullary fixation for intertrochanteric hip fractures. A Multi-center Study," *Journal of Arthroplasty*, vol. 28, no. 8, pp. 45–47, 2013.
- [2] L. Faunø, C. Rasmussen, K. K. Sloth, A. M. Sloth, and A. Tøttrup, "Low complication rate after stoma closure. Consultants attended 90% of the operations," *Colorectal Disease*, vol. 14, no. 8, pp. e499–e505, 2012.
- [3] T. Umuroglu, K. Bostanci, D. T. Thomas, M. Yuksel, and F. Yilmaz Gogus, "Perioperative anesthetic and surgical complications of the nuss procedure," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 27, no. 3, pp. 436–440, 2013.
- [4] L. Lao, G. R. Hamilton, J. Fu, and B. M. Berman, "Is acupuncture safe? A systematic review of case reports," *Alternative Therapies in Health and Medicine*, vol. 9, no. 1, pp. 72–83, 2003.
- [5] S. F. Xu, L. Z. Wang, E. Cooper et al., "Adverse events of acupuncture: a systematic review of case reports," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 581203, 15 pages, 2013.
- [6] Y. D. Yang, "Clinical examples of adverse events of acupuncture," *Shanxi Journal of Traditional Chinese Medicine*, vol. 7, no. 7, p. 319, 1986.

- [7] Y. L. Wang, "A case about death because of pneumothorax caused by needling LI17-tianding," *Journal of Forensic Medicine*, vol. 15, no. 1, pp. 47–48, 1999.
- [8] Y. D. Yang, R. Shi, and S. H. Ge, "Presentation about one case of subarachnoid hemorrhage caused by needling," *Liaoning Journal of Traditional Chinese Medicine*, vol. 8, p. 37, 1985.
- [9] Q. L. Song and T. Y. Wu, "Report of three cases about malpractice of acupuncture," *Clinical Misdiagnosis & Mistherapy*, vol. 14, no. 1, p. 73, 2001.
- [10] K. F. Wang, "Some thoughts about acupuncture accidents," *Journal of Clinical Acupuncture and Moxibustion*, vol. 15, no. 5, pp. 57–58, 1999.
- [11] A. Chen, "Analysis on four cases about acupuncture accident," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 28, no. 2, pp. 112–113, 2009.
- [12] J. Mi, "A case about cerebral hemorrhage caused by acupuncture," *Heilongjiang Journal of Traditional Chinese Medicine*, no. 2, p. 34, 1993.
- [13] S. X. Li, H. Wen, and X. H. Yao, "A case about death caused by leukemia acute intracerebral hemorrhage with acupuncture damage," *Chinese Journal of Forensic Medicine*, vol. 26, no. 4, pp. 334–335, 2011.
- [14] X. J. Liu, "Four cases accidents of schizophrenia treating by acupuncture," *Chinese Journal of Nervous and Mental Diseases*, vol. 5, p. 317, 1981.
- [15] X. L. Tang and Q. P. Fang, "Aggravation of infranuclear facial palsy induced by strong stimulation of electro-acupuncture," *People's Military Surgeon*, no. 6, p. 69, 1986.
- [16] X. F. Nie and A. J. Zhou, "Analysis on the reason of respiratory and cardiac arrest induced by needling in SJ17-yifeng," *Hubei Journal of Traditional Chinese Medicine*, vol. 5, p. 39, 1990.
- [17] B. X. Yan, "One case of phrenic nerve damage caused by needling in brachial plexus," *Shaanxi Journal of Traditional Chinese Medicine*, vol. 15, no. 11, p. 513, 1994.
- [18] G. Yang and S. L. Wang, "Two reports about blindness caused by acupuncture," *Tianjin Journal of Traditional Chinese Medicine*, vol. 13, no. 1, p. 6, 1996.
- [19] L. H. Xu and A. H. Liu, "One case about oculomotor nerve damage caused by acupuncture," *Journal of Injuries and Occupational Diseases of the Eye with Ophthalmic Surgeries*, vol. 19, no. 3, article 226, 1997.
- [20] R. H. Huang and S. H. Wei, "A case of eye damage in treating trigeminal nerve pain with electro-acupuncture," Chinese Journal of Ocular Trauma and Occupational Eye Disease (with Ophthalmic Surgery), vol. 19, no. 4, p. 307, 1997.
- [21] J. W. Ruan, S. M. Li, M. Wen, Z. D. Rao, and Y. H. Hu, "Analysis on adverse effects of acupuncture in clinical practices," *Chinese Acupuncture & Moxibustion*, vol. 29, no. 11, pp. 939–942, 2009.
- [22] J. Zhu, "A case about death caused by thoracic aorta hemorrhage through needling in LR14-qimen," Shanghai Journal of Acupuncture and Moxibustion, no. 2, p. 31, 1990.
- [23] G. W. Shi, "A case about death caused by aortic rupture through needling in the chest," *Chinese Journal of Forensic Medicine*, vol. 8, no. 4, pp. 237–242, 1993.
- [24] J. Z. Xie and W. Z. Lin, "A case about death because of cardiac trauma caused by acupuncture," *Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care*, vol. 10, no. 1, p. 51, 2003.
- [25] Y. Z. Luo, L. Dong, H. S. Yuan, and Q. L. Xiang, "A case about delayed cardiac tamponade caused by acupuncture," *Chinese Journal of Clinical Thoracic and Cardiovascular Surgery*, vol. 13, no. 5, p. 343, 2006.

- [26] J. H. Zhang and X. R. Dong, "A case about death because of cardiac rupture caused by acupuncture," *Journal of Forensic Medicine*, no. 2, p. 49, 2006.
- [27] W. T. Zhu, X. S. Li, Y. T. Zhang, and W. Li, "A case about death because of cardiac rupture caused by acupuncture," *Chinese Journal of Forensic Medicine*, vol. 24, no. 4, p. 312, 2008.
- [28] S. T. Yang, "A case about chylothorax caused by needling in BL 13-Feishu," *Journal of Clinical Acupuncture and Moxibustion*, no. 4, p. 19, 1991.
- [29] Q. L. Duan and S. R. Wang, "Lesson learn from three cases about severe complications caused by acupuncture," *Hebei Journal of Traditional Chinese Medicine*, no. 1, pp. 36–37, 1984.
- [30] B. S. Zheng and M. L. Zhao, "Lessons learn from two cases about perforation of gallbladder and biliary peritonitis caused by acupuncture," *Chinese Journal for Clinicians*, no. 3, p. 44, 1983.
- [31] M. H. Deng, "Report of one case about gallbladder perforation caused by needling in ST21-liangmen," *Journal of Sichuan of Traditional Chinese Medicine*, vol. 4, p. 13, 1985.
- [32] X. F. Bai, "One case about perforation of gallbladder and biliary peritonitis caused by acupuncture," *Inner Mongolia Medical Journal*, vol. 11, no. 2, article 80, 1991.
- [33] J. H. Zhang, "Four reports of peritonitis caused by needling in the abdomen," *Chinese Journal of Rural Medicine and Pharmacy*, vol. 4, no. 6, pp. 20–21, 1997.
- [34] X. T. Xiao, "Lessons learned from one case about gastric perforation caused by acupuncture," *Chinese Journal for Clinicians*, no. 1, p. 9, 1985.
- [35] L. H. Huang, "A case of gastric ulcer with perforation caused by needling in ST36-zusanli," *Journal of Clinical Acupuncture and Moxibustion*, vol. 15, no. 10, p. 43, 1999.
- [36] T. Tang, Q. Li, and J. X. Gao, "A case about clinical acupuncture accident," *Chinese Acupuncture & Moxibustion*, vol. 26, no. 6, pp. 459–460, 2006.
- [37] W. G. Liu, L. J. Duan, and D. T. Sun, "Report of one case about intestinal obstruction caused by needling in ST25-tianshu," *Chinese Journal of Integrated Traditional and Western Medicine*, vol. 2, no. 3, p. 147, 1992.
- [38] C. Y. Zhang, S. M. Zhen, and Y. F. Pei, "Report of five cases about visceral injury caused by acupuncture," *Heilongjiang Journal of Traditional Chinese Medicine*, no. 1, p. 38, 1992.
- [39] S. M. Chen, "One case about cervical common carotid aneurysm caused by acupuncture," *Journal of Traditional Chinese Medicine*, no. 7, p. 49, 1980.
- [40] Z. Z. Wang, "A case of shock induced by acupuncturing in carotid sinus," *Chinese Journal of Practical Surgery*, vol. 7, no. 2, p. 66, 1987.
- [41] J. Zhu, "A case about death because of asphyxia caused by needling in RN 22-tiantu," *Jiangsu Journal of Traditional Chinese Medicine*, vol. 2, article 28, 1986.
- [42] L. W. Gao, "A case about dyspnea caused by needling LI18-futu," China Journal of Traditional Chinese Medicine and Pharmacy, no. 2, p. 50, 1989.
- [43] B. S. Liu, Z. X. Li, and F. Lei, "A case about amotio retinae caused by acupuncture," *Chinese Journal of Ocular Trauma and Occupational Eye Disease(With Ophthalmic Surgery)*, vol. 1, pp. 43–44, 1988.
- [44] S. F. Wang, "Adverse reaction about two cases caused by needling in Ex-HN5-taiyang with improper technique," *Chinese Journal of Practical Meicine*, no. 3, p. 135, 1982.
- [45] Y. M. Li and Z. Q. Zhou, "Report of one case about femoral neck fracture induced by electro-acupuncture," *Chinese Journal* of Nervous and Mental Diseases, vol. 3, p. 153, 1980.

- [46] Y. T. Liang and L. F. Song, "One case of flexor hallucis muscle and digitorum longus muscle scar contracture caused by repeated acupuncture," *People's Military Surgeon*, no. 5, pp. 79–80, 1984.
- [47] Y. Z. Chen, "Analysis on one case of nape spasm induced by electro-acupuncturing in GB20-fengchi and Ex-HN17-yiming," *Journal of Clinical Acupuncture and Moxibustion*, vol. 1, article 50, 1992.
- [48] J. H. Wang, "A case of subluxation of wrist caused by improper electro-acupuncture," Guangxi Journal of Traditional Chinese Medicine, no. 1, p. 45, 1994.
- [49] G. P. Shi and Z. M. Chen, "Analysis on three cases of adverse events caused by acupuncture," *Journal of Clinical Acupuncture and Moxibustion*, vol. 10, no. 5, p. 38, 1994.
- [50] C. Y. Luo and H. Y. Huang, "Two cases of fasciculation induced by acupuncture," *Chinese Acupuncture and Moxibustion*, vol. 26, no. 6, p. 460, 2006.
- [51] W. L. Shao, "Report of one case about syncope after drink," Journal of Nanjing University of Traditional Chinese Medicine, no. 4, p. 41, 1989.
- [52] C. B. Liu, "Report of four case about syncope induced by acupuncture," *Journal of Clinical Acupuncture and Moxibustion*, vol. 17, no. 3, article 51, 2001.
- [53] L. Li, J. Y. Huang, and G. M. Lu, "Two cases of lag syncope induced by acupuncture," *Chinese Acupuncture and Moxibustion*, vol. 29, no. 9, p. 732, 2009.
- [54] Z. H. Ma, "A case of sudden cardiac arrest induced by acupuncture," *Hebei Journal of Traditional Chinese Medicine*, vol. 27, no. 8, p. 589, 2005.
- [55] Z. Y. Long, D. S. Chen, and L. P. Chen, "Analysis on cases of severe syncope during acupuncture treatment," *Hubei Journal* of *Traditional Chinese Medicine*, vol. 28, no. 9, p. 52, 2006.
- [56] Z. Q. Wu, J. C. Lv, and H. F. Ma, "A case about ear-acupuncture treatment of abnormal sense after needling," *Journal of Hebei Traditional Chinese Medicine and Pharmacology*, vol. 16, no. 4, p. 32, 2001.
- [57] B. S. Yang, Y. Wu, L. Y. Wang, and Y. X. Xu, "One case about tetanus caused by needling in Ex-UE19," *Chinese Community Doctors*, no. 2, p. 31, 1990.
- [58] G. X. Liu, "One case about tetanus caused by acupuncture," *The Journal of Medical Theory and Practice*, vol. 4, no. 3, article 30, 1991.
- [59] C. R. Liu, "One case about tetanus caused by acupuncture," *Chinese Community Doctors*, no. 4, p. 30, 1992.
- [60] Y. E. Sun and Q. G. Hu, "A case about tetanus caused by acupuncture during the treatment for Facioplegia," *Journal of Oral and Maxillofacial Surgery*, vol. 7, no. 2, p. 108, 1997.
- [61] Z. G. Chen, J. Zhang, J. J. Li, and D. Z. Jia, "One case about death because of tetanus caused by acupuncture," *Forensic Science and Technology*, no. 2, p. 74, 2008.
- [62] D. X. Xie and S. W. Zong, "One lesson about abdominal metastatic hepatic hydatid caused by acupuncture," *Chinese Journal for Clinicians*, no. 3, p. 45, 1983.
- [63] Y. S. Chen and L. Gao, "One case about encephalopyosis caused by needling on the head," *People's Military Surgeon*, vol. 4, article 58, 1995.
- [64] Z. Zhou, "Report of three cases about tuberculous abscess on the body surface caused by acupuncture and moxibustion," *Journal of Jiujiang University*, no. 1, p. 47, 1999.
- [65] F. Gao and Y. Z. Qi, "Report of one case about locally burn caused by electro-acupuncture," Shanghai Journal of Acupuncture and Moxibustion, vol. 4, p. 15, 1989.

- [66] Z. Z. Gan, "A case about massive orbital hemorrhage caused by neeldling in Ex-HN05," *Chinese Journal of Ocular Trauma and Occupational Eye Disease*, vol. 22, no. 3, p. 246, 2000.
- [67] D. P. Li, "One case report of extraperitoneal hematoma casued by needling in the abdomen," *Shaanxi Medical Journal*, vol. 18, no. 11, pp. 53–54, 1989.
- [68] X. J. Cai, "One case about apnea caused by thyroid intracapsular hemorrhage because of needling," *Medical Journal of Chinese People's Liberation Army*, no. 6, p. 494, 1991.
- [69] L. X. Han, "One case of sublingual fold hematoma caused by needling RN23-lianquan," Shanghai Journal of Acupuncture and Moxibustion, vol. 13, no. 3, p. 107, 1994.
- [70] N. R. Wang, "A case about sublingual hematoma caused by needling in Ex-HN20," *Journal of Clinical Acupuncture and Moxibustion*, vol. 1, no. 8, p. 8, 1996.
- [71] X. F. Zeng and Z. Y. Liu, "A case about death caused by needling in ST 9-renying," in Proceedings of the 5th National Clinical Forensic Medicine Symposium of Chinese forensic Medicine Association, p. 408, 1996.
- [72] Y. Jiang, "Analysis on one case of hematoma induced by hegustimulate in LI4-hegu," *Journal of Clinical Acupuncture and Moxibustion*, vol. 17, no. 5, p. 46, 2001.
- [73] H. Duan, "One case report of hematoma after acupuncture in acquired hemophilia B," *Practical Journal of Clinical Medicine*, vol. 4, no. 2, p. 32, 2007.
- [74] H. Liu and X. H. Liu, "Prevention and treatment of haematoma in acupuncture," *Chinese Journal of Misdiagnostics*, vol. 7, no. 29, p. 71, 2007.
- [75] Y. D. Lu and Q. S. Teng, "A case about hemopneumothorax caused by breaking needle in the chest during acupuncture," *Medical Journal of Chinese People's Liberation Army*, vol. 19, no. 5, article 381, 1994.
- [76] J. Q. Geng, "A case about successful rescue of acute pericardial tamponade caused by acupuncturing coronary artery," *Journal of Clinical Cardiology*, vol. 21, no. 7, p. 392, 2005.
- [77] S. S. Quan, "A case of metal foreign body in the heart," *Journal of Medical Science Yanbian University*, vol. 31, no. 4, p. 304, 2008.
- [78] W. H. Liu and G. X. Yu, "A case about pulmonary bulla caused by acupuncture," *Chinese Acupuncture and Moxibustion*, vol. 30, no. 8, p. 674, 2010.
- [79] R. S. Cheng, "One case about broken needle caused by wrist-ankle acupuncture," Shanghai Journal of Acupuncture and Moxibustion, vol. 29, no. 7, p. 463, 2010.
- [80] H. F. Wang, "One case of sticking and damage of needles in acupuncture treatment of trauma patient," *Journal of Clinical Acupuncture and Moxibustion*, vol. 16, no. 11, p. 42, 2000.
- [81] S. F. Wang and Y. H. Lan, "Acute aphonia caused by acupuncture in PC6-neiguan," *New Chinese Medicine*, vol. 11, no. 11, pp. 587–588, 1980.
- [82] L. Z. Zhou, D. G. Zhao, and L. Peng, "Some thoughts of hoarseness casued by acupuncture," Shanghai Journal of Acupuncture and Moxibustion, vol. 24, no. 1, p. 27, 2005.
- [83] Y. G. Peng, "Report of one case about allergy induced by electroacupuncture," *Jiangxi Journal of Traditional Chinese Medicine*, vol. 3, article 19, 1982.
- [84] Q. S. Gao and Y. J. Zheng, "Two cases about acupuncture allergy," *Chinese Acupuncture and Moxibustion*, vol. 28, no. 11, p. 818, 2008.
- [85] L. Wang, "One case of epilepsy seizures caused by acupuncture," *Chinese Acupuncture Moxibustion*, vol. 24, p. 96, 2004.

- [86] S. Dai, "Two cases of epilepsy caused by acupuncture," *Jiangxi Journal of Traditional Chinese Medicine*, vol. 43, no. 6, p. 38, 2012.
- [87] J. S. Li, "A case about fever induced by acupuncture," *Chinese Acupuncture and Moxibustion*, vol. 20, no. 10, p. 639, 2000.
- [88] Y. T. Shang, "Two adverse reactions induced by acupuncture," Journal of New Chinese Medicine, vol. 38, no. 11, article 76, 2006.
- [89] G. S. Quan and L. Jiang, "One case report of infusion reaction caused by acupuncture," *Jilin Medical Journal*, vol. 29, no. 1, p. 79, 2008.
- [90] W. Fang, "Case report of hyperventilation syndrome induced by acupuncture," *Journal of Emergency in Traditional Chinese Medicine*, vol. 19, no. 3, pp. 486–488, 2010.
- [91] C. H. Wang, "A case of adverse reaction induced by acupuncture when treating sequelae of radiotherapy in nasopharyngeal carcinoma," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 29, no. 8, pp. 536–537, 2010.
- [92] Z. Xue, C. Z. Liu, G. X. Shi et al., "Efficacy and safety of acupuncture for chronic dizziness: study protocol for a randomized controlled trial," *Trials*, vol. 14, p. 429, 2013.
- [93] D. C. A. Ferreira, A. De Rossi, C. P. Torres et al., "Effect of laser acupuncture and auricular acupressure in a child with trismus as a sequela of medulloblastoma," *Acupuncture in Medicine*, vol. 32, no. 2, pp. 190–193, 2014.
- [94] G. Karlson and P. Bennicke, "Acupuncture in asthmatic children: a prospective, randomized, controlled clinical trial of efficacy," *Alternative Therapies in Health and Medicine*, vol. 19, no. 4, pp. 13–19, 2013.
- [95] M. Y. Elseify, N. H. Mohammed, A. A. Alsharkawy, and M. E. Elseoudy, "Laser acupuncture in treatment of childhood bronchial asthma," *Journal of Complementary and Integrative Medicine*, vol. 10, no. 1, pp. 199–203, 2013.
- [96] Y. Moustafa, A. N. Kassab, J. el Sharnoubi, and H. Yehia, "Comparative study in the management of allergic rhinitis in children using LED phototherapy and laser acupuncture," *International Journal of Pediatric Otorhinolaryngology*, vol. 77, no. 5, pp. 658–665, 2013.
- [97] E. F. Anders, A. Findeisen, A. Nowak, M. Rüdiger, and T. I. Usichenko, "Acupuncture for treatment of hospital-induced constipation in children: a retrospective case series study," *Acupuncture in Medicine*, vol. 30, no. 4, pp. 258–260, 2012.
- [98] X. L. Ni, Y. N. Xie, Q. Wang et al., "Cardioprotective effect of transcutaneous electric acupoint stimulation in the pediatric cardiac patients: a randomized controlled clinical trial," *Paediatric Anaesthesia*, vol. 22, no. 8, pp. 805–811, 2012.
- [99] M. Reinthal, I. Lund, D. Ullman, and T. Lundeberg, "Gastrointestinal symptoms of infantile colic and their change after light needling of acupuncture: a case series study of 913 infants," *Chinese Medicine*, vol. 6, no. 1, article 28, 2011.
- [100] J. W. Ochi, "Acupuncture instead of codeine for tonsillectomy pain in children," *International Journal of Pediatric Otorhinolaryngology*, vol. 77, no. 12, pp. 2058–2062, 2013.
- [101] A. L. Zhang, S. J. Parker, D. M. Taylor, and C. C. Xue, "Acupuncture and standard emergency department care for pain and/or nausea and its impact on emergency care delivery: a feasibility study," *Acupuncture in Medicine*, 2014.
- [102] G. P. C. Gribel, L. G. Coca-Velarde, and R. A. Moreira de Sá, "Electroacupuncture for cervical ripening prior to labor induction: a randomized clinical trial," *Archives of Gynecology* and Obstetrics, vol. 283, no. 6, pp. 1233–1238, 2011.
- [103] J. B. G. da Silva, M. U. Nakamura, J. A. Cordeiro, L. Kulay, and R. Saidah, "Acupuncture for dyspepsia in pregnancy: a

- prospective, randomised, controlled study," *Acupuncture in Medicine*, vol. 27, no. 2, pp. 50–53, 2009.
- [104] J. B. G. Da Silva, "Acupuncture for mild to moderate emotional complaints in pregnancy—a prospective, quasi-randomised, controlled study," *Acupuncture in Medicine*, vol. 25, no. 3, pp. 65–71, 2007.
- [105] J. B. Guerreiro Da Silva, M. U. Nakamura, J. A. Cordeiro, and L. Kulay Jr., "Acupuncture for insomnia in pregnancy—a prospective, quasi-randomised, controlled study," *Acupuncture* in Medicine, vol. 23, no. 2, pp. 47–51, 2005.
- [106] J. B. Guerreiro da Silva, M. U. Nakamura, J. A. Cordeiro, and L. Kulay Jr., "Acupuncture for low back pain in pregnancy—a prospective, quasi-randomised, controlled study," *Acupuncture* in Medicine, vol. 22, no. 2, pp. 60–67, 2004.
- [107] N. Kvorning, C. Holmberg, L. Grennert, A. Aberg, and J. Akeson, "Acupuncture relieves pelvic and low-back pain in late pregnancy," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 83, no. 3, pp. 246–250, 2004.
- [108] K. Wedenberg, B. Moen, and Å. Norling, "A prospective randomized study comparing acupuncture with physiotherapy for low-back and pelvic pain in pregnancy," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 79, no. 5, pp. 331–335, 2000.
- [109] T. Rosen, M. de Veciana, H. S. Miller, L. Stewart, A. Rebarber, and R. N. Slotnick, "A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy," Obstetrics and Gynecology, vol. 102, no. 1, pp. 129–135, 2003.
- [110] H. Lei, W. Wang, and G. Huang, "Acupuncture benefits a pregnant patient who has Bell's palsy: a case study," *The Journal* of Alternative and Complementary Medicine, vol. 16, no. 9, pp. 1011–1014, 2010.
- [111] L. Ekdahl and K. Petersson, "Acupuncture treatment of pregnant women with low back and pelvic pain—an intervention study," *Scandinavian Journal of Caring Sciences*, vol. 24, no. 1, pp. 175–182, 2010.
- [112] X. Y. Ding, S. Y. Liu, and J. Zhu, "One case about clinical acupuncture accident," *Chinese Acupuncture & Moxibustion*, vol. 28, no. 11, pp. 817–818, 2008.
- [113] World Health Organization, Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials, World Health, 2002.
- [114] H. G. Endres, A. Molsberger, M. Lungenhausen, and H. J. Trampisch, "An internal standard for verifying the accuracy of serious adverse event reporting: the example of an acupuncture study of 190,924 patients," *European Journal of Medical Research*, vol. 9, no. 12, pp. 545–551, 2004.
- [115] C. M. Witt, D. Pach, B. Brinkhaus et al., "Safety of acupuncture: results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form," Research in Complementary Medicine, vol. 16, no. 2, pp. 91–97, 2009.
- [116] W. J. He, Y. Q. Li, X. Zhao et al., "Overview of the acupuncture safety standards at home and abroad," in *Proceedings of Chinese Acupuncture Association Annual Meeting*, pp. 62–67, 2011.
- [117] D. G. Jiang, "Report of one case about pneumothorax caused by needling in RN15-jiuwei," *Chongqing Medicine*, no. 6, p. 47, 1980.
- [118] Y. Z. Cai and Q. L. Wang, "A case about large hemothorax caused by deep needling," *Chinese Journal of Medicine*, no. 6, p. 54, 1982.
- [119] P. D. Zheng and S. H. Pang, "One case about severe hemopneumothorax caused by acupuncture," *Journal of Traditional Chinese Medicine*, vol. 5, article 32, 1983.
- [120] C. G. Gao, "Report of two cases about pneumothorax caused by acupuncture," *The Journal of Practical Medicine*, vol. 3, pp. 38– 39, 1984.

- [121] J. Y. Chang, "A case about large hemopneumothorax caused by needling in the back," *Hebei Journal of Traditional Chinese Medicine*, no. 3, p. 48, 1984.
- [122] Z. C. Yan, "A case about severe pneumothorax caused by needling RN22-tiantu," *New Chinese Medicine*, vol. 16, no. 12, p. 655, 1985.
- [123] Q. X. Hu, "A case about pneumothorax caused by improper acupuncture," Shanghai Journal of Acupuncture and Moxibustion, vol. 3, p. 34, 1986.
- [124] S. P. Zhang, "A case about large hemopneumothorax caused by acupuncture," Shanghai Journal of Acupuncture and Moxibustion, vol. 6, no. 4, p. 21, 1986.
- [125] B. R. Jin, "A case about pneumothorax caused by needling SI13quyuan," *Shanghai Journal of Acupuncture and Moxibustion*, no. 3, p. 45, 1987.
- [126] B. Z. Song and J. S. Xu, "Report of one case about hemothorax caused by needling left GB21-jianjing," *Journal of Anhui Tradi*tional Chinese Medical College, vol. 6, no. 3, p. 45, 1987.
- [127] K. Y. Ruan, K. J. Qi, and Z. C. Mou, "A case about hydropneumothorax caused by needling supraclavicular fossae," *Journal of New Chinese Medicine*, vol. 4, p. 33, 1992.
- [128] B. Lu, "Report of one case about traumatic pneumothorax caused by needling too deep," *Guizhou Medicine Journal*, vol. 17, no. 2, p. 125, 1993.
- [129] C. Xia, "Handling method and experience of accident occurred during acupuncture," *Journal of Clinical Acupuncture and Moxibustion*, no. 2-3, pp. 75–76, 1993.
- [130] Y. W. Li and X. L. Chen, "A case about pneumothorax caused by acupuncture," *Journal of Handan Medical College*, vol. 10, no. 3, pp. 72–73, 1997.
- [131] L. Ma and C. J. Zhang, "Clinical analysis of pneumothorax caused by acupuncture," *Journal of Clinical Acupuncture and Moxibustion*, vol. 13, no. 2, p. 40, 1997.
- [132] M. X. Qin and W. H. Ao, "Pneumothorax caused by improper acupuncture and moxibustion," *Clinical Misdiagnosis & Mistherapy*, vol. 16, no. 1, article 76, 2003.
- [133] C. H. Zha, "Injury identification of one case about hemopneumothorax caused by acupuncturing left lung," *Chinese Journal of Forensic Medicine*, no. 21, pp. 75–76, 2006.
- [134] J. Y. Gan, G. Q. Lei, and J. S. Zhu, "One case about hemopneumothorax and dyspnea caused by acupuncture," in *Proceedings of the 9th National Clinical Forensic Medicine Symposium of Chinese forensic Medicine Association*, pp. 58–59, 2006.
- [135] S. H. Huo, Y. P. Tian, Q. L. Ma et al., "One case about cardiac trauma and pneumothorax caused by acupuncture," *Chinese Journal of Critical Care Medicine*, vol. 27, no. 10, p. 908, 2007.
- [136] L. Y. Liu, "Analysis on one case of hemopneumothorax induced by acupuncture," *Journal of Changchun University of Traditional Chinese Medicine*, vol. 23, no. 3, p. 58, 2007.
- [137] B. Z. Ma, "Report of one case about traumatic pneumothorax caused by acupuncture and moxibustion," *Qinghai Medical Journal*, vol. 37, no. 2, p. 41, 2007.
- [138] J. Zhang and L. Zhao, "Analysis and treatment of pneumothorax caused by needling GB21-jianjing," *Hubei Journal of Traditional Chinese Medicine*, vol. 34, no. 11, pp. 60–61, 2012.
- [139] S. X. Liu, "Subarachnoid hemorrhage caused by needling in GB20-fengchi," *Shanxi Medical Journal*, vol. 9, no. 6, article 53, 1980.
- [140] L. P. Bao and C. T. Gao, "Report of three cases about sub-arachnoid hemorrhage induced by needling GB20-fengchi and DU15-yamen," *Jilin Medical Journal*, vol. 4, no. 3, pp. 45–53, 1983.

- [141] Q. T. Chen and L. J. Wu, "Case about subarachnoid hemorrhage and medulla oblogata hemorrhage caused by needling in anmian point," *Journal of Apoplexy and Nervous Diseases*, vol. 2, no. 3, pp. 158–159, 1985.
- [142] Y. Z. Chen and W. C. Huang, "One case of subarachnoid hemorrhage caused by needling in the nape," *Shanxi Journal of Traditional Chinese Medicine*, vol. 1, no. 1, pp. 47–48, 1985.
- [143] Y. Su, H. X. Chen, C. C. Chen, and Z. J. Yang, "One case of subarachnoid hemorrhage caused by needling in Du15-yamen," Shanghai Journal of Acupuncture and Moxibustion, vol. 3, p. 22, 1985
- [144] B. R. Yu, "Subarachnoid hemorrhage caused by needling in the nape—with report of seven cases," *Journal of Apoplexy and Nervous Diseases*, vol. 3, no. 2, pp. 74–75, 1986.
- [145] M. X. Chen, "One case of subarachnoid hemorrhage caused by needling in Du15-yamen," *Chinese Journal of Practical Internal Medicine*, vol. 7, no. 7, p. 355, 1987.
- [146] S. C. Jiang and X. Q. Chen, "A case about death caused by needling in GB20-fengchi," *Chinese Journal of Forensic Medicine*, vol. 2, no. 2, pp. 116–117, 1987.
- [147] J. W. Zhou, "A case about death caused by needling in GB20-fengchi," *Journal of Sichuan of Traditional Chinese Medicine*, no. 10, p. 52, 1988.
- [148] X. H. Mi, S. K. Li, and S. K. Jia, "One case of subarachnoid hemorrhage caused by needling in Du15-yamen," *Shandong Journal of Traditional Chinese Medicine*, vol. 8, no. 2, p. 22, 1989.
- [149] B. C. Wu and Q. Z. Xu, "Report of one case about death caused by spinal cord injury through acupuncturing in acupoint near C3," *Chinese Journal of Forensic Medicine*, vol. 5, no. 1, pp. 32–33, 1990.
- [150] F. Y. Liu, "One case of posterior fossa acute subdural hematoma caused by needling in GB20-fengchi," *Medical Journal of Liaon*ing, vol. 6, no. 1, p. 25, 1992.
- [151] T. Z. Jiang, W. D. Chen, B. Zhang, and R. M. Yang, "Report of two cases about subarachnoid hemorrhage caused by needling in the nape," *Journal of Anhui Traditional Chinese Medicine College*, vol. 15, no. 1, p. 48, 1996.
- [152] M. Liu, S. P. Shen, H. Tong, and T. Wang, "Autopsy report of medulla oblongata hemorrhage caused by needling in DU16fengfu," in Proceedings of the 5th National Clinical Forensic Medicine Symposium of Chinese Forensic Medicine Association, p. 85, 1996.
- [153] F. Bian, X. L. Zhang, and S. P. Tian, "A case about subarachnoid hemorrhage caused by needling in GB20-fengchi," *Journal of Hebei North University (Medical Edition)*, vol. 14, no. 6, article 73, 1997.
- [154] L. Wang, "A case about death caused by needling in cervical spinal cord," Forensic Science and Technology, no. 4, p. 20, 1999.
- [155] Y. Q. Li, G. W. Chen, and X. C. Zeng, "A case about cervical spinal cord epidural hematoma caused by acupuncture," *Chinese Journal of Rural Medicine and Pharmacy*, vol. 10, no. 3, p. 20, 2003.
- [156] L. J. Niu and R. W. Zhang, "A case about cisterna magna hemorrhage caused by acupuncture," *Practical Journal of Medicine & Pharmacy*, vol. 23, no. 8, p. 932, 2006.
- [157] L. F. Li, X. Cong, and Q. W. Jin, "Subarachnoid hemorrhage caused by needling in DU16-fengfu," *Chinese Acupuncture & Moxibustion*, vol. 28, no. 4, p. 292, 2008.
- [158] Y. C. Guo, "Lag syncope cannot be ignored," Shanghai Journal of Acupuncture and Moxibustion, vol. 14, no. 6, article 254, 1995.

- [159] Y. Z. Liu, "Analysis on two cases about abnormal condition induced by improper position during acupuncture," *Lishizhen Medicine and Materia Medica Research*, vol. 18, no. 7, p. 1756, 2007.
- [160] Y. Liao and Y. Q. Guo, "Report of one case about syncope induced by acupuncture," *Journal of Clinical Acupuncture and Moxibustion*, vol. 25, no. 8, article 21, 2009.
- [161] J. P. Zhang, "Disinfection must be done when needling in Ex-UE19," Chinese Journal for Clinicians, vol. 2, article 14, 1980.
- [162] C. Z. Xu, "One case about intracranial infection caused by acupuncture," Nei Mongol Journal of Traditional Chinese Medicine, no. 1, p. 12, 1990.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 641742, 29 pages http://dx.doi.org/10.1155/2015/641742

Review Article

Neuroimaging and Neuromonitoring Effects of Electro and Manual Acupuncture on the Central Nervous System: A Literature Review and Analysis

Brigitte Elisabeth Scheffold, Ching-Liang Hsieh, and Gerhard Litscher^{3,4}

Correspondence should be addressed to Ching-Liang Hsieh; clhsieh@mail.cmuh.org.tw and Gerhard Litscher; gerhard.litscher@medunigraz.at

Received 27 August 2014; Accepted 15 September 2014

Academic Editor: Lu Wang

Copyright © 2015 Brigitte Elisabeth Scheffold et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The aim of this review is to provide an overview of the different effects of manual and electroacupuncture on the central nervous system in studies with different neuroimaging interventions. The Database PubMed was searched from 1/1/2000 to 1/6/2014 with restriction to human studies in English language. Data collection for functional magnetic resonance (fMRI) studies was restricted to the period from 1/1/2010 to 1/6/2014 due to a recently published review which included all published randomized and nonrandomized controlled clinical studies as well as observational studies with control groups, no blinding required. Only studies comparing manual or electroacupuncture with sham acupuncture were eligible. All participants were healthy adult men and women. A majority of 25 studies compared manual versus sham, a minority of 7 trials compared electro versus sham and only 1 study compared electro versus manual acupuncture. In 29 out of 33 studies verum acupuncture results were found to present either more or different modulation effects on neurological components measured by neuroimaging and neuromonitoring methods than sham acupuncture. Only four studies reported no effects of verum in comparison to sham acupuncture. Evaluation of the very heterogeneous results shows evidence that verum acupuncture elicits more modulation effects on neurological components than sham acupuncture.

1. Introduction

Acupuncture has been used as a traditional medical treatment in China for over 2000 years [1] and is now rapidly gaining popularity in the field of western complementary medicine [2].

In 2007, the World Health Organization (WHO) defined acupuncture as the insertion of needles into the human body for therapeutic purposes. However, treatment styles vary significantly in terms of stimulation (manual or electrical), manipulation (tonifying or draining), needling depth, and duration of needle retention. Likewise, different styles of

acupuncture can elicit various needling sensations called deqi, which can be described as soreness, numbness, distension, heaviness, or electric shock sensation [3].

Depending on the style of application and the related deqi sensation, acupuncture evokes several complex somatosensory stimulations [4]. The following effects in the central nervous system might regulate homeostatic balance and modulate cognitive affective pain perception through a network of brain areas involved in sensory, autonomic, and cognitive/affect processing [5].

Even though many studies about neurophysiologic correlates have been done, the specific effects of acupuncture

 $^{^1}$ Graduate Institute of Acupuncture Science, International Master Program, China Medical University, Taichung 40402, Taiwan

²Graduate Institute of Integrated Medicine, China Medical University, Taichung 40402, Taiwan

³China Medical University, Taichung 40402, Taiwan

⁴Research Unit for Complementary and Integrative Laser Medicine, Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, and TCM Research Center Graz, Medical University of Graz, 8036 Graz, Austria

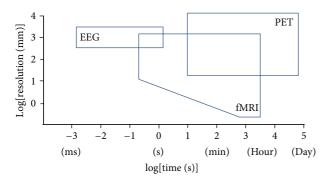


FIGURE 1: Spatial and temporal resolution of MRI, PET, and EEG (modified from [117]).

mechanisms on the central nervous system (CNS) still remain unclear. In the past decade an increasing number of studies used modern neuroimaging modalities like functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) for further investigation.

Using neuroimaging technologies, researchers are able to examine the acupuncture process in the brain noninvasively. Due to their good spatial resolution fMRI and PET are especially suitable for investigating the localization of active brain networks, whereas a comparatively better temporal resolution makes EEG and evoked potentials (EP) suitable for investigating the timing of activation [5].

This review paper presents a summary of current studies about neuroimaging technologies in acupuncture research. Data will be discussed regarding aspects of research methodology and the according challenges. For this purpose, the study outcomes will be compared in several subgroups.

The results shall provide an overview on neurophysiologic correlates of different acupuncture modalities in the brain.

2. Background

2.1. Neuroimaging Technologies. Figure 1 gives an overview of the temporal and spatial resolution of the different neuroimaging techniques this review is dedicated to.

2.1.1. Functional Magnetic Resonance Imaging (fMRI). fMRI measures the so-called BOLD (hemodynamic blood oxygenation level dependent) effect, which reflects the ratio between oxygenated and deoxygenated hemoglobin. This ratio represents the brain's neuronal activity and the resulting regional changes in metabolism and circulation. fMRI has a high spatial resolution (1–3 mm³) but limited temporal resolution as the hemodynamic response peaks 4-5 seconds after neuronal activity [6].

For research settings, it is very important to choose an adequate fMRI experimental design in order to enable suitable data analysis. The most common research designs are block or event related designs. Optimized designs for localizing brain activity usually apply the general linear model (GLM), the independent components analysis (ICA) for uncertain timing, or the Granger causality for effective connectivity, just to mention a few of the multiple possible analyses [7].

2.1.2. Positron Emission Tomography (PET). For imaging with a PET device, radiotracers are applied into the blood stream. At their destination, these tracers represent the brain's regional blood flow, oxygen, or glucose metabolism and reflect the activity in the according brain region. PET markers are very specific and imaging their effects is not limited in depth. However, the limited spatial resolution and its time-consuming and expensive procedure make PET less attractive than fMRI [8].

2.1.3. Electroencephalography (EEG). EEG typically measures the macrorhythms in the cortex, with impulses from subcortical structures. These rhythms are signals at frequencies below 100 Hz, reflecting primarily postsynaptic potentials [9] with high temporal resolution.

In addition, EEG measurements can also numerically describe the depth of sedation by assessing the bispectral index (BIS). BIS values in a range between 40 and 60 indicate general anesthesia [10].

2.1.4. Evoked Potentials (EP). In this review, somatosensory evoked potentials (SEPs) and auditory evoked potentials (AEPs) will be discussed. SEPs are activities of the somatosensory cortex after stimulation of peripheral nerves (e.g., median nerve), whereas AEPs are generated by sound, usually by clicks.

The amplitude of an EP measurement reflects the number of cortical cells activated and the magnitude of spatial summation of inhibitory postsynaptic potentials (IPSPs) and excitatory postsynaptic potentials (EPSPs) [11]. These present not only the intensity of the stimulus, but also the subjective experience [12]. Because of this, late SEP components might represent correlates of cognitive and evaluative stimulus processing [13].

2.2. Acupuncture Analgesia

2.2.1. Perception of Pain. The perception of pain consists of a sensory and an affective component.

The sensory/spinothalamic pathway starts at peripheral nociceptors, which deliver the noxious stimulus via the spinal cord, brainstem, and thalamus to the somatosensory cortex to provide information about the location and intensity of the painful stimulus (primary (S1) and secondary somatosensory cortex (S2), sensory aspect: "there is a dull pain in my right hand").

The affective component of pain is delivered via the spinobrachial pathway from the superficial dorsal horn to a network of amygdala, insula, anterior cingulate cortex (ACC, affective aspect: "it really hurts"), and medial regions of the frontal lobe (prefrontal cortex (PFC), cognitive aspect: "when will it stop?") [14].

- 2.2.2. Brain Regions Involved in Processing Pain. Several brain regions engage in processing the affective (amygdala, hippocampus), sensory (thalamus, S1 and S2), and cognitive (ACC, anterior insula) components of experiencing pain [15].
- 2.2.3. Acupuncture Analgesia Mechanisms. Leung [16] claims that acupuncture analgesia might be induced by the release of endogenous opioids, by the modulation of the adrenergic system/the serotonin signaling system/the N-methyl-D-aspartic acid/AMPA/kainate signaling system, by the modulation of long-term depression and long-term potentiation of neural plasticity, or finally by the activation of the diffuse noxious inhibitory control system.
- 2.2.4. Acupuncture Modulates Brain Regions. On top of the possible mechanisms of acupuncture analgesia mentioned above, more recent research proposes that acupuncture needling modulates certain areas of the pain matrix in the brain.

In 2007, Dhond et al. [5] presented a review about neuroimaging studies, which demonstrates that acupuncture modulates a wide network of brain areas including cortical, subcortical/limbic, and brainstem areas [17–22].

The review summarizes that after the first localization and characterization of the acupuncture stimulus in the somatosensory cortices (S1, S2), limbic brain regions like the hypothalamus, amygdala, cingulate, and hippocampus are recruited.

While hippocampus and amygdala are supposed to support learning and memory in pain pathways, the amygdala might encode the affective component of pain [23]. Additionally, Dhond et al. [5] propose that stress reduction by shifting autonomic nervous system (ANS) balance, affect, and cognition could be another possible benefit.

The paper also points to a further connection that links the hippocampus and amygdala with the brainstem and the hypothalamus. As the latter modulates neuroendocrine and homeostatic function, these interactions could possibly affect arousal and motivation.

Moreover, Dhond et al. [5] state that modulation of the anterior and posterior insula might also play a role in acupuncture effects, as these areas influence changes of attention and effect [22, 24], similar to the PFC, which, respectively, connects to the limbic system and modulates expectancy [25].

2.2.5. Acupuncture Modulates Brain Networks. In the last years of fMRI research, many studies concerning acupuncture's effect on the CNS came across the influence of resting state networks in the brain. The most important of these networks is the default mode network (DMN), which consists of the PFC, posterior cingulate cortex (PCC), and precuneus as well as lateral, parietal, and temporal regions [26–28]. The DMN is active when the individual focuses on internal tasks.

In a review from 2012, Otti and Noll-Hussong [29] point out that the above-mentioned effects of acupuncture on the brain could possibly trace back to an enhanced functional connectivity between the DMN and several brain areas

(including the hippocampus, periaqueductal gray (PAG), amygdala, and anterior cingulate).

This connection might explain why real acupuncture reintegrates balance of emotions, thinking, and the body.

3. Methods

- *3.1. Eligibility Criteria.* For the literature research the following eligibility criteria were set.
- 3.1.1. Types of Studies. This review includes all published randomized and nonrandomized controlled clinical studies as well as observational studies (cohort and case studies) with control groups, no blinding required. Inclusion of studies was restricted to English language.

Meta-analyses, reviews, and studies without control were not considered.

- *3.1.2. Types of Participants.* Only trials with 10 or more healthy participants of either gender, aged 18 or older, were included. Patients or people with any record of substance abuse or addiction were excluded.
- 3.1.3. Types of Interventions. Only those studies were accepted in which at least one group received needle acupuncture at one or more acupuncture point, A-Shi or trigger points.

Needle acupuncture interventions refer to recommendations of the WHO 2002:

- (i) manual acupuncture (MA): stimulation of points on the body through penetrating the skin with thin, solid, metallic needles that are manipulated by the hands,
- (ii) electroacupuncture (EA): passing a pulsed current through the body using acupuncture needles.
- *3.1.4. Control Groups.* Studies were included if the control group received any style of sham acupuncture stimulation, which did not intend to be a treatment.

However, groups comparing different kinds of needle acupuncture treatments and groups with no intervention or with any treatment unrelated to acupuncture point stimulation did not constitute an eligible control group.

Accepted sham acupuncture procedures were

- (i) manual sham acupuncture with needle insertion: superficial penetration of the skin or needling at a NMP (nonmeridian point) or NAP (nonacupuncture point), even if performed with stimulation or manipulation,
- (ii) manual sham acupuncture without needle insertion: blunt needles or Streitberger needles,
- (iii) sham EA with disconnected electrodes,
- (iv) sham laser acupuncture with a switched off laser device,
- (v) tactile stimulation of acupuncture points (comparable to blunt needling).

3.1.5. Search Methods for Identification of Studies. The PubMed Database was initially searched from 1/1/2000 to 1/6/2014 with restriction to human studies in English language.

During the course of the study, data collection for fMRI studies was restricted to the time from 1/1/2010 to 1/6/2014 due to a recently published review.

PubMed sources were searched with the following medical subject heading terms and search strategies:

- (i) ((fMRI) OR (MRI, Functional) OR (Functional MRI) OR (Functional MRIs) OR (MRIs, Functional) OR (Magnetic Resonance Imaging, Functional)) AND acupuncture.
- (ii) ((Positron Emission Tomography) OR (PET Scan) OR (PET Scans) OR (Scan, PET) OR (Scans, PET) OR (Tomography, Positron-Emission) OR (Tomography, Positron Emission)) AND acupuncture.
- (iii) ((EEG) OR (Electroencephalogram) OR (Electroencephalograms)) AND acupuncture.
- (iv) ((Evoked Potential) OR (Potential, Evoked) OR (Potentials, Evoked) OR (Potentials, Event-Related) OR (Event-Related Potential) OR (Potential, Event-Related) OR (Potentials, Event Related) OR (Event-Related Potentials) OR (Event Related Potentials)) AND acupuncture.

Searching Other Resources. References of selected publications and bibliographies of reviews (found during the first screening of publications) were inspected for more potentially useful articles.

3.2. Study Selection. Title and abstract of all results in the literature search list were examined and full texts were retrieved if possible.

During the first screening duplicates, reviews and studies with unrelated topics were removed as well as any studies where full text was not available.

In the second step full texts of potential studies were evaluated according to predefined inclusion and exclusion criteria.

3.3. Data Collection. Data of all included studies were extracted with regard to the STRICTA (standards for reporting interventions in clinical trials) guidelines. The considered study characteristics and variables were then transferred to Excel.

Publishing Data:

- (i) author,
- (ii) year,
- (iii) title,
- (iv) journal.

Methodology:

(i) number of participants,

- (ii) participants' handedness,
- (iii) number of intervention groups,
- (iv) number of treatment sessions.

Needling Details:

- (i) acupuncture rationale: manual/electro,
- (ii) acupuncture points (uni-/bilateral),
- (iii) needling depth,
- (iv) style of manipulation,
- (v) response elicited (De-Qi),
- (vi) needle retention time.

Control Intervention:

- (i) types of control intervention,
- (ii) size of intervention groups.

Technology:

- (i) neuroimaging method,
- (ii) technical device,
- (iii) data processing software.

Objective/Outcome:

- (i) objective,
- (ii) findings,
- (iii) group differences,
- (iv) increase/decrease, activation/deactivation.
- 3.4. Subgroup Analyses and Assessment of Heterogeneity. Within neuroimaging groups with sufficient data, subgroup analysis was applied to evaluate the differences of MA versus EA in all kinds of neuroimaging, meaning fMRI, EEG + EP, and PET.

In addition, results of studies needling the same point(s) were compared within their respective imaging intervention group.

4. Results

4.1. Study Selection. Literature search was conducted from 1/12/2013 to 1/3/2014. From 1/3/2014 updates were signed up and followed by PubMed newsletter.

For the first screening, the search period ranged from 1/1/2000 to the end of May 2014. Later during the course of the study, data collection for fMRI trials was restricted to a narrower time frame ranging from 1/1/2010 to 1/6/2014 due to a recently published review.

The study selection process is illustrated in Figures 2, 3, 4, and 5.

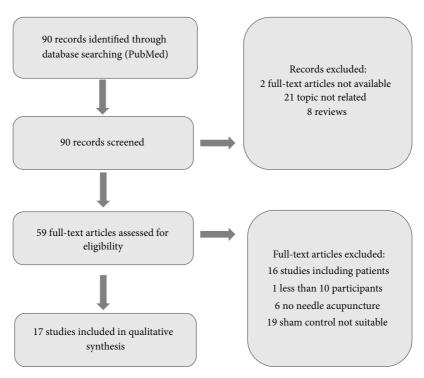


FIGURE 2: Flowchart of screening fMRI studies.

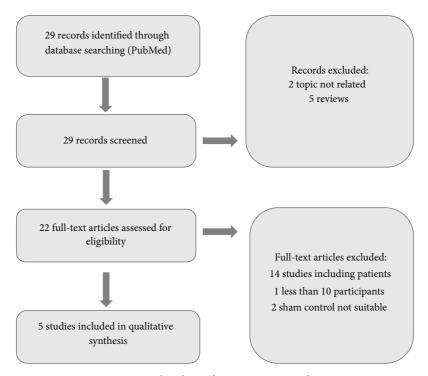


FIGURE 3: Flowchart of screening PET-studies.

4.2. Total Studies Considered in This Review Paper. In total, the first PubMed Database search resulted in 238 studies about acupuncture and neuroimaging—including all categories (fMRI, EEG, EP, and PET).

Out of the 238 studies, 90 were found in the field of acupuncture and fMRI, 47 in EEG, 72 in EP, and 29 in PET.

After removing 94 duplicates, reviews, studies with unrelated topics, and trials where no full text was available, a total of 144 papers were included for further evaluation—including 59 fMRI, 30 EEG, 33 EP, and 22 PET trials.

During the second screening, these 144 potential studies were evaluated according to predefined eligibility criteria.

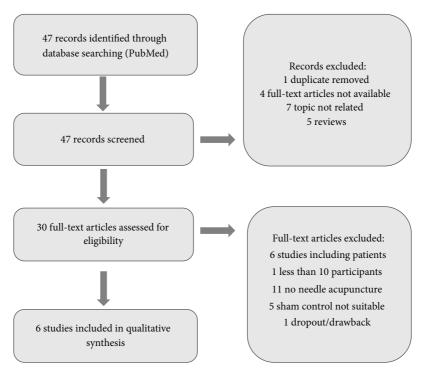


FIGURE 4: Flowchart of screening electroencephalogram studies.

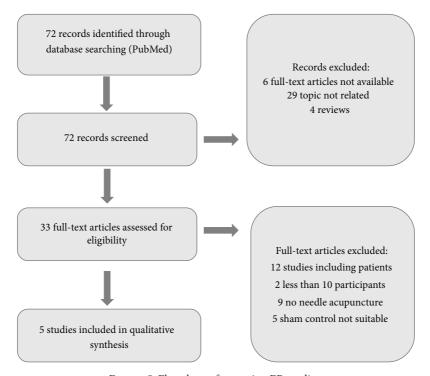


FIGURE 5: Flowchart of screening EP-studies.

After exclusion of another 111 trials, this step resulted in the final inclusion of 33 studies on acupuncture and neuroimaging, comprising 17 fMRI, 6 EEG, 5 EP, and 5 PET studies.

4.3. Studies Excluded from the Review. In the process of selection, a total number of 205 studies were excluded.

During the first course of eligibility screening 94 duplicates, reviews, studies with unrelated topics, and trials where no full text was available were excluded.

Further on, the second evaluation excluded another 111 studies due to the following reasons: study included patients, number of participants < 10, no group received needle acupuncture, or no suitable control group included.

4.4. Studies Included in the Review. PubMed database screening revealed 238 studies about neuroimaging acupuncture effects, including 90 fMRI, 47 EEG, 72 EP, and 29 PET trials.

After evaluation according to the exclusion criteria above, a total number of 33 studies on acupuncture and neuroimaging were included in this review, comprising 17 fMRI, 6 EEG, 5 EP, and 5 PET studies.

4.5. Participants. 33 studies with a total number of 687 participants were selected, comprising 399 participants in fMRI, 72 in PET, 99 in EEG, and 117 in EP trials.

All included papers stated their inclusion and exclusion criteria clearly enough to enable this review to only consider healthy adult volunteers. In addition to general data extraction, participants' handedness was considered in all fMRI studies.

4.6. Sample Size. All studies had a sample size of at least 10 participants per study, with a range from 6 to 25 participants per intervention group.

4.7. Interventions

4.7.1. *Main Interventions: MA and EA*. Distribution of the two main interventions MA and EA varied significantly between the studies of different neuroimaging methods.

Out of 33 studies, 25 applied MA versus sham, only 7 applied EA versus sham. One study compared EA versus MA.

All 5 EP studies applied EA and compared EA versus sham acupuncture [30–34]. All 5 PET studies applied MA versus sham acupuncture [17, 24, 35–37]. Five out of 6 EEG studies applied MA versus sham acupuncture [38–42]; one EEG study used EA versus sham acupuncture [43]. Fifteen out of 17 fMRI trials applied MA versus sham acupuncture [44–58]; one fMRI study used EA versus sham acupuncture [59], and one fMRI trial compared EA versus MA [60].

- 4.7.2. Needling Depth. Needling depth varied significantly throughout all studies, ranging from 0.3 mm (EEG, [43]) up to 3 cm (fMRI, [44, 50, 53, 55]). Mean needling depth of the available 25 studies was 14.03 mm. Eight studies did not report details about needling depth (fMRI, [45, 47–49]; EP, [30, 32, 33, 38]).
- 4.7.3. Acupuncture Points. Out of the 33 trials, 28 only chose one single acupuncture point, 5 used a combination of two points, and 3 studies applied a combination of 3 or more points. Point selection varied significantly and included points on both arms, both legs, and the head.

Altogether 50 points were reported. Their application was distributed as follows: ST36, n=13; LI4, n=10; PC6, n=4; LV3, n=4; GB37, n=3; SP6, n=2; SP9, n=2; TH5, n=2; and Yintang, n=2. Points used in one study only were LI3, LI11, BL60, BL62, LU5, PC5, HT7, and Ear Shenmen.

4.7.4. Needle Retention Time. 30 studies reported the needle retention time of their main interventions. The average duration was approximately 12 min.

4.7.5. Control Interventions. As listed below, most of the studies (29 out of 33) only used one single control intervention.

Non-acupuncture-points (NAP) were used 20 times: fMRI: 11 studies with MA versus NAP [44, 45, 47–53, 57, 58]; PET: 3 studies with MA versus NAP [17, 24, 37]; EEG: 1 study with EA versus NAP [43]; EEG: 3 studies with MA versus NAP [38–40]; and EP: 2 studies with EA versus NAP [33, 34].

Streitberger needles were used 3 times: fMRI: EA versus Streitberger sham EA [59]; PET: MA versus Streitberger sham [35]; and EEG: MA versus Streitberger sham [42].

Von Frey filaments were used twice: fMRI: MA versus von Frey [55] and fMRI: MA versus von Frey versus tactile stimulation [54].

Overt sham with blunt needling was used once: fMRI: MA versus blunt needle [56].

Painful tactile stimulation with cotton tip at an acupuncture point was used once: fMRI: MA versus tactile stimulation [46].

Sham EA with no needle but electro tape was used twice: EP: EA versus sham EA [31, 32].

Five out of 33 studies used the following combinations of control interventions: EEG: NAP acupressure versus manual versus laser [41]; EP: NAP versus electro without deqi versus with deqi versus painful overstimulation [30]; PET: Streitberger versus MA versus overt blunt needling [36]; and fMRI: von Frey filament versus MA versus EA versus transcutaneous electrical acupoint stimulation (TEAS) [60].

- 4.8. Study Objectives and Outcomes. Tables 1–4 present an overview of the outcomes of the studies included in this review.
- 4.9. Result Tables. A comparison of all included studies with regard to technical devices used, control intervention, number of participants, and so forth can be found in Tables 5, 6, 7, and 8.
- 4.10. Subgroup Comparisons
- 4.10.1. Comparison of Main Interventions
- (1) MA versus EA (fMRI: Zyloney et al., 2010 [60])
 - (i) Of the 33 studies, only one fMRI study compared MA versus EA. Zyloney et al. [60] investigated the spatial and temporal effects of manual, EA, and TEAS at ST36 at the left leg.
 - (ii) By using a modified generalized linear model analysis to compare block-designed and resting-state fMRI scans they detected positive activation in the sensorimotor areas and negative activation in the default mode areas in both of the two 1 min simulation periods for tactile stimulation with a von Frey filament and in the first 1 min stimulation of MA, EA, and TEAS. However, in the second 1 min stimulation period, no positive activation result was observed and EA showed a more extensive deactivation compared to MA and TEAS.

Table 1: fMRI studies on the effect of MA and EA.

Author	Year	Title	Objective	Outcomes
Bai et al. [44]	2010	Acupuncture modulates temporal neural responses in wide brain networks: evidence from fMRI study	Temporal investigation of (late) MA effects at ST36 (r) versus nearby NAP	They found that the amygdala and perigenual anterior cingulate cortex (pACC) exhibited increased activities during needling but decreased to reach a peak below the baseline. The PAG and hypothalamus presented intermittent activations across the whole session. Apart from the time-dependent responses, relatively persistent activities were also identified in the anterior insula and PFCs. In comparison, verum and sham shared a similar activation pattern in somatosensory areas (S1 and S2) during needling. However, during the postacupuncture resting period acupuncture at ST36 was followed by sustained activation of the S2, whereas acupuncture at NAP showed inhibition of the S1.
Cheng et al. [45]	2013	Exploration of whole brain networks modulated by acupuncture at analgesia acupoint ST36 using scale-specific wavelet correlation analysis	Investigation of MA effects at ST36 (r) versus nearby NAP effects on pairwise correlations between 90 cortical and subcortical regions	Their correlations presented frequency-specific modularity functional brain networks during poststimulus resting state following acupuncture at ST36 and NAP. Graph metrics in brain activity are different in verum and sham groups and also show that the brain network following manual acupuncture has higher global and local efficiency in parallel information transfer in the brain network compared with acupuncture at a NAP.
Cho et al. [46]	2010	fMRI study of effect on brain activity according to stimulation method at LIII, ST36: Painful pressure and acupuncture stimulation of same acupoints	Investigation of differences between MA versus painful sham stimulation at LI11 (l) versus ST36 (l)	In comparison to painful tactile stimulation, MA at LI11 led to activation of both sides of the parahippocampal gyrus, cerebellum, left side of thalamus, and right side of posterior cingulate regions. Acupuncture but not tactile stimulation at ST36 produced activation at the secondary motor cortex (M2), limbic system (cingulate gyrus, posterior cingulate), primary visual cortex, pons, and medulla regions, at the left BA6, BA8, and ACC. In comparison with the left LI11 acupuncture stimulation, left BA6, BA8, and ACC were more activated by the left ST36 acupuncture stimulation. Acupuncture activated more regions than painful tactile stimulation, especially areas of the limbic system, such as the parahippocampal gyrus and ACC.
Dong et al. [47]	2012	Tempo-spatial analysis of vision-related acupoint specificity in the occipital lobe using fMRI: An ICA study	Spatial and temporal investigation of the effects of MA at vision-related GB37 versus BL60 versus nearby NAP on the occipital lobe	Although the ICA of all kinds of acupuncture showed activity at the visual cortex V1 in the occipital lobe, temporal activities in this region differed for acupuncture at GB37 versus NAP, as well as for BL60 versus NAP.
Feng et al. [48]	2011	Investigation of the large-scale functional brain networks modulated by acupuncture	Spatial investigation of MA effects at ST36 (r) versus nearby NAP	Within a network of 90 predefined regions in the poststimulus resting brain, limbic/paralimbic regions (such as the amygdala, hippocampus, and anterior cingulate gyrus) emerged as network hubs after verum but not sham acupuncture. Compared with needling at a NAP, manual acupuncture at ST36 presented increased correlations, related with the limbic/paralimbic and subcortical regions (such as the insula, amygdala, and anterior cingulate gyrus) and thalamus. Decreased correlations for verum acupuncture were related with the sensory and frontal cortex.
Zyloney et al. [60]	2010	Manipulation of and sustained effects on the human brain induced by different modalities of acupuncture: An fMRI study	Spatial + temporal investigation of MA effects versus EA versus TEAS at ST36 (l)	Using a modified generalized linear model analysis to compare block-designed and resting-state fMRI scans they detected positive activation in the sensorimotor areas and negative activation in the default mode areas in both areas in both of the two 1-min-stimulation periods for tactile stimulation with a von Frey filament and in the first 1-min-stimulation of MA, EA, and TEAS. However, in the second 1-min-stimulation period, no positive activation result was observed and EA showed a more extensive deactivation compared to MA and TEAS.

Table 1: Continued.

Author	Year	Title	Objective	Outcomes
Li et al. [49]] 2010	Exploring vision-related acupuncture point specificity with multivoxel pattern analysis	Spatial investigation of MA effects at vision-related GB37 versus nearby NAP	They found different effects for verum acupuncture versus NAP in the subregions of occipital cortex (left cuneus of occipital gyrus and regions of lingual gyrus, middle occipital gyrus and fusiform gyrus), the limbic-cerebellar system (including insula, rACC and pACC, pons, amygdala, culmem in anterior lobe and declive of vermis in posterior lobe of cerebellum), and the somatosensory cortex. For GLM, the neutral response patterns of acupuncture stimulation at acupoints and NAP had multiple overlapping regions and did not differ significantly from each other.
Liu et al. [50]	2010	The hybrid GLM-ICA investigation on the neural mechanism of acupoint ST36: An fMRI study	Spatial and temporal investigation of MA effects at ST36 (r) versus nearby NAP	Their results showed manipulation-related effects and sustained acupuncture effects in the cortical-subcortical areas, including the ACC, ventrolateral prefrontal cortex (VLPFC), and supplementary motor area (SMA) and decreases in the S1 and S2. These reactions lasted until the resting period after needling, where then activations were induced in many regions including the insula, caudate, putamen, and thalamus.
Jiang et al. [58]	2013	Divergent neural processes specific to the acute and sustained phases of verum and sham acupuncture	Spatial investigation of immediate and delayed effects of MA at ST36 (r) versus nearby NAP	The immediate effect of verum as well as sham acupuncture consisted of signal changes in the limbic/paralimbic areas, neocortical regions, brainstem, and cerebellum. For a delayed effect, several regions showed strong functional connectivity. During the overall process of acupuncture, the insula played a critical role. Acupuncture at NAP produced positive activations with a small extent of spatial distribution and less intensive signal changes compared to ST36, mainly in the insula, S2, and cerebellum.
Liu et al. [51]	2012	Altered small-world efficiency of brain functional networks in acupuncture at ST36: A functional MRI study	Spatial investigation of MA effects at ST36 versus nearby NAP	The results presented increased local efficiency after acupuncture stimulation. No significant differences were found for sham acupuncture at a NAP. Significant effects of real acupuncture but not sham were detected on nodal degree of the left hippocampus. Point-related effects were observed in the ACC, frontal and occipital regions, while stimulation-related effects were found in various brain regions of frontal, parietal, and occipital cortex regions. Several limbic and subcortical brain regions exhibited point- and stimulation-related alterations in their regional homogeneity.
Liu et al. [52]	2012	Determining the precise cerebral response to acupuncture: An improved fMRI study	Investigation of effects of MA at LR3 versus nearby NAP, each tested with expectations versus no expectations	The superior part of the secondary visual cortex (V2) was activated in real acupuncture versus sham, and the interior part of V2 was activated in the other contrasting condition. All three contrasting conditions aimed to elicit cerebral responses to expectancy, the ipsilateral MFG, contralateral orbitofrontal cortex (OFC), contralateral S2, and contralateral cerebellum were activated. The contralateral DLPFC, temporal pole, and hippocampi uncus were activated in groups with expectation versus no expectation (medial frontal gyrus- and DLPFC-related expectancy is validated for emotion and cognitive control).
Liu et al. [53]	2013	Additional evidence for the sustained effect of acupuncture at the vision-related acupuncture point, GB37	Spatial and temporal investigation of MA effects at vision-related GB37 versus nearby NAP	GLM analysis showed a more extensive spatial distribution signal decrease in the limbic-cerebellar regions (such as the occipital cortex, pons, PH/Hipp, putamen, and cerebellum) but with a smaller signal increase (such as in the STG, S2, and thalamus). Special temporal investigation showed that the neural response evoked by acupuncture did not turn on and off rapidly but lasted longer, violating the basic assumption of standard GLM analysis. fMRI signals of the limbic-paralimbic-neocortical system increased, so that changes in the occipital cortex showed different temporal patterns between GB37 and NAP.

Table 1: Continued.

Author	Year	Title	Objective	Outcomes
Murase et al. [54]	2013	Deconvolution analyses with tent functions reveal delayed and long-sustained increases of BOLD signals with acupuncture stimulation	Temporal + spatial investigation of MA effects versus von Frey filament sham acupuncture at LI4 (r) versus tactile stimulation right palm	MA showed activation on both sides in the S2 and the insula, on both sides in the S1, the primary motor cortex (M1), ACC, SMA, thalamus, and PFC. Sham acupuncture with von Frey filament showed that activation in the contralateral S1 and SMA and on both sides in the S2 and insula. Tactile stimulation showed activated areas in the contralateral S1, M1, and SMA and on both sides in the S2 and insula. Real acupuncture induced more widespread, more delayed, and long-sustained increases and decreases of BOLD signal in the somatosensory region and in areas related to pain perception.
Napadow et al. [55]	2013	Brain correlated of phasic autonomic response to acupuncture stimulation: An event-related fMRI study	Spatial + temporal investigation of ANS response and psychophysiological response patterns to MA at ST36 (l) versus SP9 (l) versus von Frey filament sham acupuncture at NAP (near ST36 (l))	GLM measurements showed that acupuncture events with strong skin conductance response produced greater anterior insula activation and acupuncture at SP9, which produced greater skin conductance response and also produced stronger sharp pain sensation and greater anterior insula activation. Acupuncture-induced heart rate (HR) deceleration was associated with greater DMN deactivation. This association was strongest for ST36, which produced more robust HR deceleration. DMN deactivation was significantly more pronounced across acupuncture stimuli producing HR deceleration versus those events characterized by acceleration.
Yeo et al. [56]	2010	Consecutive acupuncture stimulations lead to significantly decreased neural responses	Temporal investigation of repeated MA effects versus blunt sham acupuncture at BL62 (r)	They found that, after the first verum acupuncture stimulation block at the left BL62, the left hemisphere showed activation in the hypothalamus, thalamus, claustrum, cerebellum, inferior frontal gyrus, and the superior temporal gyrus, while the right hemisphere presented activation in the middle frontal gyrus. In both hemispheres, a significant focus of activation was found in the inferior parietal lobule. During the second block, only the cerebellum in the left hemisphere and the inferior parietal lobule in the right hemisphere were significantly activated, showing decreased activations during the second verum acupuncture stimulation. During sham, no significant brain activations were found.
You et al. [57]	2013	Altered hub configurations within default mode network following acupuncture at ST36: A multimodal investigation combining fMRI and MEG	Spatial + temporal investigation of MA effects at ST36 (r) versus nearby NAP on DMN hub configurations	They found that after sham acupuncture at NAP, the PCC remained to serve consistently as DMN hub across all five frequency bands. However, the PCC was regulated and only acted as a DMN hub within delta and gamma bands after verum acupuncture at ST36.
Liu et al. [59]	2011	Imaging the functional connectivity of the periaqueductal gray during genuine and sham electroacupuncture treatment	Spatial investigation of EA effects on PAG functional connectivity versus sham EA with Streitberger needles at LI3 (r) and LI4 (r), each with high versus low expectancy	They found greater connectivity between the PAG, left PCC, and precuneus in the comparison of verum EA versus Streitberger sham EA, whereas there was greater connectivity in the PAG and right anterior insula for sham EA. No significant differences were observed between high and low expectancy groups.

- (iii) All modalities increased the instinct brain network in rest. A more secure and spatially extended connectivity of the DMN was observed following MA and EA, whereas TEAS specifically increased the functional connectivity in the sensorimotor network.
- $4.10.2.\ Comparison\ of\ Verum\ Acupuncture\ versus\ Sham$
- (1) Comparison of EA versus Control Group
- (a) EA versus Streitberger Sham EA (fMRI: Liu et al., 2011 [59])

TABLE 2: PET studies on the effect of MA and EA.

Author	Year	Title	Objective	Outcomes
Biella et al. [24]	2001	Acupuncture produces central activations in pain regions	Investigation of cerebral blood flow (CBF) changes after MA at ST36 (bil) and LU5 (bil) versus two nearby NAPs (bil)	Verum acupuncture but not sham acupuncture activated the left anterior cingulus, the insulae bilaterally, the cerebellum bilaterally, the left superior frontal gyrus, and the right medial and inferior frontal gyri.
Dougherty et al. [35]	2008	A combined [11C] diprenorphine PET study and fMRI study of acupuncture analgesia	Investigation of changes in binding of opioid agonists and changes of heat pain after MA versus Streitberger sham acupuncture at LI4 (r)	In comparison to Streitberger acupuncture, they observed significant changes during verum acupuncture in the medial and lateral pain networks, such as opioid-binding decreases (associated with greater endogenous opioid release) in the right OFC, left medial PFC, right insula, and right thalamus, as well as binding increases in the bilateral insula, right medial PFC/ACC, left OFC, and right brainstem. An overlap of results between fMRI signals and [11C] diprenorphine blood pressure changes was only exhibited in the right medial OFC.
Hsieh et al. [17]	2001	Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: A positron emission tomography study	Investigation of point specific CBF changes during MA at LI4 (r) versus nearby NAP	In comparison to acupuncture at a NAP, only MA at LI4 elicited activation of the regional CBF (rCBF) in the areas of the hypothalamus with extension to midbrain, the insula, the ACC, and the cerebellum. In addition, a further comparison of needling with deqi contrasted with minimal manipulation acupuncture and showed activation in the hypothalamus and the cerebellum. The activation by deqi in the hypothalamus extended to the midbrain/brain stem when contrasted with the brain at rest. Minimal stimulation activated neither the hypothalamus nor the insula when compared with rest situation.
Lai et al. [36]	2009	A cerebral functional imaging study by positron emission tomography in healthy volunteers receiving true or sham acupuncture needling	Investigation of CBF changes during MA versus Streitberger needle versus overt blunt needling at TH5 (r)	For MA in comparison with overt blunt needling, more brain areas (BA7, 13, 18, 19, 21, 22, 27, 38, 40, 42, and 45) were activated, whereas, in comparison with Streitberger-like sham acupuncture, slightly less MA activation was found in the areas of BA13 and 42. During Streitberger-like sham acupuncture the areas BA4, 6, 7, 19, 22, and 41 showed activation.
Schlünzen et al. [37]	2007	Acupuncture of LI-4 in anesthetized healthy humans decreases cerebral blood flow in the putamen measured with positron emission tomography	Investigation of CBF changes during MA at LI4 (r) versus nearby NAP in anesthetized participants	Their results showed a decrease in CBF in the right medial frontal gyrus and in the left putamen for verum acupuncture. Acupuncture at a nearby NAP only caused a decrease of CBF in the right medial frontal gyrus.

- (i) Out of 7 EA studies, only one study used Streitberger needles for sham EA. Liu et al. [59] analyzed the functional connectivity of the PAG during real EA and sham EA at LI3 and LI4 on the right hand in volunteers with high and low expectancy.
- (ii) They found greater connectivity between the PAG, left PCC, and precuneus in the comparison of verum
- EA versus Streitberger sham EA, whereas there was greater connectivity in the PAG and right anterior insula for sham EA. No significant differences were observed between high and low expectancy groups.
- (b) EA versus Sham EA with Tapes/Patches (EP: Kvorning et al., 2003 [31]; Meissner et al., 2004 [32])

Author	Year	Title	Objective	Outcomes
Cabrini et al. [38]	2006	Bispectral Index evaluation of the sedative effect of acupuncture in healthy volunteers	Evaluation of BIS changes due to bilateral MA at PC6, LR3, HT7, Yintang, ear point Shenmen versus nearby NAP	BIS values did not differ between true and sham acupuncture at any time point during the study period and BIS changes over time did not differ between the two treatments.
Hsu et al. [39]	2011	Variations of brain activities of acupuncture to TE5 of left hand in normal subjects	Evaluation of effects on the EEG during and after MA at TH5 (l) versus nearby NAP	During acupuncture stimulation, the theta energy was increased. During acupuncture, only alpha energy was noted to have statistical difference.
Kim et al. [40]	2008	The effect of acupuncture at PC-6 on the electroencephalogram and electrocardiogram	Evaluation of MA effects on the EEG during PC6 versus nearby NAP	EEG signals increased after acupuncture stimulation. In each frequency band, the average amplitude of EEG power was higher after acupuncture stimulation than after NAP stimulation.
Kim et al. [43]	2009	A characteristic estimation of bio-signals for electro-acupuncture stimulations in human subjects	Evaluation of bilateral EA effects at PC5 versus PC6 versus nearby NAP on the EEG	Their findings showed that during verum acupuncture the power spectrum of the low frequency bands in the EEG increased in all lobes.
Litscher [41]	2004	Effects of acupressure, manual acupuncture and laserneedle acupuncture on EEG bispectral index and spectral edge frequency in healthy volunteers	Evaluation of the effects on BIS during MA versus laser acupuncture versus acupressure at Yintang versus acupressure at NAP (near Yintang)	The study reports a decrease of BIS and spectral edge frequency values for acupressure and laser acupuncture at Yintang and for acupressure at the NAP, but not for manual acupuncture.
Streitberger et al. [42]	2008	Effects of verum acupuncture compared to placebo acupuncture on quantitative EEG and heart rate variability in healthy volunteers	Evaluation of the effects on the quantitative EEG during MA at LI4 (bil) versus Streitberger sham acupuncture at nearby NAP	In linear relation to heart rate variability (HRV) changes, verum acupuncture influenced the power EEG with increase in the alphal-frequency of the occipital region with a shift of the alphal/theta ratio to the benefit of alphal over all electrodes. A negative linear correlation was found between the theta-band of the quantitative EEG and the HRV parameters, and a negative linear correlation was also found between low frequency and alphal as well as between high

TABLE 3: EEG studies on the effect of MA and EA.

- (i) Two studies observed the influence of EA versus sham EA on EPs. Kvorning et al. [31] investigated the effects on AEPs and Meissner et al. [32] investigated changes of SEPs.
- (ii) Kvorning et al. [31] explored the effects on AEPs of bilateral verum EA versus sham EA at LI4, PC6, ST36, SP9, LR3, and SP6 in anesthetized participants. However, they found no significant difference of (mid-latency or any other) AEPs between the two groups, which could have correlated with the depth of anesthesia.
- (iii) Meissner et al. [32] evaluated SEP changes after bilateral verum EA versus sham EA at ST36 and LR3 in anesthetized volunteers. They detected a decrease in the magnitudes of late SEP amplitudes (P260) after verum but not sham EA.

(c) EA versus NAP (EEG: Kim et al., 2009 [43]; EP: Wei et al., 2000 [33]; and Zeng et al., 2006 [34])

frequency and alpha1.

- (i) Three trials studied the differences of verum EA versus EA at a nearby NAP. Kim et al. [43] investigated the effects on the EEG, whereas Wei et al. [33] inspected changes of SEPs. Zeng et al. [34] combined temporal examination of EEG activities and SEP changes.
- (ii) As studies comparing acupuncture at a certain acupuncture point versus NAP mostly aim at neuroimaging point specific effects on the CNS, this subgroup analysis will only be discussed below, where trials using one single acupuncture point will be grouped according to the point they investigated. For Kim et al. [43] please refer to Table 3, and for Wei et al.

Author	Year	Title	Objective	Outcomes
Abad-Alegría and Pomarón [30]	2004	About the neurobiological foundations of the De-Qi-stimulus-response relation	Evaluation of EA effects without deqi during needle insertion at LI4 versus EA with deqi versus painful overstimulation versus EA at NAP on SEPs	Their measurements showed a direct relation between F-waves and SEPs with increasing electrostimulus, with main inflexion during deqi, whereas, with ongoing stimulation, greater variations took place, especially in case of SEP latency. In contrast, EA at a NAP did not produce any of the aforementioned effects.
Kvorning et al. [31]	2003	Acupuncture facilitates neuromuscular and oculomotor responses to skin incision with no influence on auditory evoked potentials under sevoflurane anaesthesia	Evaluation of bilateral EA effects at LI4, PC6, ST36, SP9, LR3, SP6 versus sham EA on AEPs	They found no significant difference of mid-latency or any other AEPs between the two groups, which could have correlated with the depth of anesthesia.
Meissner et al. [32]	2004	Acupuncture decreases somatosensory evoked + potential amplitudes to noxious stimuli in anesthetized volunteers	Evaluation of SEP changes after bilateral EA at ST36, SP6, LR3 versus sham EA	They detected a decrease in the magnitudes of late SEP amplitudes (P260) after verum but not sham EA.
Wei et al. [33]	2000	Early-latency somatosensory evoked potentials elicited by electrical acupuncture after needling acupoint LI-4	Evaluation of SEPs elicited by EA at LI4 (r) versus nearby NAP	Their results presented longer N1 and N2 latencies by acupuncture at LI4 as well as acupuncture at a nearby NAP than by median nerve stimulation, but showed no significant SEP differences between acupuncture at LI4 versus NAP.
Zeng et al. [34]	2006	Electroacupuncture modulates cortical activities evoked by noxious somatosensory stimulations in human	Temporal evaluation of EEG activities and evaluation of effects on painful SEPs after EA at LI4 (l) versus nearby NAP	EA at LI4 but not at a nearby NAP produced later-latency SEPs (P150) in bilateral ACC and attenuated pain specific amplitudes of P170 and N280 after median nerve stimulation.

TABLE 4: EP studies on the effect of MA and EA.

[33] and Zeng et al. [34] please refer to Section 4.10.3 *Point specificity comparison.*

- (2) Comparison of MA versus Control Group
- (a) MA versus Overt Painful Tactile Stimulation (fMRI: Cho et al., 2010 [46])
 - (i) The fMRI study by Cho et al. [46] compared manual versus overt painful tactile stimulation with a cotton tip at LII1 on the left arm versus ST36 on the left leg.
 - (ii) In comparison to painful tactile stimulation, MA at LI11 led to activation of both sides of the parahip-pocampal gyrus, cerebellum, left side of thalamus, and right side of posterior cingulate regions.
 - (iii) Acupuncture but not tactile stimulation at ST36 produced activation at the S2, limbic system (cingulate gyrus, posterior cingulate), V1, pons, medulla regions at the left BA 6, BA 8, and ACC.
 - (iv) In comparison with the left LII1 acupuncture stimulation, left BA 6, BA 8, and ACC were more activated by the left ST36 acupuncture stimulation.

- (v) Acupuncture activated more regions than painful tactile stimulation, especially areas of the limbic system, such as the parahippocampal gyrus and ACC.
- (b) MA versus Overt Blunt Needling (fMRI: Yeo et al., 2010 [56])
 - (i) Yeo et al. [56] focused on investigating the effect of previous acupuncture stimulations on brain activations of later acupuncture stimulations.
 - (ii) They found that after the first verum acupuncture stimulation block at the left BL62, the left hemisphere showed activation in the hypothalamus, thalamus, claustrum, cerebellum, inferior frontal gyrus, and the superior temporal gyrus, while the right hemisphere presented activation in the middle frontal gyrus. In both hemispheres, a significant focus of activation was found in the inferior parietal lobule.
 - (iii) During the second block, only the cerebellum in the left hemisphere and the inferior parietal lobule in the right hemisphere were significantly activated,

Table 5: Results fMRI.

A A		Methodology	gy				Needling details	letails						Control intervention	rention			Technology	logy
Autuoi	Participants	Participants Handedness Groups Sessions	Groups	Sessions	Points (uni-/bilateral)	Needling depth	Manipulation	deqi	Retention time	Intervention 1	Group 1	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Group I:	ntervention 3	Group 3	Intervention Group Intervention Group 3 3 4 4 4		Technical device	Software
Bai et al. [44]	16	Right		2	ST36 (r)	20-30 mm	90 sec, 1 Hz	yes	15 min	Manual	16	NAP	16					3 Tesla	SPM5
Cheng et al. [45]	32	Right	2	7	ST36 (r)	n/a	90 sec, 1 Hz	n/a	15 min	Manual	16	NAP	16					3 Tesla	SPM5
Cho et al. [46]	10	Right	-	4	LII1 (l), ST36 (l)	15-20 mm	3×30 sec, 2 Hz	yes	180 sec	Manual	10	Cotton tip	10					3 Tesla	SPM2
Dong et al. [47]	39	Right	3	1	GB37, BL60	n/a	2×30 sec, 1 Hz	yes	3 min 40 sec	Manual	13	NAP	13	BL60	13			3 Tesla	SPM5
Feng et al. [48]	14	Right	П	2	ST36 (r)	n/a	90 sec	yes	15 min	Manual	14	NAP	14					3 Tesla	SPM5
Zyloney et al. [60]	18	Right	-		ST36 (I)	15-25 mm	$2 \times 60 \text{ sec} + 1$ $\times 300 \text{ sec},$ 1-2 Hz	yes	10.5 min	Manual	18	vFrey	18	Electro	18	TEAS	18	3 Tesla	SPM5
Li et al. [49] Liu et al. [50]	22 18	Right Right	2 1	1 2	GB37 ST36 (r)	n/a 20-30 mm	$2 \times 30 \text{sec}$ 90 sec, 1 Hz	yes yes	3 min 8.5 min	Manual Manual	11 81	NAP NAP	11 81					3 Tesla 3 Tesla	SPM5 SPM5
Jiang et al. [58]	14	n/a	-	2	ST36 (r)	10-20 mm	90 sec, 1 Hz	yes	15 min	Manual	14	NAP	14					3 Tesla	SPM5
Liu et al. [51]	18	Right	2	2	ST36	15 mm	$3 \times 60 \text{ sec}$, 2 Hz	Yes	20 min	Manual	6	NAP	6					1.5 Tesla	SPM5
Liu et al. [52]	41	Right	4	1	LR3	10 mm	120 sec, 1 Hz	Yes	2 min	Manual	11 + 10	NAP	10 + 9					1.5 Tesla	SPM2
Liu et al. [53]	22	Right	П	2	GB37	20-30 mm	$2 \times 60 \text{ sec}$, 1 Hz	Yes	220 sec	Manual	22	NAP	22					3 Tesla	SPM5
Murase et al. [54]	26	Right	2	1	LI4 (r)	15 mm	4×15 sec, 1 Hz	n/a	270 sec	Manual	13	vFrey	13					1.5 Tesla	SPM8
Napadow et al. [55]	18	Right	-	7	ST36 (I), SP9 (I)	20-30 mm	2 sec, 1 Hz	Yes	300 sec	Manual	18	vFrey	18					3 Tesla	FSL, AFMI
Yeo et al. [56]	15	Right	1	7	BL62 (r)	10 mm	$2 \times 30 \text{ sec}$, 2 Hz	Yes	4 min	Manual	15	Blunt needle	15					3 Tesla	SPM5
You et al. [57]	28	Right	7 .			15-25 mm	120 sec, 1 Hz	Yes	9 min	Manual	14	NAP	14					3 Tesla	SPM5
Liu et al. [59]	48	Right	4	-	Ll3 (r), Ll4 (r)	15 mm	2 Hz	Xes	25 min	Electro	n/a	Streitberger	n/a					3 Tesla	n/a

TABLE 6: Results PET.

Technology	Technical Software device	GE- Advance SPM96	PC-4096 SPM2			•,
	Imaging	PET H2(15)O bolus	PET [11C] diprenorphine	T	PET rCBF	PET rCBF
	Group 3					6
Control intervention	Intervention 3					Blunt
ontrol in	Group 2	13	9		∞	8 6
J	Manipulation deqi Retention Intervention Group Intervention Group Manipulation deqi time $1 1 2 2 3 3 $	2x NAP	Streitberger		NAP	NAP Streitberger
	Group 1	13	9		∞	8 6
	Intervention 1	Manual	Manual		Manual	Manual Manual
	Retention time	25 min	29 min		180 sec	180 sec 19 min
Needling details	n deqi	Yes	Yes		Yes	
Needlin	Manipulatior	n/a	$3 \times 420 \text{ sec}$, 3 Hz		30 sec, 2 Hz	30 sec, 2 Hz 1 Hz
;	Needling _N depth	10-20 mm	10 mm		3 mm	3 mm 15 ± 2 mm
	Points Participants Handedness Groups Sessions (uni-/bilateral)	ST36 (bil), LU5 (bil)	LI4 (r)		LI4 (r)	LI4 (r) TH5 (r)
	Sessions	2	2		1	
gy	Groups	1	2		2	3 2
Methodology	Handedness	n/a	Right		Right	Right Right
	Participants	13	12		16	16
Author		Biella et al. [24]	Dougherty et al. [35]	LIviola at a	Fisien et al. [17]	risien et al. [17] Lai et al. [36]

TABLE 7: Results EEG.

Atthe		Methodology	ogy				Needling details	details				Co	ntrol inte	Control intervention			Technology	
Tombo	Participants	Handedness	Groups	Sessions	Participants Handedness Groups Sessions (uni-/bilateral) depth	Needling depth	Manipulation	deqi	Retention time	Intervention 1	Group 1	Manipulation deqi Retention Intervention Group Intervention Group Intervention Group Annipulation degi time $\frac{1}{1}$ $\frac{2}{2}$ $\frac{3}{3}$	Group I	Intervention (Group 3	Imaging	Technical device Software	Software
Cabrini et al. [38]	10	n/a	п	2	PC6, LR3, HT7, Yintang, ear Shenmen (bil)	n/a	n/a	Yes	20 min	Manual	10	NAP	20			BIS	n/a	n/a
Hsu et al. [39]	24	n/a	2	-	TH5 (1)	15 mm	n/a	Yes	20 min	Manual	12	NAP	12			EEG	Biopac brain wave detection	IOPAC
Kim et al. [40]	01	n/a	1	3		5-10 mm	n/a	n/a	15 min	Manual	10	NAP	10			EEG	helmets Biopac Systems	Daubechies
Kim et al. [43]	10	n/a	2	-	PC5 (bil) versus PC6	0.3 mm	20 Hz	n/a	5 min	Electro	n/a	NAP	n/a			EEG	n/a	ADC
Litscher [41]	25	n/a	1	4	(OII) Yintang	5 mm	4×20 sec	n/a	10 min	Manual	25	NAP acupressure	25	Laser	25	EEG + BIS	Zipprep Electrodes,	n/a
Streitberger et al. [42]	t 20	n/a	1	2	L14 (bil)	1 mm	15 sec	Yes	10 min	Manual	10	Streitberger at NAP	10			EEG	CATEEM	Vision Analyzer

TABLE 8: Results EP.

١.		Methodology	ogy				Needling details	details				ŭ	ontrol in	Control intervention			Technology	
Author	Participant	s Handedness	Groups	Sessions	Participants Handedness Groups Sessions (uni-/bilateral) depth	Needling depth	Manipulation	deqi	Retention time	Intervention 1	Group 1	Intervention 2	Group 2	Manipulation deqi Retention Intervention Group Intervention Group Group Operation 1 1 2 2 3 3 3 3 $^{\circ}$	Group 3	Imaging	Technical device Software	Software
Abad-Alegría and Pomarón [30]	21	n/a		4	L14	n/a	10 Hz	Yes	10 min	Electro + deqi	21	NAP	21	Electro + no deqi	21	SSEP	n/a	n/a
Kvorning et al. [31]	45	n/a	7	г	LI4, PC6, ST36, SP9, LR3, SP6 (bil)	5–15 mm	180 sec, 2 Hz + 80 Hz pulses	n/a	20 min	Electro	22	Sham electro	23			AEP	AEP monitor	ARX Aline
Meissner et al. [32]	. 16	n/a	7	-	ST36, SP6, LR3 (bil)	n/a	10 Hz	n/a	15 min	Electro	∞	Sham electro	∞			SEP	EEG	Vision Analyzer
Wei et al. [33]	11	Right	1	2	LI4 (r)	n/a	1Hz	n/a	n/a	Electro	Ξ	NAP	Ξ			SEP	128-channel system	n/a
Zeng et al. [34]	24	Right	-1	9	LI4 (l)	12.5 + 4.5 mm	2 Hz	n/a	n/a	Electro	24	NAP	24			SEP	64-channel Quikcaps Neuroscan ESI-128 system	SCAN 4.1

showing decreased activations during the second verum acupuncture stimulation.

- (c) MA versus Von Frey Filaments (fMRI: Murase et al., 2013 [54]; Napadow et al., 2013 [55])
 - (i) Two studies observed the effects of MA versus tactile stimulation with von Frey filaments on the fMRI. Both studies examined spatial and temporal effects of acupuncture, but Napadow et al. [55] focused mainly on ANS responses.
 - (ii) Murase et al. [54] investigated the fMRI effects of MA versus von Frey filament stimulation at LI4 on the right hand versus touch stimulation at the right palm with a deconvolution analysis with Tent functions.
 - (iii) MA showed activation on both sides in the S2 and the insula, on both sides in the S1, the M1, ACC, SMA, thalamus, and PFC.
 - (iv) Sham acupuncture with von Frey filament showed activation in the contralateral S1 and SMA and on both sides in the S2 and insula. Tactile stimulation showed activated areas in the contralateral S1, M1, and SMA and on both sides in the S2 and insula.
 - (v) Real acupuncture induced more widespread, more delayed, and long-sustained increases and decreases of BOLD signal in the somatosensory region and in areas related to pain perception.
 - (vi) Napadow et al. [55] combined fMRI with several interventions to measure the ANS response to MA on the left leg at ST36 versus SP9 versus tactile stimulation with von Frey filaments at a NAP near ST36
 - (vii) GLM measurements showed that acupuncture events with strong skin conductance response produced greater anterior insula activation and acupuncture at SP9, which produced greater skin conductance response, also produced stronger sharp pain sensation and greater anterior insula activation.
 - (viii) Acupuncture-induced HR deceleration was associated with greater DMN deactivation. This association was strongest for ST36, which produced more robust HR deceleration.
 - (ix) DMN deactivation was significantly more pronounced across acupuncture stimuli producing HR deceleration versus those events characterized by acceleration.
- (d) MA versus Streitberger Needles (PET: Dougherty et al., 2008 [35]; EEG: Streitberger et al., 2008 [42])
 - (i) Two trials compared MA and Streitberger needles sham acupuncture.
 - (ii) Dougherty et al. [35] used PET and Streitberger et al. [42] applied quantitative EEG (qEEG) to view acupuncture's effects on the brain.

- (iii) Dougherty et al. [35] studied the binding of PET opioid agonists and according fMRI changes after MA versus Streitberger needle acupuncture at LI4 on the right hand.
- (iv) In comparison to Streitberger acupuncture, they observed significant changes during verum acupuncture in the medial and lateral pain networks, such as opioid-binding decreases (associated with greater endogenous opioid release) in the right OFC, left medial PFC, right insula, and right thalamus, as well as binding increases in the bilateral insula, right medial PFC/ACC, left OFC, and right brainstem.
- (v) An overlap of results between fMRI signals and [11C] diprenorphine blood pressure changes was only exhibited in the right medial OFC.
- (vi) Streitberger et al. [42] examined the quantitative effects of bilateral MA at LI4 versus Streitberger needle acupuncture at a nearby NAP on the qEEG.
- (vii) In linear relation to HRV changes, verum acupuncture influenced the power EEG with increase in the alphal-frequency of the occipital region with a shift of the alphal/theta ratio to the benefit of alphal over all electrodes.
- (viii) A negative linear correlation was found between the theta-band of the qEEG and the HRV parameters, and a negative linear correlation was also found between low frequency and alphal as well as between high frequency and alphal.

(e) MA versus NAP

- (i) A total of 17 trials studied the differences of verum MA versus MA at a nearby NAP.
- (ii) Three studies investigated changes with PET (Biella et al., 2001 [23]; Hsieh et al., 2001 [17]; Schlünzen et al., 2007 [37]), and another three studies applied EEG (Cabrini et al., 2006 [38]; Hsu et al., 2011 [39]; and Kim et al., 2008 [40]) and the majority of eleven studies compared the fMRI effects of manual acupuncture versus acupuncture at NAP (Bai et al., 2010 [44]; Cheng et al., 2013 [45]; Dong et al., 2012 [47]; Feng et al., 2011 [48]; Li et al., 2010 [49]; Liu et al., 2010 [50]; Jiang et al. 2013 [58]; Liu et al., 2012 [51]; Liu et al. 2012 [52]; Liu et al., 2013 [53]; and You et al., 2013 [57]).
- (iii) As studies comparing acupuncture at a certain acupuncture point versus NAP mostly aim at neuroimaging point specific effects on the CNS, this subgroup analysis will only be discussed below, where trials using one single acupuncture point will be grouped according to the point they investigated.
- (iv) For Biella et al. (PET) [24]; Cabrini et al. [38] and Hsu et al. [39] (EEG); Kim et al. [40]; and Liu et al. [52] (fMRI) please refer to the Tables 1, 2, and 3.
- (v) For Hsieh et al. [17], Schlünzen et al. [37] (PET) and Bai et al. [44], Cheng et al. [45], Dong et al. [47], Feng et al. [48], Li et al. [49], Liu et al. [50], Jiang et al.

[58], Liu et al. [51], Liu et al. [53], and You et al. [57] (fMRI) please refer to Section 4.10.3 *Point specificity comparison*.

- (3) Verum versus Combined Control Interventions
- (a) EA with deqi versus without deqi versus Painful Stimulation versus NAP (EP: Abad-Alegría and Pomarón, 2004 [30])
 - (i) Abad-Alegría and Pomarón [30] investigated SEP changes due to EA at LI4 during different time points of needling at LI4, including puncturing the skin without deqi and needling with deqi as well as painful overstimulation, versus EA at a NAP.
 - (ii) Their measurements showed a direct relation between F-waves and SEPs with increasing electrostimulus, with main inflexion during deqi, whereas, with ongoing stimulation, greater variations took place, especially in case of SEP latency.
 - (iii) In contrast, EA at a NAP did not produce any of the aforementioned effects.
- (b) MA versus Several Control Interventions
 - (i) MA versus EA versus TEAS versus von Frey filament (Zyloney et al. [60]) refer to Section 4.10.1(1) (MA versus EA).
 - (ii) Litscher compared the effects of MA versus laser acupuncture versus acupressure at Yintang versus acupressure at a nearby NAP on the BIS.
 - (iii) The study reports a decrease of BIS and spectral edge frequency values for acupressure and laser acupuncture at Yintang and for acupressure at the NAP but not for manual acupuncture.
 - (iv) Lai et al. [36] evaluated CBF changes with 18-fluoridedeoxyglucose PET during MA versus overt blunt needling versus sham blunt needling (similar to a Streitberger needle) of TH5 on the right arm.
 - (v) For MA in comparison to overt blunt needling, more brain areas (BA7, 13, 18, 19, 21, 22, 27, 38, 40, 42, and 45) were activated, whereas, in comparison with Streitberger-like sham acupuncture, slightly less MA activation was found in the areas of BA13 and 42.
 - (vi) During Streitberger-like sham acupuncture the areas BA4, 6, 7, 19, 22, and 41 showed activation.

4.10.3. Point Specificity Comparison. Out of the 33 trials, 28 chose needling at only one single acupuncture point.

If within the same neuroimaging group there was more than one study about a single acupuncture point in comparison to another point or to a NAP, these studies were compared. In total, this resulted in the comparison of 15 studies, comprising 3 studies on GB37, 5 studies on LI4, and 7 studies on ST36.

(1) GB37. In total, three fMRI studies investigated acupuncture at GB37 versus NAP. Li et al. [49] and Liu et al.

- [53] compared MA at GB37 versus NAP. Dong et al. [47] additionally compared MA at GB37 with MA at BL60 versus acupuncture at NAP.
 - (i) Dong et al. [47] aimed at studying the temporal fMRI effects of MA at the vision-related acupuncture points GB37 versus BL60 versus a nearby NAP.
 - (ii) Although the ICA of all kinds of acupuncture showed activity at the V1 in the occipital lobe, temporal activities in this region differed for acupuncture at GB37 versus NAP, as well as for BL60 versus NAP.
 - (iii) Li et al. [49] focused on distinguishing the fMRI effects of MA at GB37 versus NAP with multi-voxel pattern analysis (MVPA).
 - (iv) They found different effects for verum acupuncture versus NAP in the subregions of occipital cortex (left cuneus of occipital gyrus and regions of lingual gyrus, middle occipital gyrus and fusiform gyrus), the limbic-cerebellar system (including insula, rACC and pACC, pons, amygdala, culmem in anterior lobe and declive of vermis in posterior lobe of cerebellum), and the somatosensory cortex.
 - (v) For GLM, the neural response patterns of acupuncture stimulation at acupoint and NAP had multiple overlapping regions and did not significantly differ from each other.
 - (vi) Liu et al. [53] examined the different spatial and temporal effects of MA at GB37 versus NAP.
 - (vii) GLM analysis showed a more extensive spatial distribution signal decrease in the limbic-cerebellar regions (such as the occipital cortex, pons, PH/Hipp, putamen and cerebellum), but with a smaller signal increase (such as in the STG, S2 and thalamus).
 - (viii) Special temporal investigation showed that the neural response evoked by acupuncture did not turn on and off rapidly but lasted longer, violating the basic assumption of standard GLM analysis.
 - (ix) fMRI signals of the limbic-paralimbic-neocortical system increased, so that changes in the occipital cortex showed different temporal patterns between GB37 and NAP.

(2) LI4

- (a) Two PET Studies Compared Acupuncture at LI4 versus NAP
 - (i) Hsieh et al. [17] compared MA at LI4 with acupuncture at a nearby NAP and Schlünzen et al. [37] compared MA with acupuncture at a NAP in anesthetized participants.
 - (ii) Hsieh et al. [17] studied point specific changes of CBF during MA at LI4 on the right hand versus a nearby NAP.
 - (iii) In comparison to acupuncture at a NAP, only MA at LI4 elicited activation of the rCBF in the areas of the

- hypothalamus with extension to midbrain, the insula, the ACC, and the cerebellum.
- (iv) In addition, a further comparison of needling with deqi contrasted with minimal manipulation acupuncture and showed activation in the hypothalamus and the cerebellum. The activation by deqi in the hypothalamus extended to the midbrain/brainstem when contrasted with the brain at rest. Minimal stimulation activated neither the hypothalamus nor the insula when compared with rest situation.
- (v) Schlünzen et al. [37] also observed point specific changes of CBF during MA at LI4 on the right hand versus a nearby NAP. Different from Hsieh et al. [17], the study participants were anesthetized prior to acupuncture treatment.
- (vi) Their results showed a decrease in CBF in the right medial frontal gyrus and in the left putamen for verum acupuncture. Acupuncture at a nearby NAP only caused a decrease of CBF in the right medial frontal gyrus.
- (b) Three EP Studies Explored EA Effects at LI4 versus NAP
 - (i) Abad-Alegría and Pomarón [30] applied EA without deqi and with deqi at LI4 and compared it to a nearby NAP. Wei et al. [33] only inspected changes of SEPs whereas Zeng et al. [34] combined temporal examination of EEG activities and SEP changes after EA at LI4 versus NAP.
 - (ii) Abad-Alegría and Pomarón [30] 2004 investigated SEP changes due to EA at LI4 during different time points of needling at LI4, including puncturing the skin without deqi and needling with deqi as well as painful overstimulation, versus EA at a NAP.
 - (iii) Their measurements showed a direct relation between F-waves and SEPs with increasing electrostimulus, with main inflexion during deqi, whereas, with ongoing stimulation, greater variations took place, especially in case of SEP latency.
 - (iv) In contrast, EA at a NAP did not produce any of the aforementioned effects.
 - (v) Wei et al. [33] examined SEPs elicited by verum EA at LI4 on the right arm versus EA at a nearby NAP in comparison to median nerve stimulation.
 - (vi) Their results presented longer N1 and N2 latencies by MA at LI4 as well as acupuncture at a nearby NAP than by median nerve stimulation but showed no significant SEP differences between MA at LI4 versus NAP.
 - (vii) Zeng et al. [34] evaluated EEG activities after EA at LI4 versus NAP and the acupuncture effects on painful SEPs of median nerve stimulation.
 - (viii) EA at LI4 but not at a nearby NAP produced laterlatency SEPs (P150) in bilateral ACC and attenuated pain specific amplitudes of P170 and N280 after median nerve stimulation.

- (3) ST36. Seven fMRI studies compared MA effects at ST36 with MA at a nearby NAP (Bai et al., 2010 [44]; Cheng et al., 2013 [45]; Feng et al., 2011 [48]; Liu et al., 2010 [50]; Jiang et al., 2013 [58]; Liu et al., 2012 [51]; and You et al., 2013 [57]).
 - (i) Bai et al. [44] investigated the temporal effects of MA at ST36 versus NAP with a nonrepeated event-related (NRER) fMRI paradigm and change-point analysis.
 - (ii) They found that the amygdala and pACC exhibited increased activities during needling but decreased to reach a peak below the baseline. The PAG and hypothalamus presented intermittent activations across the whole session.
 - (iii) Apart from the time-dependent responses, relatively persistent activities were also identified in the anterior insula and PFCs.
 - (iv) In comparison, verum and sham shared a similar activation pattern in somatosensory areas (S1 and S2) during needling. However, during the postacupuncture resting period acupuncture at ST36 was followed by sustained activation of the S2, whereas acupuncture at NAP showed inhibition of the S1.
 - (v) Cheng et al. [45] applied graph theoretical analysis with pairwise correlations of cortical and subcortical regions to evaluate NRER fMRI effects of manual acupuncture.
 - (vi) Their correlations presented frequency-specific modularity functional brain networks during poststimulus resting state following acupuncture at ST36 and NAP.
 - (vii) Graph metrics in brain activity are different in verum and sham groups and also show that the brain network following MA has higher global and local efficiency in parallel information transfer in the brain network compared with acupuncture at a NAP.
 - (viii) Feng et al. [48] evaluated interaction and changes of large scale networks after MA at ST36 versus NAP.
 - (ix) Within a network of 90 predefined regions in the poststimulus resting brain, limbic/paralimbic regions (such as the amygdala, hippocampus, and ACC) emerged as network hubs after verum but not sham acupuncture.
 - (x) Compared with needling at a NAP, MA at ST36 presented increased correlations, related with the limbic/paralimbic and subcortical regions (such as the insula, amygdala, and ACC) and thalamus. Decreased correlations for verum acupuncture were related with the sensory and frontal cortex.
 - (xi) Liu et al. [50] studied the spatial and temporal effects of MA at ST36 versus NAP in a nonevent-related paradigm with GLM and ICA.
 - (xii) Their results showed manipulation-related effects and sustained acupuncture effects in the cortical-subcortical areas, including the ACC, VLPFC, and SMA, and decreases in the S1 and S2.

- (xiii) These reactions lasted until the resting period after needling, where then activations were induced in many regions including the insula, caudate, putamen, and thalamus.
- (xiv) Liu et al. [58] examined the immediate and delayed effects of acupuncture at ST36 versus NAP with GLM and graph theory analysis.
- (xv) The immediate effect of verum as well as sham acupuncture consisted of signal changes in the limbic/paralimbic areas, neocortical regions, brainstem, and cerebellum.
- (xvi) For a delayed effect, several regions showed strong functional connectivity. During the overall process of acupuncture, the insula played a critical role.
- (xvii) Acupuncture at NAP produced positive activations with a small extent of spatial distribution and less intensive signal change as compared to ST36, mainly in the insula, S2, and cerebellum.
- (xviii) Liu et al. [51] focused on searching the spatial effects of MA at ST36 versus NAP with applying small-world brain networks.
- (xix) The results presented increased local efficiency after acupuncture stimulation. No significant differences were found for sham acupuncture at a NAP. Significant effects of real acupuncture but not sham were detected on nodal degree of the left hippocampus.
- (xx) Point-related effects were observed in the ACC, frontal, and occipital regions while stimulationrelated effects were found in various brain regions of frontal, parietal, and occipital cortex regions. Several limbic and subcortical brain regions exhibited pointand stimulation-related alterations in their regional homogeneity.
- (xxi) You et al. [57] used pairwise functional connectivity analysis in 8 regions of the DMN with 5 conventional frequency bands (delta, theta, alpha, beta, and gamma) to investigate band-specific alterations of DMN hub configurations after MA at ST36 on the right leg versus NAP.
- (xxii) They found that after sham acupuncture at NAP, the PCC remained to serve consistently as DMN hub across all 5 frequency bands.
- (xxiii) However, the PCC was regulated and only acted as a DMN hub within delta and gamma bands after verum acupuncture at ST36.
- (xxiv) 28 of the 33 trials were further included into the subgroup analysis and assigned to one of the three main groups: A = comparison of main interventions, B = verum acupuncture versus sham acupuncture, and C = point specificity (see Table 9).

In conclusion, it was not reasonable to further compare the results within their subgroups due to the heterogeneity of studies, with different research questions and diverse methodology protocols. In Table 9, the outcomes shall therefore only be listed as short descriptive results.

5. Discussion

5.1. Summary of Evidence. In the following, the results of all 33 trials included in this review will be presented in groups according to their neuroimaging intervention and outcome.

Out of 17 fMRI studies, one found greater connectivity for verum EA, 5 found changes of network efficiency or network correlations, 9 found activation of different areas, and 6 found different temporal changes with verum MA.

Out of 5 PET studies, 3 found more activation of CBF, one found a greater release of endogenous opioids, and one found a decrease of CBF with verum MA.

Out of 6 EEG studies, 2 found no changes of BIS with verum MA and 4 found EEG signal increases in different bands with verum acupuncture (3 MA and 1 EA).

Out of 5 EP studies with verum EA, one found no influence on AEPs, one found no difference in acupuncture or sham SEPs, and 3 found an influence on late SEPs.

5.2. Limitations. Although this review paper provides a detailed structured overview of the current literature with respect to neuroimaging and acupuncture, the data evaluation encountered typical, all too well known difficulties in acupuncture mechanism research due to heterogeneous methodology protocols.

While conducting studies about acupuncture's neurological mechanisms, every research question, every neuroimaging device, and every verum and control acupuncture intervention holds its own risk of bias. Therefore, a few of the most important limitations of the studies included in this review shall be addressed in the following.

5.2.1. Methodology Protocol

(1) Different Interventions: EA versus MA. So far, several neuroimaging studies compared the effects of MA and EA on the brain and many of their findings were different. These differences should be addressed and kept in mind while choosing and discussing various interventions.

Several clinical studies made the assertion that EA shows stronger analyseic effects than MA [61, 62].

In addition, Hsieh [63] observed different ANS outflows for 2 Hz-EA versus MA, with larger latency and smaller amplitude of sympathetic skin response for EA than MA.

Several years later, Kong et al. [64] showed that EA mainly elicited fMRI signal increases in several brain areas, whereas MA produced strong decreases of fMRI signals.

One year later, Li et al. [65] found that different brain areas were activated by MA and EA and by EA of different frequencies.

Napadow et al. [21] furthermore extended these findings, by observing that EA elicited fMRI signal increases in more brain areas than MA.

Finally, a review by Huang et al. [66] stated that EA produces more activation and less deactivation compared to MA.

(2) Different Acupuncture Points. For clinical treatment, different doctors choose different individualized points for

TABLE 9: Subgroup results table.

	(A) Comparison of main interventions
(a) MA versus EA	MA increased DMN connectivity and EA showed DMN deactivation [58]
	(B) Verum versus sham
EA versus sham	
(a) Streitberger needling	EA increased functional connectivity of PAG [60]
(b) Patch/tape	No difference of AEP after EA or sham [31]
(-)	Decrease of late SEP amplitude after EA [32]
MA versus sham	
(a) Painful tactile stimulation	More areas activated by MA (ST36 > LI11) than painful stimulus [46]
(b) Blunt overt sham	More activation by (1st > 2nd) MA than blunt overt sham [56]
(c) Von Frey filament	More areas activated after MA than von Frey filaments + delayed, sustained in/decreases afte MA [54]
	Stronger ANS responses (HR, skin conductance resistance) and DMN changes after ST36 an SP9 than sham [55]
(d) Streitberger needling	More areas with PET opioid agonist binding decrease after MA than Streitberger needle [35]
(a, onemoriger meaning	MA influences qEEG power bands changes in linear relation with HRV changes [42]
Verum versus combined sham	
(a) EA	Correlation of SEP F-waves with increasing EA stimulation [30]
(b) MA	BIS decrease for acupressure, laser and pressure at NAP, not MA [41]
(6) 1411	More areas activated for MA in comparison with blunt and MA in comparison with Streitberger [36]
	(C) Point specificity
GB37 versus NAP	
	Different temporal activities for GB37, BL60 and NAP [47]
MA	ICA but not GLM showed more affected areas by GB37 than NAP [49]
	Wider spatial distribution, long-lasting responses for GB37 than NAP [53]
LI4 versus NAP	
(a) MA	More rCBF activation for LI4 (with deqi > without) than NAP [17]
(4) 1.111	CBF decreases in more areas for LI4 than NAP [37]
	Correlation of SEP F-waves with increasing EA stimulation [30]
(b) EA	No difference in SEP for LI4 and NAP [33]
	LI4 but not NAP produced later latency SEP and attenuation of n. medianus amplitude [34]
ST36 versus NAP	
	Wider and sustained activation effects after ST36 than NAP [44]
	Higher network efficiency after ST36 than NAP [45]
	Different network correlations after ST36 and NAP [48]
MA	Manipulation-related and longer-lasting effects for ST36 than NAP [50]
	Immediate activation of larger areas and sustained, stronger functional connectivity for ST30 in comparison to NAP [59]
	Different nodal and point-related effects, but similar efficiency after ST36 and NAP [51]
	Changes of PCC action as DMN hub after ST36 but not NAP [57]

each patient. These treatment programs also vary based on different clinical experiences, styles, and schools. Above this, studies showed that even if the same points were chosen in theory, point locations still varied between doctors [67].

For research, so far no guidelines exist if, next to classical acupuncture points, A-Shi points or trigger points could also be considered real acupuncture points with similar mechanism of action. A far bigger problem still remains

which is the fact that many studies even found similar effects for sham and real acupuncture points [68].

Referring to this, sham acupuncture points also should be chosen very carefully. Until now, no unified standards for locating NAPs exist. As there are many extra acupuncture points besides the meridians, sham points should best be chosen at nonacupoint, nonmeridian, and nonsegmental places [69]. (3) Acupuncture Needling Depth. In this review a broad range of needling depth was observed with big differences even for the same acupoints. With such striking differences, influences on the results are very likely and therefore detailed documentation is very important.

As White et al. [70] stated, needling depth differs on condition, age, and body weight. Also, different depth applies for safety issues of various acupuncture points [71].

Regarding the above statements, no generalization of advisable needling depth is possible. However, a study by Ceccherelli et al. [72] found that, for pain conditions, deep needling was superior to shallow needling.

Park et al. [73] reported different sensations according to the needling depth. This trial found that superficial penetration produced prominent pricking and sharp sensations, whereas deep penetration produced a high degree of deep, dull, heavy, spreading, and electric shock sensations.

Moreover, Zhang et al. [74] reported that deep needling produced more fMRI activation signals in almost all brain areas. In contrast, Wu et al. [18] found more activation from superficial needling in the somatosensory area, motor area, and language areas and more deactivation in the limbic system for deep needling.

(4) Manipulation or Electrical Stimulation. While the effects for electrical stimulation of different frequencies are well known since Han's publication in 2003 [75], less congruent data exist about the differences in strength, duration, and repetition of manual stimulation [75].

In clinical practice, various ways of stimulation can be applied, ranging from single stimulation and immediate pullout (single acupuncture stimulation) to keeping a needle inserted for some time (retaining needle) and continuous rotation of a needle with vertical movements during insertion (sparrow pecking method) [76].

Sakai et al. [77] found that rotation of a needle with vertical movements produced a stronger stimulation than holding or single stimulation.

Furthermore, Marcus [78] found that not only the style, but also the time of stimulation could make a difference. The study recorded that longer duration of manual stimulation contributed much more to the strength of acupuncture than the depth or gauge of the needle. Similarly, Li et al. [79] showed that longer duration of manipulation induced more activation of brain areas.

In addition, Zaslawski et al. [80] also confirmed that needling manipulation produced increased pain thresholds, even if a NAP was needled.

A newer fMRI review by Huang et al. [66] confirmed these statements as it found more activation in several brain areas for acupuncture with stimulation compared to no stimulation.

However, all of the above effects should always be investigated carefully, as repetition of stimulation causes the so-called "carryover effect," which might lead to different results after several treatments [56, 81, 82].

(5) Treatment Duration/Needle Retention Time. In addition to considering the time of stimulation as discussed above,

it is also important to think about the complete duration of needling, with or without stimulation.

For clinical treatment standard needle retention time averages 20 to 30 minutes [83]. He [84], Cheng et al. [85], and Peng and Fei [86] stated that practitioners should first wait for qi arrival after placing the needle. In their opinion, afterwards no further limitations for treatment time apply, once deqi was achieved.

In contrast, is more difficult to decide on the best needle retention time for research protocols. This question should be approached from different perspectives. From a theoretical point of view, researchers could consider the optimum time to release neurotransmitters after needle application [87], while practically needle retention time has to be adapted to the limitations and conditions of the respective neuroimaging intervention (e.g., block designs for fMRI, measurement time for EEG and BIS, etc.).

(6) Deqi. In traditional Chinese medicine (TCM) the deqi sensation is considered to be related to clinical efficacy [88].

From an anatomical viewpoint, different types of nerve fibers conduct different types of sensation. Soreness, dull pain, and heat sensations are transmitted by slow conductive, A-delta and C fibers, whereas numbness and tingling are transmitted by A-beta/gamma fibers. Pressure is transmitted through multiple different types of nerve fibers [83].

In an early study, Wang et al. [89] found numbness to be mostly associated with A-beta/gamma fibers, distension and heaviness with A-delta fibers, and soreness with C fibers [89].

Hendry et al. [90] furthermore stated that as A-beta fibers terminate in lamina III to VI of the dorsal horn and A-delta fibers terminate on large cells in lamina II, different acupuncture modalities might trigger different brain networks based on the types of afferent input.

According to this, deqi might vary in different treatment settings, depending on styles of acupuncture and stimulation. Park et al. [91] found that deqi from MA was slightly different from that of EA, but deqi from sham acupuncture was significantly lower than that of MA or EA. In contrast, Kong et al. [64] reported the difference that deqi of MA mainly induced soreness, fullness, and distention, whereas deqi of EA rather produced tingling and numbness.

It therefore seems advisable for EA treatments to first evoke deqi before applying electricity [92].

In line with this advice, Napadow et al. [55] also assumed that a brief manual stimulation which elicits sensation was more clinically relevant than longer duration (30 s–2 min) block-like stimulation.

Recently an fMRI study by Sun et al. [93] found different brain responses to various deqi sensations. They reported that BOLD responses around cortical areas were activation-dominated due to processing of somatosensory or pain signals. This study claimed a need for standardization of qualification and quantification methods of deqi [93].

In addition, Kong et al. [92] advised future researchers to use a standardized scale, for example, the MASS (Massachusetts general hospital acupuncture sensation scale), for

documenting the elicited perception of deqi in order to make different deqi effects better comprehensible.

(7) Placebo and Expectancy. Acupuncture research protocols include a broad range of sham acupuncture models, ranging from placebo acupuncture which does not involve needling at all (like transcutaneous nerve stimulation), over nonpenetrating needling (like blunt overt needling on a patch or Streitberger needling), up to penetrating sham needling at a NMP or a NAP.

While Stux and Hammerschlag [94] suggested that all sham acupuncture models are convincing enough to patients to produce clinical equivalent effects, Birch et al. [95] stated that only placebo with needle insertion produces similar effects to those of acupuncture.

In agreement with the latter, Zaslawski et al. [80] declared that placebo without puncturing the skin could easily enable people to discriminate between sham and real acupuncture and might therefore not be effective.

However, no matter which kind of placebo is chosen, it is still hard to differentiate between the specific and nonspecific effects of sham acupuncture. As pain consists of a sensory and an affective component, both components also play an important role in the effects of placebo interventions [70].

In general, placebo analgesia is associated with striatal dopamine release [96], which points out a coupling of pain matrix and reward system. Similarly, Pariente et al. [22] found that the striatal reward system was activated when expectancy for (sham) acupuncture was high.

Studies by Huang et al. [66] and Kong et al. [97] corroborated this effect of expectancy. Huang et al. found that positive expectation increased acupuncture analgesia [66]. Kong et al. also reported that real and sham with high expectancy produced similar analgesia [97].

Due to so many similarities, Dhond et al. [5] investigated the differences between specific and placebo components of acupuncture. Real acupuncture, like placebo analgesia, modulated regions of pain perception in the limbic areas, sensorimotor and prefrontal cortices, brainstem nuclei, and cerebellum. While differences in the PFC and rACC indicated nonspecific pain expectancy, the modulation of amygdala, insula, and hypothalamus might suggest acupuncture specificity.

5.2.2. Interpretation of Results

- (1) *Interpretation of fMRI Results*. Activation and deactivation effects of certain brain areas in fMRI neuroimaging have to be interpreted with caution.
- (a) Activation and Deactivation. Beissner and Henke [98] discussed the problem of activation and deactivation in their review on the difficulties of fMRI studies. They stated that deactivation could be regarded either as a reduction of neuronal activity compared to baseline due to acupuncture or as a neuronal activity stronger in the baseline than compared with acupuncture stimulation. Both possibilities cannot be distinguished, if compared to baseline.
- (b) Baseline. This leads to the next problem of defining an adequate baseline. So far, most of the baselines tell people

to close their eyes and think of nothing special or just to focus on the stimulation. However, Gusnard and Raichle [99] and Stark and Squire [100] stated that the cortical activity associated with this "low" baseline is neither well defined nor stationary.

Furthermore, Beckmann et al. [101] and DeLuca et al. [102] pointed out that brain activity does not cease when the subject is at rest, instead several resting state networks are active. Beissner and Henke [98] therefore proposed that a continuous attention task throughout the entire experiment would be a better option.

(c) Interpretation of Spatial Effects. One more difficulty of interpreting the broad range of fMRI signal changes in various brain areas was addressed by a review from Napadow et al. [103]. They pointed out that acupuncture is a complex somatosensory stimulus, as it elicits sensorimotor, affective, and higher cognitive/evaluative processes in the brain.

Therefore, they assumed that changes in certain brain areas could be specific for acupuncture analgesia, whereas others might be unspecific and rather linked with expectancy and emotional effects.

Their review data presented that the somatosensory cortex (S1, S2) could display early somatosensory stimuli, whereas the limbic brain regions (like hypothalamus, amygdala, ACC, and hippocampus) could mediate affective or emotional responses.

Similar to these findings, Pariente et al. [22] discussed the fact that many studies demonstrated modulation of the insula and the PFC. They presumed that the insula might play a specific role in pain processing whereas the PFC and its connections with the limbic system rather would to be linked with expectancy.

(d) Measuring Temporal Effects. It is supposed that, after needling stimulation in deep tissue with biochemical reactions to tissue damage, acupuncture still elicits prolonged effects after needle removal [104–107].

In line with this assumption, Napadow et al. [103] and Dhond et al. [107] also found that acupuncture does not just affect the brain during needling but can enhance the poststimulation spatial extent of resting brain networks.

Liu et al. [59] therefore pointed out that the common block- and event-related paradigms neither are suitable for long acupuncture stimulation periods similar to clinical treatment nor are they applicable for measuring the delayed and longer lasting effects of acupuncture.

- (2) *Interpretation of PET Results*. For PET studies the same precautions apply as discussed for fMRI.
- (3) Difficulties of Acupuncture EEG Studies. Results of acupuncture EEG studies often report different and even contradicting effects. Li et al. [108] pointed out that these variations in EEG findings often depend on the physical and psychological state of the subject (e.g., attention). Hsu et al. [39] also noted that the participants' brain waves could be affected by environmental, mental, and physical factors such as anxiety and nervousness.

Some acupuncture EEG studies claimed that possible correlations with the ANS might as well modulate the EEG effects [109–111]. Another study also reported correlations between the EEG and autonomic functions in accordance with the acupuncture pain score [112].

On top of these inhomogeneous findings, EEG signals also often show a poor signal-to-noise ratio and reliable objectification can be difficult.

(4) Difficulties of Acupuncture EP Studies. For the interpretation of EPs in acupuncture trials, the possible influences of attentional manipulation and the activation of antinociceptive systems have to be taken into consideration.

Miltner et al. [113] earlier assumed that manipulation of a subject's attention could decrease the perception of pain. Shifting attention during acupuncture manipulation could therefore also influence the EP signals in acupuncture studies, especially those of long latency.

Kenntner-Mabiala [114] reinforced these early assumptions with a study proving that emotion and attention had distinct effects on EPs: modulation of N150 amplitudes reflected an affective pain modulation, whereas the modulation of P260 amplitudes was linked to attentional processes.

On top of these attention and pain modulating issues, Xu et al. [115] criticized that the conventional SEP methodology measuring fast conduction fibers might not be suitable for studying acupuncture mechanisms.

6. Conclusion

This review paper provides an overview of 33 neuroimaging studies, including trials with fMRI, PET, EEG, and EP. A majority of 25 studies compared MA versus sham acupuncture, while a minority of 7 trials compared EA versus sham, and only one study compared EA versus MA.

As acupuncture elicited a broad range of neurological responses, including somatosensory, affective, and cognitive aspects, only descriptive conclusions can be drawn. Evaluation of the very heterogeneous results shows evidence that in 29 out of 33 studies verum acupuncture elicits more/different modulation effects on neurological components measured by fMRI, PET, EEG, and EP than sham acupuncture.

For future studies using neuroimaging technology, more consistent methodology protocols are recommended. Stricter protocols would allow better comparison of results and could accelerate and consolidate advances in the field of acupuncture mechanism research.

In order to limit the most common mistakes while developing an acupuncture neuroimaging trial, it seems advisable for future researchers to seek advice from Witt et al.'s document "effectiveness guidance" [116] for clinical research. Furthermore, all researchers should closely follow the STRICTA guidelines in designing and reporting acupuncture studies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The study was supported by the Austrian Federal Ministries of Science, Research and Economy and of Health. The authors would like to thank Ms. Ingrid Gaischek, MS (Medical University of Graz) for her help in paper preparation.

References

- [1] F. R. Liang and X. Wu, "The developmental status and prospect of the science of acupuncture and moxibustion abroad," *Zhongguo Zhen Jiu*, vol. 26, no. 2, pp. 79–82, 2006.
- [2] G. Bodeker, "Traditional & complementary medicine in health care: public policy dimensions," in *Herbal Medicines: Molecular Basis of Biological Activity and Health*, L. Packer, B. Halliwell, and C. N. Ong, Eds., Marcel Dekker, New York, NY, USA, 2005.
- [3] C. Z. Liu, G. Litscher, F. R. Liang, J. Kong, and L. P. Wang, "Deqi sensation in different kinds of acupuncture," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 121573, 1 page, 2014.
- [4] K. Linde, A. Streng, S. Jürgens et al., "Acupuncture for patients with migraine: a randomized controlled trial," *The Journal of the American Medical Association*, vol. 293, no. 17, pp. 2118–2125, 2005
- [5] R. P. Dhond, N. Kettner, and V. Napadow, "Neuroimaging acupuncture effects in the human brain," *Journal of Alternative* and Complementary Medicine, vol. 13, no. 6, pp. 603–616, 2007.
- [6] N. K. Logothetis and B. A. Wandell, "Interpreting the BOLD signal," *Annual Review of Physiology*, vol. 66, pp. 735–769, 2004.
- [7] M. A. Lindquist, "The statistical analysis of fMRI data," *Statistical Science*, vol. 23, no. 4, pp. 439–464, 2008.
- [8] L. G. Nilsson and H. J. Markowitsch, Cognitive Neuroscience of Memory, Hogrefe & Huber, Seattle, Wash, USA, 1999.
- [9] B. Telenczuk, S. N. Baker, A. V. M. Herz, and G. Curio, "High-frequency EEG covaries with spike burst patterns detected in cortical neurons," *Journal of Neurophysiology*, vol. 105, no. 6, pp. 2951–2959, 2011.
- [10] I. Kissin, "Depth of anesthesia and bispectral index monitoring," *Anesthesia and Analgesia*, vol. 90, no. 5, pp. 1114–1117, 2000.
- [11] O. D. Creutzfeldt, S. Watanabe, and H. D. Lux, "Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and epicortical stimulation," *Electroencephalography and Clinical Neurophysiology*, vol. 20, no. 1, pp. 1–18, 1966.
- [12] A. C. N. Chen, C. Richard Chapman, and S. W. Harkins, "Brain evoked potentials are functional correlates of induced pain in man," *Pain*, vol. 6, no. 3, pp. 365–374, 1979.
- [13] W. H. R. Miltner and T. Weiss, "Brain electrical correlates of pain processing," *Zeitschrift für Rheumatologie*, vol. 57, no. 2, pp. S14–S18, 1998.
- [14] P. Rainville, "Brain mechanisms of pain affect and pain modulation," *Current Opinion in Neurobiology*, vol. 12, no. 2, pp. 195–204, 2002.
- [15] I. Tracey and P. W. Mantyh, "The cerebral signature for pain perception and its modulation," *Neuron*, vol. 55, no. 3, pp. 377–391, 2007.
- [16] L. Leung, "Neurophysiological basis of acupuncture-induced analgesia—an updated review," *Journal of Acupuncture and Meridian Studies*, vol. 5, no. 6, pp. 261–270, 2012.
- [17] J.-C. Hsieh, C.-H. Tu, F.-P. Chen et al., "Activation of the hypothalamus characterizes the acupuncture stimulation at the

- analgesic point in human: a positron emission tomography study," *Neuroscience Letters*, vol. 307, no. 2, pp. 105–108, 2001.
- [18] M.-T. Wu, J.-C. Hsieh, J. Xiong et al., "Central nervous pathway for acupunture stimulation: localization of processing with functional MR imaging of the brain—preliminary experience," *Radiology*, vol. 212, no. 1, pp. 133–141, 1999.
- [19] K. K. Hui, J. Liu, N. Makris et al., "Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects," *Human Brain Mapping*, vol. 9, no. 1, pp. 13–25, 2000.
- [20] S. S. Yoo, E. K. Teh, R. A. Blinder, and F. A. Jolesz, "Modulation of cerebellar activities by acupuncture stimulation: evidence from fMRI study," *NeuroImage*, vol. 22, no. 2, pp. 932–940, 2004.
- [21] V. Napadow, N. Makris, J. Liu, N. W. Kettner, K. K. Kwong, and K. K. S. Hui, "Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI," *Human Brain Mapping*, vol. 24, no. 3, pp. 193–205, 2005.
- [22] J. Pariente, P. White, R. S. J. Frackowiak, and G. Lewith, "Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture," *NeuroImage*, vol. 25, no. 4, pp. 1161–1167, 2005.
- [23] D. H. Zald, "The human amygdala and the emotional evaluation of sensory stimuli," *Brain Research Reviews*, vol. 41, no. 1, pp. 88–123, 2003.
- [24] G. Biella, M. L. Sotgiu, G. Pellegata, E. Paulesu, I. Castiglioni, and F. Fazio, "Acupuncture produces central activations in pain regions," *NeuroImage*, vol. 14, no. 1, part 1, pp. 60–66, 2001.
- [25] K. L. Casey, "Forebrain mechanisms of nociception and pain: analysis through imaging," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 14, pp. 7668–7674, 1999.
- [26] M. D. Greicius, B. Krasnow, A. L. Reiss, and V. Menon, "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 1, pp. 253–258, 2003.
- [27] B. Mazoyer, L. Zago, E. Mellet et al., "Cortical networks for working memory and executive functions sustain the conscious resting state in man," *Brain Research Bulletin*, vol. 54, no. 3, pp. 287–298, 2001.
- [28] G. L. Shulman, J. A. Fiez, M. Corbetta et al., "Common blood flow changes across visual tasks: II. Decreases in cerebral cortex," *Journal of Cognitive Neuroscience*, vol. 9, no. 5, pp. 648– 663, 1997.
- [29] A. Otti and M. Noll-Hussong, "Acupuncture-induced pain relief and the human brain's default mode network—an extended view of central effects of acupuncture analgesia," Forschende Komplementarmedizin, vol. 19, no. 4, pp. 197–201, 2012.
- [30] F. Abad-Alegría and C. Pomarón, "About the neurobiological foundations of the De-Qi—stimulus-response relation," *Ameri*can Journal of Chinese Medicine, vol. 32, no. 5, pp. 807–814, 2004.
- [31] N. Kvorning, C. Christiansson, and J. Åkeson, "Acupuncture facilitates neuromuscular and oculomotor responses to skin incision with no influence on auditory evoked potentials under sevoflurane anaesthesia," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 9, pp. 1073–1078, 2003.
- [32] W. Meissner, T. Weiss, R. H. Trippe, H. Hecht, C. Krapp, and W. H. Miltner, "Acupuncture decreases somatosensory evoked potential amplitudes to noxious stimuli in anesthetized volunteers," *Anesthesia and Analgesia*, vol. 98, no. 1, pp. 141–147, 2004.

- [33] H. Wei, J. Kong, D. Zhuang, H. Shang, and X. Yang, "Early-latency somatosensory evoked potentials elicited by electrical acupuncture after needling acupoint Ll-4," *Clinical EEG Electroencephalography*, vol. 31, no. 3, pp. 160–164, 2000.
- [34] Y. Zeng, X.-C. Liang, J.-P. Dai et al., "Electroacupuncture modulates cortical activities evoked by noxious somatosensory stimulations in human," *Brain Research*, vol. 1097, no. 1, pp. 90– 100, 2006.
- [35] D. D. Dougherty, J. Kong, M. Webb, A. A. Bonab, A. J. Fischman, and R. L. Gollub, "A combined [11C] diprenorphine PET study and fMRI study of acupuncture analgesia," *Behavioural Brain Research*, vol. 193, no. 1, pp. 63–68, 2008.
- [36] X. Lai, G. Zhang, Y. Huang et al., "A cerebral functional imaging study by positron emission tomography in healthy volunteers receiving true or sham acupuncture needling," *Neuroscience Letters*, vol. 452, no. 2, pp. 194–199, 2009.
- [37] L. Schlünzen, M. S. Vafaee, and G. E. Cold, "Acupuncture of LI-4 in anesthetized healthy humans decreases cerebral blood flow in the putamen measured with positron emission tomography," *Anesthesia and Analgesia*, vol. 104, no. 2, pp. 308–311, 2007.
- [38] L. Cabrini, L. Gioia, M. Gemma, V. Cedrati, and M. Crivellari, "Bispectral index evaluation of the sedative effect of acupuncture in healthy volunteers," *Journal of Clinical Monitoring and Computing*, vol. 20, no. 5, pp. 311–315, 2006.
- [39] S.-F. Hsu, C.-Y. Chen, M.-D. Ke, C.-H. Huang, Y.-T. Sun, and J.-G. Lin, "Variations of brain activities of acupuncture to TE5 of left hand in normal subjects," *The American Journal of Chinese Medicine*, vol. 39, no. 4, pp. 673–686, 2011.
- [40] M. S. Kim, H. D. Kim, H. D. Seo, K. Sawada, and M. Ishida, "The effect of acupuncture at PC-6 on the electroencephalogram and electrocardiogram," *American Journal of Chinese Medicine*, vol. 36, no. 3, pp. 481–491, 2008.
- [41] G. Litscher, "Effects of acupressure, manual acupuncture and laserneedle acupuncture on EEG bispectral index and spectral edge frequency in healthy volunteers," *European Journal of Anaesthesiology*, vol. 21, no. 1, pp. 13–19, 2004.
- [42] K. Streitberger, J. Steppan, C. Maier, H. Hill, J. Backs, and K. Plaschke, "Effects of verum acupuncture compared to placebo acupuncture on quantitative EEG and heart rate variability in healthy volunteers," *Journal of Alternative and Complementary Medicine*, vol. 14, no. 5, pp. 505–513, 2008.
- [43] M. S. Kim, Y. C. Cho, J. H. Moon, and S. C. Pak, "A characteristic estimation of bio-signals for electro-acupuncture stimulations in human subjects," *The American Journal of Chinese Medicine*, vol. 37, no. 3, pp. 505–517, 2009.
- [44] L. Bai, J. Tian, C. Zhong et al., "Acupuncture modulates temporal neural responses in wide brain networks: evidence from fMRI study," *Molecular Pain*, vol. 6, article 73, 2010.
- [45] H. Cheng, H. Yan, L.-J. Bai, and B.-G. Wang, "Exploration of whole brain networks modulated by acupuncture at analgesia acupoint ST36 using scale-specific wavelet correlation analysis," *Chinese Medical Journal*, vol. 126, no. 13, pp. 2459–2464, 2013.
- [46] S.-Y. Cho, G.-H. Jahng, S.-U. Park, W.-S. Jung, S.-K. Moon, and J.-M. Park, "FMRI study of effect on brain activity according to stimulation method at LIII, ST36: painful pressure and acupuncture stimulation of same acupoints," *Journal of Alternative and Complementary Medicine*, vol. 16, no. 4, pp. 489–495, 2010.
- [47] M. Dong, W. Qin, J. Sun et al., "Tempo-spatial analysis of vision-related acupoint specificity in the occipital lobe using fMRI: an ICA study," *Brain Research*, vol. 1436, pp. 34–42, 2012.

- [48] Y. Feng, L. Bai, Y. Ren et al., "Investigation of the large-scale functional brain networks modulated by acupuncture," *Magnetic Resonance Imaging*, vol. 29, no. 7, pp. 958–965, 2011.
- [49] L. Li, W. Qin, L. Bai, and J. Tian, "Exploring vision-related acupuncture point specificity with multivoxel pattern analysis," *Magnetic Resonance Imaging*, vol. 28, no. 3, pp. 380–387, 2010.
- [50] P. Liu, G. Zhou, Y. Zhang et al., "The hybrid GLM-ICA investigation on the neural mechanism of acupoint ST36: an fMRI study," *Neuroscience Letters*, vol. 479, no. 3, pp. 267–271, 2010.
- [51] B. Liu, J. Chen, J. Wang et al., "Altered small-world efficiency of brain functional networks in acupuncture at ST36: a functional MRI study," *PLoS ONE*, vol. 7, no. 6, Article ID e39342, 2012.
- [52] H. Liu, J. Xu, B. Shan et al., "Determining the precise cerebral response to acupuncture: an improved fMRI study," *PLoS ONE*, vol. 7, no. 11, Article ID e49154, 2012.
- [53] J. Liu, J. Nan, S. Xiong, G. Li, W. Qin, and J. Tian, "Additional evidence for the sustained effect of acupuncture at the vision-related acupuncture point, GB37," *Acupuncture in Medicine*, vol. 31, no. 2, pp. 185–194, 2013.
- [54] T. Murase, M. Umeda, M. Fukunaga, C. Tanaka, and A. T. Higuchi, "Deconvolution analyses with tent functions reveal delayed and long-sustained increases of BOLD signals with acupuncture stimulation," *Magnetic Resonance in Medical Sciences*, vol. 12, no. 2, pp. 121–127, 2013.
- [55] V. Napadow, J. Lee, J. Kim et al., "Brain correlates of phasic autonomic response to acupuncture stimulation: an eventrelated fMRI study," *Human Brain Mapping*, vol. 34, no. 10, pp. 2592–2606, 2013.
- [56] S. Yeo, I.-H. Choe, M. van den Noort, P. Bosch, and S. Lim, "Consecutive acupuncture stimulations lead to significantly decreased neural responses," *Journal of Alternative and Comple*mentary Medicine, vol. 16, no. 4, pp. 481–487, 2010.
- [57] Y. You, L. Bai, R. Dai et al., "Altered hub configurations within default mode network following acupuncture at ST36: a multimodal investigation combining fMRI and MEG," PLoS ONE, vol. 8, no. 5, Article ID e64509, 2013.
- [58] Y. Jiang, H. Wang, Z. Liu et al., "Manipulation of and sustained effects on the human brain induced by different modalities of acupuncture: an fMRI study," *PLoS ONE*, vol. 8, no. 6, Article ID e66815, 2013.
- [59] J. Liu, W. Qin, Q. Guo et al., "Divergent neural processes specific to the acute and sustained phases of verum and sham acupuncture," *Journal of Magnetic Resonance Imaging*, vol. 33, no. 1, pp. 33–40, 2011.
- [60] C. E. Zyloney, K. Jensen, G. Polich et al., "Imaging the functional connectivity of the periaqueductal gray during genuine and sham electroacupuncture treatment," *Molecular Pain*, vol. 6, pp. 80–91, 2010.
- [61] G. A. Ulett, S. Han, and J.-S. Han, "Electroacupuncture: mechanisms and clinical application," *Biological Psychiatry*, vol. 44, no. 2, pp. 129–138, 1998.
- [62] J. Schliessbach, E. van der Klift, L. Arendt-Nielsen, M. Curatolo, and K. Streitberger, "The effect of brief electrical and manual acupuncture stimulation on mechanical experimental pain," *Pain Medicine*, vol. 12, no. 2, pp. 268–275, 2011.
- [63] C.-L. Hsieh, "Modulation of cerebral cortex in acupuncture stimulation: a study using sympathetic skin response and somatosensory evoked potentials," *The American Journal of Chinese Medicine*, vol. 26, no. 1, pp. 1–11, 1998.

- [64] J. Kong, F. Li, R. Li et al., "A pilot study of functional magnetic resonance imaging of the brain during manual and electroacupuncture stimulation of acupuncture point (LI-4 Hegu) in normal subjects reveals differential brain activation between methods," *Journal of Alternative and Complementary Medicine*, vol. 8, no. 4, pp. 411–419, 2002.
- [65] G. Li, R. T. F. Cheung, Q.-Y. Ma, and E. S. Yang, "Visual cortical activations on fMRI upon stimulation of the vision-implicated acupoints," *NeuroReport*, vol. 14, no. 5, pp. 669–673, 2003.
- [66] W. Huang, D. Pach, V. Napadow et al., "Characterizing acupuncture stimuli using brain imaging with fMRI—a systematic review and meta-analysis of the literature," *PLoS ONE*, vol. 7, no. 4, Article ID e32960, 2012.
- [67] P. I. Bäumler, M. Simang, S. Kramer, and D. Irnich, "Acupuncture point localization varies among acupuncturists," Forschende Komplementarmedizin, vol. 19, no. 1, pp. 31–37, 2012.
- [68] E. M. Choi, F. Jiang, and J. C. Longhurst, "Point specificity in acupuncture," *Chinese Medicine*, vol. 7, article 4, 2012.
- [69] X.-G. Yang, Y. Li, X.-P. Tian, and F.-R. Liang, "Comments on selection of non-acupoints beyond meridians in studies of acupuncture and moxibustion," *Journal of Traditional Chinese Medicine*, vol. 30, no. 4, pp. 309–313, 2010.
- [70] A. R. White, J. Filshie, and T. M. Cummings, "Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding," *Complementary Therapies in Medicine*, vol. 9, no. 4, pp. 237–245, 2001.
- [71] P.-C. Chou, H.-Y. Chu, and J.-G. Lin, "Safe needling depth of acupuncture points," *Journal of Alternative and Complementary Medicine*, vol. 17, no. 3, pp. 199–206, 2011.
- [72] F. Ceccherelli, M. T. Rigoni, G. Gagliardi, and L. Ruzzante, "Comparison of superficial and deep acupuncture in the treatment of lumbar myofascial pain: a double-blind randomized controlled study," *Clinical Journal of Pain*, vol. 18, no. 3, pp. 149– 153, 2002.
- [73] J. J. Park, M. Akazawa, J. Ahn et al., "Acupuncture sensation during ultrasound guided acupuncture needling," *Acupuncture in Medicine*, vol. 29, no. 4, pp. 257–265, 2011.
- [74] J.-H. Zhang, X.-D. Cao, J. Li, W.-J. Tang, H.-Q. Liu, and X.-Y. Feng, "Neuronal specificity of needling acupoints at same meridian: a control functional magnetic resonance imaging study with electroacupuncture," *Acupuncture & Electro-Therapeutics Research*, vol. 32, no. 3-4, pp. 179–193, 2007.
- [75] J.-S. Han, "Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies," *Trends in Neurosciences*, vol. 26, no. 1, pp. 17–22, 2003.
- [76] J. Y. Wong, Manual of Neuro-Anatomical Acupuncture, vol. 1, Redwing Books, Taos, NM, USA, 1999.
- [77] S. Sakai, E. Hori, K. Umeno, N. Kitabayashi, T. Ono, and H. Nishijo, "Specific acupuncture sensation correlates with EEGs and autonomic changes in human subjects," *Autonomic Neuroscience: Basic and Clinical*, vol. 133, no. 2, pp. 158–169, 2007.
- [78] P. Marcus, "Towards a dose of acupuncture," *Acupuncture in Medicine*, vol. 12, no. 2, pp. 78–82, 1994.
- [79] G. Li, C. R. Jack Jr., and E. S. Yang, "An fMRI study of somatosensory-implicated acupuncture points in stable somatosensory stroke patients," *Journal of Magnetic Resonance Imaging*, vol. 24, no. 5, pp. 1018–1024, 2006.
- [80] C. J. Zaslawski, D. Cobbin, E. Lidums, and P. Petocz, "The impact of site specificity and needle manipulation on changes to pain pressure threshold following manual acupuncture: a

- controlled study," *Complementary Therapies in Medicine*, vol. 11, no. 1, pp. 11–21, 2003.
- [81] T.-J. Ho, J.-R. Duann, W.-C. Shen, and J.-G. Lin, "Needling sensation: Explanation of incongruent conclusion drawn from acupuncture fMRI study," *Journal of Alternative and Comple*mentary Medicine, vol. 13, no. 1, pp. 13–14, 2007.
- [82] T.-J. Ho, J.-R. Duann, C.-M. Chen et al., "Carryover effects alter fMRI statistical analysis in an acupuncture study," *American Journal of Chinese Medicine*, vol. 36, no. 1, pp. 55–70, 2008.
- [83] S. Chen, S. Guo, F. Marmori et al., "Appraisal of the Deqi concept among contemporary Chinese acupuncturists," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 538476, 7 pages, 2013.
- [84] P. R. He, Acupuncture Instrument and Acupuncture Therapy, Scientific and Technical Documentation Press, Beijing, China, 1989.
- [85] K. Cheng, J. S. Yang, Y. Y. Wang et al., "The opinion of academician X.N. Cheng of deqi: retaining needle and deqi," *China News of Traditional Chinese Medicine*, no. 4, p. 1, 2010.
- [86] J. S. Peng and J. Z. Fei, The Secret and Unique Skill of Acupuncture, Liaoning Science and Technology Publishing House, Shenyang, China, 2008.
- [87] J. S. Han and L. Terenius, "Neurochemical basis of acupuncture analgesia," *Annual Review of Pharmacology and Toxicology*, vol. 22, pp. 193–220, 1982.
- [88] K. K. K. S. Hui, T. N. Sporko, M. G. Vangel, M. Li, J. Fang, and L. Lao, "Perception of Deqi by Chinese and American acupuncturists: a pilot survey," *Chinese Medicine*, vol. 6, article 2, 2011.
- [89] K. M. Wang, S. M. Yao, Y. L. Xian, and Z. L. Hou, "A study on the receptive field of acupoints and the relationship between characteristics of needling sensation and groups of afferent fibres," *Scientia Sinica Series B*, vol. 28, no. 9, pp. 963–971, 1985.
- [90] S. H. C. Hendry, S. S. Hsiao, and M. C. Bushnell, "Somatic sensation," in *Fundamental Neuroscience*, M. J. Zigmond, F. E. Bloom, and S. C. Landis, Eds., pp. 761–789, Academic Press, San Diego, Calif, USA, 1999.
- [91] J.-E. Park, Y.-H. Ryu, Y. Liu et al., "A literature review of de qi in clinical studies," *Acupuncture in Medicine*, vol. 31, no. 2, pp. 132–142, 2013.
- [92] J. Kong, R. Gollub, T. Huang et al., "Acupuncture De Qi, from qualitative history to quantitative measurement," *Journal of Alternative and Complementary Medicine*, vol. 13, no. 10, pp. 1059–1070, 2007.
- [93] J. Sun, Y. Zhu, Y. Yang et al., "What is the de-qi-related pattern of BOLD responses? A review of acupuncture studies in fMRI," Evidence-Based Complementary and Alternative Medicine, vol. 2013, Article ID 297839, 11 pages, 2013.
- [94] G. Stux and R. Hammerschlag, Eds., *Clinical Acupuncture: Scientific Basis*, Springer, Berlin, Germany, 2001.
- [95] S. Birch, R. Hammerschlag, K. Trinh, and C. Zaslawski, "The non-specific effects of acupuncture treatment: when and how to control for them," *Clinical Acupuncture and Oriental Medicine*, vol. 3, no. 1, pp. 20–25, 2002.
- [96] D. J. Scott, C. S. Stohler, C. M. Egnatuk, H. Wang, R. A. Koeppe, and J.-K. Zubieta, "Individual differences in reward responding explain placebo-induced expectations and effects," *Neuron*, vol. 55, no. 2, pp. 325–336, 2007.
- [97] J. Kong, T. J. Kaptchuk, G. Polich et al., "Expectancy and treatment interactions: a dissociation between acupuncture analgesia and expectancy evoked placebo analgesia," *NeuroImage*, vol. 45, no. 3, pp. 940–949, 2009.

- [98] F. Beissner and C. Henke, "Methodological problems in fMRI studies on acupuncture: a critical review with special emphasis on visual and auditory cortex activations," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 607637, 7 pages, 2011.
- [99] D. A. Gusnard and M. E. Raichle, "Searching for a baseline: functional imaging and the resting human brain," *Nature Reviews Neuroscience*, vol. 2, no. 10, pp. 685–694, 2001.
- [100] C. E. L. Stark and L. R. Squire, "When zero is not zero: the problem of ambiguous baseline conditions in fMRI," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 22, pp. 12760–12765, 2001.
- [101] C. F. Beckmann, M. DeLuca, J. T. Devlin, and S. M. Smith, "Investigations into resting-state connectivity using independent component analysis," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 360, no. 1457, pp. 1001– 1013, 2005.
- [102] M. DeLuca, C. F. Beckmann, N. de Stefano, P. M. Matthews, and S. M. Smith, "fMRI resting state networks define distinct modes of long-distance interactions in the human brain," *NeuroImage*, vol. 29, no. 4, pp. 1359–1367, 2006.
- [103] V. Napadow, A. Ahn, J. Longhurst et al., "The status and future of acupuncture clinical research," *The Journal of Alternative and Complementary Medicine*, vol. 14, no. 7, pp. 861–869, 2008.
- [104] Z.-Q. Zhao, "Neural mechanism underlying acupuncture analgesia," *Progress in Neurobiology*, vol. 85, no. 4, pp. 355–375, 2008.
- [105] L. Bai, W. Qin, J. Tian et al., "Time-varied characteristics of acupuncture effects in fMRI studies," *Human Brain Mapping*, vol. 30, no. 11, pp. 3445–3460, 2009.
- [106] L. Bai, W. Qin, J. Tian et al., "Acupuncture modulates spontaneous activities in the anticorrelated resting brain networks," *Brain Research*, vol. 1279, pp. 37–49, 2009.
- [107] R. P. Dhond, C. Yeh, K. Park, N. Kettner, and V. Napadow, "Acupuncture modulates resting state connectivity in default and sensorimotor brain networks," *Pain*, vol. 136, no. 3, pp. 407– 418, 2008.
- [108] Z. Li, C. Wang, A. F. T. Mak, and D. H. K. Chow, "Effects of acupuncture on heart rate variability in normal subjects under fatigue and non-fatigue state," *European Journal of Applied Physiology*, vol. 94, no. 5-6, pp. 633–640, 2005.
- [109] L. Aftanas and S. Golosheykin, "Impact of regular meditation practice on EEG activity at rest and during evoked negative emotions," *International Journal of Neuroscience*, vol. 115, no. 6, pp. 893–909, 2005.
- [110] R. J. Barry and J. A. Rushby, "An orienting reflex perspective on anteriorisation of the P3 of the event-related potential," *Experimental Brain Research*, vol. 173, no. 3, pp. 539–545, 2006.
- [111] F. Jurysta, J.-P. Lanquart, P. Van De Borne et al., "The link between cardiac autonomic activity and sleep delta power is altered in men with sleep apnea-hypopnea syndrome," *American Journal of Physiology: Regulatory Integrative and Comparative Physiology*, vol. 291, no. 4, pp. R1165–R1171, 2006.
- [112] W. T. Zhang, Z. Jin, G. H. Cui et al., "Relations between brain network activation and analgesic effect induced by low vs. high frequency electrical acupoint stimulation in different subjects: a functional magnetic resonance imaging study," *Brain Research*, vol. 982, no. 2, pp. 168–178, 2003.
- [113] W. Miltner, R. Johnson Jr., C. Braun, and W. Larbig, "Somatosensory event-related potentials to painful and non-painful stimuli: effects of attention," *Pain*, vol. 38, no. 3, pp. 303–312, 1989.

- [114] R. Kenntner-Mabiala, Affective and attention-based modulation of somatosensory evoked potentials: the effects of emotion and attention on pain processing [Ph.D. thesis], 2006.
- [115] X. Xu, H. Shibasaki, and K. Shindo, "Effects of acupuncture on somatosensory evoked potentials: a review," *Journal of Clinical Neurophysiology*, vol. 10, no. 3, pp. 370–377, 1993.
- [116] C. M. Witt, M. Aickin, D. Cherkin et al., "Effectiveness guidance document (EGD) for Chinese medicine trials: a consensus document," *Trials*, vol. 15, pp. 169–180, 2014.
- [117] A. Meyer-Lindenberg, "From maps to mechanisms through neuroimaging of schizophrenia," *Nature*, vol. 468, no. 7321, pp. 194–202, 2010.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 457390, 7 pages http://dx.doi.org/10.1155/2015/457390

Research Article

Auricular Acupressure Can Modulate Pain Threshold

Antonietta Santoro,¹ Stefania Lucia Nori,¹ Letizia Lorusso,¹ Carmine Secondulfo,¹ Marcellino Monda,² and Andrea Viggiano¹

¹Department of Medicine and Surgery, University of Salerno, 84084 Fisciano, Salerno, Italy

Correspondence should be addressed to Stefania Lucia Nori; snori@unisa.it

Received 9 October 2014; Revised 1 January 2015; Accepted 2 January 2015

Academic Editor: Gerhard Litscher

Copyright © 2015 Antonietta Santoro et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

The objective of our study was to investigate if auriculotherapy (AT) can modulate pain threshold. In our experiments, AT consisted of placing *Vaccaria* seeds over the "fingers point" of one ear. Two groups of healthy volunteers were enrolled for the study. Each subject was asked to perform an autoalgometric test developed by our group on three occasions: before, 1 hour after, AT and 24 hours after AT. Participants of the first group received a 2-minute long session of AT, while participants of the second group received a 2-minute long session of sham treatment, consisting of a puncture/massage above the skin of the neck. The autoalgometric test consisted of applying an increasing pressure with the finger-tips and finger-backs of four fingers by the subjects themselves (i.e., eight sites were evaluated) against a round-shaped needle for two times: until a minimum pain sensation (first time, minimal test) or a maximally tolerable pain sensation (second time, maximal test). Our results showed a significant higher pain threshold in the maximal test at 24 hours after AT compared to sham treatment. This result indicates for the first time that AT can increase pain tolerability, rather than affecting the minimal pain threshold.

1. Introduction

Auriculotherapy: A Brief Overview. Auriculotherapy (AT) is a treatment method aimed at normalizing body's dysfunction through the stimulation of definite points on the surface of the ear. AT is a treatment diffused all over the world, and its patterns follow the principles of Chinese acupuncture. In Chinese traditional medicine it was believed that the stimulation of auricular acupoints could regulate self-energy balance alleviating pathological conditions and pain through restoring flow energy into the body [1, 2]. In the last decades, an increasing number of data provided scientific data corroborating the efficacy of AT. A significant contribution was given by Nogier [3], who published the somatotopic map pattern of the external ear on the bases of studies carried out by the French acupuncturist Georges Soulie de Morant [4]. Nogier argued that the ear surface is the image of an inverted fetus in the womb and proposed that points in the body would correspond precisely with

fetal representation in the auricle [5]. Nogier's map was comparable to the neurological homunculus for the human cerebral cortex by Penfield and Rasmussen [6] thus suggesting that AT could be based on the principles of reflexology rather than an energetic-based stimulation. Later in 1980, Oleson et al. published an important paper that became a milestone in ear acupuncture [7]. To assess the claim by French and Chinese ear acupuncture that there was a somatotopic organization of the body represented upon the human auricle, Oleson and colleagues examined 40 subjects. Patients were medically examined to determine areas of their body where there was musculoskeletal pain. Each patient was then draped with a sheet to hide any visible physical problems. The physician conducting the auricular diagnosis had no prior knowledge of the patient's medical condition but simply examined the patient's ear for areas of elevated skin conductivity or tenderness according to the French's and the Chinese's method of diagnosis. The concordance between the established medical diagnosis and the auricular diagnoses

²Department of Experimental Medicine, Second University of Naples, 80138 Naples, Italy

was 75.2%. These results supported the hypothesis that there was a somatotopic map of the body represented on the ear surface, but it represented definite areas not meridian lines or other energetic concepts. However, the use of AT to treat diseases raised several skepticisms, as it was unclear how AT could affect distal organs. It is now generally accepted that the stimulation of a specific region of external ear does not flow directly to distal organs, but the stimulation of a peripheral reflex on the ear surface travels along neuron fibers from the auricle to the brain, from the brain through the spinal cord, and from spinal nerves to the correspondent region of the body [8]. This complex pathway of communication along the nervous system could be responsible for reducing pain in distal organs. Therefore, AT can be considered as a clinical procedure for stimulating peripheral reflexes, which in turn activates the central brain pathways, thus inhibiting the maladaptive reflexes that contribute to pain and pathological disorders [8, 9].

Auriculotherapy in the Treatment of Pain. From the ancient traditional medicine to our days, AT has been considered an alternative therapy to treat pain. Types of AT include auricular acupuncture, electroacupuncture stimulation, and acupressure. The former two approaches include needle insertion or application of electrical stimulation to ear acupoints, while auricular acupressure utilizes very little plant seeds taped on the patient's ear lobe for acupoint stimulation. Studies using AT have strongly suggested promising effects in the pain management of several diseases, including low-back pain [10-12], hip fracture [13], dysmenorrhea [14, 15], polycystic ovary syndrome [16], and postoperative pain [17, 18]. A recent meta-analysis of randomized controlled trials, comprising studies carried out up to December 2008, suggested that AT can be effective for the treatment of various types of pain. In particular, AT reduced analgesic use in perioperative pain and decreased pain intensity in acute and chronic pain compared with control groups [19]. By evaluating larger sample size and more randomized controlled trials (up to 2013), Yeh and collaborators [20] expanded and corroborated data of the previous study and, in terms of the efficacy of the different treatment methods, showed that auricular acupressure exhibited the largest strength of evidence for pain relief, followed by auricular acupuncture. Electroacupuncture stimulation did not show significant evidence for efficacy, but few subjects were included in the analysis.

The mechanisms by which AT exerts its therapeutic effects are still unclear, but it has been demonstrated that electrical stimulation of rabbit auricular lobe in the region corresponding to the jaw and teeth in humans produced a significant decrease in behavioral reflexes and in cortical potentials evoked by electrical stimulation of the tooth pulp [21]. The opiate antagonist naloxone blocks both stimulation-produced analgesia from brain stimulation and analgesia from stimulation of acupuncture points, thus suggesting that a descending pain system able to inhibit pain perception can be associated with the endorphinergic pathway in the brain and spinal cord [22, 23]. This hypothesis has been corroborated by the findings of higher levels of endorphins after auricular stimulation [24–26]. Subsequent research has also

suggested that cortisol, serotonin, and norepinephrine also play a significant role in these neural pathways which regulate pain [27]. Interestingly, recent data show that auricular point acupressure during the treatment of low-back pain decreased serum level of some cytokines such as IL-4 and IL-10 while TNF- α , IL-2, and IL-6 were increased [28]. This observation suggests that AT can also modulate the inflammatory process in chronic low-back pain treatment. On the other hand, Chan et al. [29] found an increased concentration of the spinal antinociceptive neurotransmitter substance P in skin tissue samples derived from acupuncture points in anesthetized dogs, thus suggesting that there is a difference in the neurochemical profile between acupuncture points and control points. Concerning the molecular mechanisms involved in the nociceptive signaling pathways modulated by AT, it has been reported that AT by acupuncture-based techniques exerts its therapeutic effects causing a decrease in activity of the p38 signaling pathway in the spinal cord [30], an increase in NF- κ B activity [31, 32], and a negative regulation of nerve growth factor (NGF) [32-34].

Although increasing data indicate promising benefits of AT in pain management of several pathologies, it is still unclear whether it can affect pain threshold. Therefore, we stimulated the ear surface by using Vaccaria seeds and measured pain threshold after such AT treatment by using an autoalgometer [35]. Briefly, the autoalgometer is a pressure detector put in a small box and connected to a personal computer equipped with custom software able to take force readings (10 samples/sec). On the top of the box there is a metal needle fixed to a force transducer. People can apply a gradually increasing pressure on the needle with their finger until they feel a minimal or a maximal pain sensation and the apparatus is able to record these data, determining pain threshold [35]. To date, pain threshold can be evaluated also with other methods including cuff algometry [36], skin or oral pressure algometry [37–39], and algometry with electric stimulation [36, 37]. However, all these methods require to be performed by expert investigators and the stimulus intensity requires to be gradually increased by a tester or by an electronic device while the patient reports his/her sensation. Our method does not require a particular expertise and the subject under examination applies himself/herself the pressure on the blunt tip that evokes pain. This has the advantage that only the subject under evaluation can control the pressure applied to the tip, so that the experimenter could not physically interfere with the procedure.

2. Materials and Methods

2.1. Method. The design of the study consisted of comparing the pain threshold of a group of healthy peoples receiving an auricular acupressure treatment by using Vaccaria seeds with that of another group of healthy people (matched for sex, age, weight, and height with the previous group) receiving a "sham treatment" (acupressure on the neck). For each group, the pain threshold was evaluated with an autoalgometer (described below) on three different occasions: (1) before the treatment, (2) 1 hour after the treatment, and (3) 24 hours after the treatment. On each occasion, both a "minimal pain"

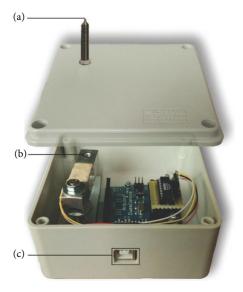


FIGURE 1: The autoalgometer. The device consisted of a round metal tip of 1 mm in diameter (a) fixed to a load-cell (b). The digital reading of the force applied to the metal tip was transmitted to a PC through a USB link (c).

threshold and a "maximal pain" threshold were evaluated as described below.

- 2.2. Participants and Setting. 16 healthy volunteers were recruited among young people attending the University of Salerno (Fisciano, Italy), and they were divided into two groups, with ages between 20 and 24 years (8 women and 8 men), weights between 50 and 93 kg, and heights between 152 and 184 cm (Table 1). All participants did not have any piercing on the point of interest for auricular acupressure.
- 2.3. Measures. Pain threshold was evaluated by using an autoalgometer. The autoalgometer is a pressure detector (pressure gage device) put in a small box of this size: 5.7 cm \times 10.4 cm \times 10.6 cm (Figure 1). In the back side of the box there is a USB port that links the device to a PC. On the top of the box there is a metal needle of 1.0 mm in diameter fixed to a force transducer (cell load). After the driver has been installed, custom software takes force readings (10 samples/sec) and saves them for subsequent analysis. Before the experiment was conducted, to evaluate the pain threshold, people were instructed to apply a gradually increasing pressure on the metal tip with their finger-tips or finger-backs until they felt a sensation that they would describe as the "minimal pain intensity that is possible to feel"; then they took off the finger from the metal tip. The software recorded the pressure applied to the metal tip all over the time of the test with a sampling frequency of 10 samples/sec; thus, the maximal value reached during the test was defined as the pain threshold. For each subject, the mean value from eight autoalgometric tests performed on eight different points was evaluated and considered for subsequent analysis; these points were the tip and the back of the second, third, fourth, and fifth fingers. After completing

TABLE 1: Physical characteristics of subjects' groups.

Subject	Control	Treated
	mean \pm S.E.	mean \pm S.E.
Age (years)	20.8 ± 0.2	21.6 ± 0.4
Weight (Kg)	66.0 ± 1.7	70.0 ± 3.0
Height (cm)	170.0 ± 2.0	169.0 ± 2.2

these 8 "minimal tests," the participants performed 8 more "maximal" tests, repeating the same procedure, as before, but increasing, this time, the pressure over the metal tip until they felt a sensation that they would describe as the "maximal intensity of pain they would tolerate." Thus, also the mean value of these 8 maximal tests was considered for subsequent analyses. In summary, each autoalgometric examination yielded two variables: a minimal pain threshold (the mean value from 8 minimal tests) and a maximal pain threshold (the mean value from 8 maximal tests).

- 2.4. Study Procedure. The first day, from 14:00 to 19:00, each one of the participants underwent an autoalgometric examination, before any treatment. After this first examination, a seed of Vaccaria was applied on the top of the scaphoid fossa of one earlobe in the region corresponding to the fingertips and finger-backs in Nogier's somatotopic map (Figure 2; treated group) or on the neck (control group). Vaccaria seed was applied by Dr. Nori, a qualified and trained physician [16, 32]. The acupoint was selected by searching the point most sensitive to a probe (tip tweezers) and tender to palpation. A gentle pressure with the thumb was applied to this seed, making a circular anticlockwise movement for two minutes with no further manipulation by the subject [40]. A second autoalgometric examination was then done after one hour, and a third examination was done after 24 hours by the application of the seed.
- 2.5. Statistical Analysis. Data are presented as means \pm S.E. For each subject the values at 1 hour and 24 hours were normalized (divided) by the values obtained before the treatment; these normalized values were considered for the statistical analysis. Statistical significant differences between groups were evaluated with the analysis of the variance (ANOVA); multiple pairwise comparisons were done with Student's t-test with Bonferroni correction for the P value.

3. Results

The mean pain threshold values obtained with the autoal-gometer for both treated and control groups are reported in Table 2. One hour after the treatment with *Vaccaria* seed there was no significant difference in the pain threshold between the two experimental groups, either in the minimal test or in the maximal test. 24 hours after the treatment, there was an increase in pain threshold in the treated group compared to the control group for the maximal test, but not for the minimal test (Figure 3). A two-way ANOVA, considering the variables treatment (with two levels: treated and controls)

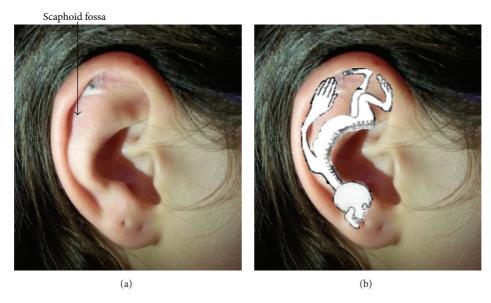


FIGURE 2: Location of *Vaccaria* seed on the surface of subject's earlobe (a). Somatotopic map of the ear showing the correspondence of fingers and fingertips with the stimulated acupoint (b).

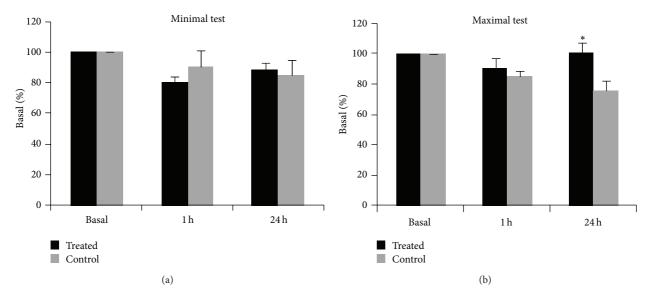


FIGURE 3: Mean \pm S.E. values for the autoalgometric tests obtained before (basal) and 1 hour and 24 hours after the auricular acupressure (treated) or the placebo treatment (control). The values are expressed in percentage compared to the basal values. The asterisk indicates a significant difference compared with the control group at the same time point (P < 0.05).

and time (with three levels: time 0, 1 hour, and 24 hours), demonstrated a significant effect for the treatment \times time interaction (the F-value with 1 and 27 degrees of freedom was 11.7; the P value was <0.01); the post hoc test demonstrated a significant difference between the treated and the control groups at 24 hours from the treatment (P < 0.05).

4. Discussion

Our study indicates that AT is able to increase pain threshold in healthy volunteers by using autoalgometry, a novel method to test pain sensation [35]. There are many techniques to evaluate pain threshold but all of them require the stimulus intensity to be gradually increased by a tester or by an electronic device while the subject reports his/her sensation [39, 41, 42]. On the contrary, our method avoids any external interference; in fact, the autoalgometry procedure permits that only the subject under evaluation can control the pressure applied to the tip, so that the experimenter could not physically interfere with the procedure. Anyway, a major limit of this procedure is that the pain threshold can be evaluated only on the fingers, because it is impractical to ask people to finely control the pressure applied against a tip with other parts of the body.

Table 2: Measures of pain thresholds obtained with the autoalgometer.

Pain threshold	Time (hours)	Control mean ± S.E.	Treated mean ± S.E.	
Minimal score	0	(g) 378 + 19	(g) 373 + 42	
	1	318 ± 11	276 ± 24	
	24	306 ± 12	317 ± 29	
Maximal score	0	436 ± 28	372 ± 52	
	1	371 ± 24	306 ± 39	
	24	331 ± 24	380 ± 51	

Our results also showed that effect of AT was significant only in the maximal test but not in the minimal pain threshold test. Because the minimal pain threshold corresponds to the minimal intensity of the physical stimulus that activates the nerve endings that are responsible for the transduction of such stimulus into a neuronal signal, it can be argued that AT does not have an effect at the level of peripheral transduction of the stimulus. On the other hand, because the perception of pain intensity, in particular the perception of the maximal tolerable intensity, involves the modulation of the transmission of pain within the central nervous system, it can be argued that AT has an effect on these mechanisms. From this point of view, our results are in agreement with the principle of reflexology since the stimulation of a precise region on the earlobe might have excited specific brain region increasing pain threshold in the distal correspondent region of the body [2, 9]. However, more functional investigations are required to address this hypothesis, that is, modern functional magnetic resonance imaging techniques. In our experimental condition, we found an increase of the pain threshold only after 24 hours of treatment. Even though we do not provide direct evidence to explain this observation, it is conceivable that higher production and storage of relevant levels of neuropeptides and the release of anti-inflammatory cytokines might be required to increase pain threshold. In fact, it has been demonstrated that the stimulation of acupoints causes the release of neuropeptide-induced antiinflammatory cytokines in long term effects [27, 28, 43, 44]. Furthermore, in our study, we used Vaccaria seeds because auricular point acupressure by botanical plant seeds is a method to deliver AT less frequently employed and not yet validated. Concerning this issue, encouraging results have been obtained by Yeh and collaborators who reported that auricular acupressure was highly accepted by patients affected by chronic low-back pain and reduced pain medication use among them [20]. The above findings were also corroborated by more recent studies indicating that auricular acupressure could reduce pain intensity and analgesic use in cancer patients [45]. In persons diagnosed with dementia, ear acupressure treatment induced beneficial effects on pain, anxiety, and depression [46]. Acupressure treatment also showed a significant improvement in menstrual distress and lowback pain during 12 months of treatment in dysmenorrheic young adult women [47]. Our results indicating that auricular

acupressure could modulate pain threshold independently from the presence of disease confirm the possibility to adopt this method in pain management. Indeed, although auricular acupressure is administered at acupoints that are the same of those of acupuncture, it is generally expected that acupressure is less efficacious than acupuncture on pain relief. This is probably due only to the more strength of evidence available for acupuncture compared to auricular acupressure [20]. In terms of the efficacy of the different treatment methods, some authors, analyzing randomized controlled trials, have recently showed that auricular acupressure exhibits the largest strength of evidence for pain relief, followed by auricular acupuncture [20]. Anyway, both auricular acupuncture and acupressure have the undeniable advantages of low cost and noninvasiveness (also compared with body acupuncture) and particularly auricular acupressure is self-managed: once seed is applied by a trained physician, it can remain in place for a long time (up to one month) and patients themselves can stimulate the acupoint by a gentle pressure with the fingers.

Vaccaria seeds were applied by us on the top of the scaphoid fossa of one earlobe; although there are differences among different schools of ear map, the finger points are at similar location either in Chinese or in Nogier's somatotopic maps; therefore our data indicating a reduction of pain perception on fingers corroborate the accuracy of the location of the hand and fingers and suggest for the first time that AT by acupressure can modulate pain threshold independently from the type and presence of disease. It is noteworthy that in our experimental condition sham therapy was administered on the neck and not on the ear; this was performed to avoid any increase of the pain threshold in other parts of the body. In fact, according to Nogier's theory [3], AT works on a microsystem basis (not meridian basis such as body acupuncture) with the ear as a self-contained microsystem that can affect corresponding areas of the whole body. Finally, despite the fact that the present investigation has been conducted on a small sample of people, the results of the statistical analysis support the ability of the proposed methodological approach to objectively verify the efficacy of acupressure treatments on pain perception. This preliminary result encourages the proposal and justifies the cost for future large scale investigations about the effects of acupressure and other nonconventional medical treatments (e.g., acupuncture or homeopathic medicaments) on pain using autoalgometry.

Abbreviations

AT: Auriculotherapy
NGF: Nerve growth factor
NF-κΒ: Nuclear factor-κΒ
II.: Interleukin

TNF- α : Tumor necrosis factor- α .

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Antonietta Santoro and Stefania Lucia Nori equally contributed to this work.

References

- [1] L. C. Huang, Auricular Medicine: A Complete Manual of Auricular Diagnosis and Treatment, Auricular International Research & Training Center, Orlando, Fla, USA, 2005.
- [2] T. Oleson, Auriculotherapy Manual: Chinese and Western Systems of Ear Acupuncture, Kidlington, UK, Churchill Livingstone, 3rd edition, 2003.
- [3] P. Nogier, *Treatise of Auriculotherapy*, Maisonneuve, Moulinsles Metz, France, 1972.
- [4] J. Helms, Acupuncture Energetics: A Clinical Approach for Physicians, Medical Acupuncture Publishers, Berkeley, Calif, USA, 1995.
- [5] P. Nogier, From Auriculotherapy to Auriculomedicine, Maisonneuve, Moulins-les Metz, France, 1983.
- [6] W. Penfield and T. Rasmussen, The Cerebral Cortex of Man, Macmillan, New York, NY, USA, 1950.
- [7] T. D. Oleson, R. J. Kroening, and D. E. Bresler, "An experimental evaluation of auricular diagnosis: the somatotopic mapping of musculoskeletal pain at ear acupuncture points," *Pain*, vol. 8, no. 2, pp. 217–229, 1980.
- [8] T. D. Oleson, "Auriculotherapy stimulation for neuro-rehabilitation," *NeuroRehabilitation*, vol. 17, no. 1, pp. 49–62, 2002.
- [9] L. Gori and F. Firenzuoli, "Ear acupuncture in European traditional medicine," *Evidence-Based Complementary and Alternative Medicine*, vol. 4, no. 1, pp. 13–16, 2007.
- [10] L. K. P. Suen, T. K. S. Wong, J. W. Y. Chung, and V. Y. B. Yip, "Auriculotherapy on low back pain in the elderly," *Complementary Therapies in Clinical Practice*, vol. 13, no. 1, pp. 63–69, 2007.
- [11] C.-H. Yeh, L.-C. Chien, Y.-C. Chiang, and L.-C. Huang, "Auricular point acupressure for chronic low back pain: a feasibility study for 1-week treatment," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 383257, 9 pages, 2012.
- [12] R. F. Hunter, S. M. McDonough, I. Bradbury et al., "Exercise and auricular acupuncture for chronic low-back pain: a feasibility randomized-controlled trial," *The Clinical Journal of Pain*, vol. 28, no. 3, pp. 259–267, 2012.
- [13] R. Barker, A. Kober, K. Hoerauf et al., "Out-of-hospital auricular acupressure in elder patients with hip fracture: a randomized double-blinded trial," *Academic Emergency Medicine*, vol. 13, no. 1, pp. 19–23, 2006.
- [14] L. C. Hwang, T. Y. Lai, H. H. Wu, J. D. Lin, and L. L. Chen, "Exploring the effect of auricular acupressure in caring dysmenorrhea," *The Journal of Health Sciences*, vol. 7, pp. 236–245, 2005.
- [15] M.-C. Wang, M.-C. Hsu, L.-W. Chien, C.-H. Kao, and C.-F. Liu, "Effects of auricular acupressure on menstrual symptoms and nitric oxide for women with primary dysmenorrhea," *Journal* of Alternative and Complementary Medicine, vol. 15, no. 3, pp. 235–242, 2009.
- [16] C. I. Aquino and S. L. Nori, "Complementary therapy in polycystic ovary syndrome," *Translational Medicine @ UniSa*, vol. 9, pp. 56–65, 2014.

- [17] D. Felhendler and B. Lisander, "Pressure on acupoints decreases postoperative pain," *Clinical Journal of Pain*, vol. 12, no. 4, pp. 326–329, 1996.
- [18] H. Wu, L. Bi, P. Shen, Z. Li, and P. Zhu, "Clinical observation and mechanism study on application of auricular-pressing pill for postoperative analgesia," *Journal of Traditional Chinese Medicine*, vol. 17, no. 1, pp. 26–31, 1997.
- [19] G. N. Asher, D. E. Jonas, R. R. Coeytaux et al., "Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials," *Journal of Alternative and Complementary Medicine*, vol. 16, no. 10, pp. 1097–1108, 2010.
- [20] C. H. Yeh, Y. C. Chiang, S. L. Hoffman et al., "Efficacy of auricular therapy for pain management: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 934670, 14 pages, 2014.
- [21] O. V. Fedoseeva, L. V. Kalyuzhnyi, and K. V. Sudakov, "New peptide mechanism of auriculo-acupuncture electro-analgesia: role of angiotensin II," *Acupuncture and Electro-Therapeutics Research*, vol. 15, no. 1, pp. 1–8, 1990.
- [22] C. Takeshige, T. Sato, T. Mera, T. Hisamitsu, and J. Fang, "Descending pain inhibitory system involved in acupuncture analgesia," *Brain Research Bulletin*, vol. 29, no. 5, pp. 617–634, 1992
- [23] A. Kumar, O. P. Tandon, A. Bhattacharya, R. K. Gupta, and D. Dhar, "Samatosensory evoked potential changes following electro-acupuncture therapy in chronic pain patients," *Anaesthesia*, vol. 50, no. 5, pp. 411–414, 1995.
- [24] B. Sjolund, L. Terenius, and M. Eriksson, "Increased cerebrospinal fluid levels of endorphins after electro-acupuncture," *Acta Physiologica Scandinavica*, vol. 100, no. 3, pp. 382–384, 1977.
- [25] H. L. Wen, W. K. K. Ho, L. Ma, G. H. Choa, and N. Ling, "The influence of electro-acupuncture on naloxone-induced morphine withdrawal: II. Elevation of immunoassayable betaendorphin activity in the brain but not the blood," *The American Journal of Chinese Medicine*, vol. 7, no. 3, pp. 237–240, 1979.
- [26] G. A. Ulett, S. Han, and J.-S. Han, "Electroacupuncture: mechanisms and clinical application," *Biological Psychiatry*, vol. 44, no. 2, pp. 129–138, 1998.
- [27] Z. Q. Zhao, "Neural mechanism underlying acupuncture analgesia," *Progress in Neurobiology*, vol. 85, no. 4, pp. 355–375, 2008.
- [28] C. H. Yeh, L. C. Chien, K. M. Albers et al., "Function of auricular point acupressure in inducing changes in inflammatory cytokines during chronic low-back pain: a pilot study," *Medical Acupuncture*, vol. 26, no. 1, pp. 31–39, 2014.
- [29] W. W. Chan, H. Weissensteiner, W. D. Rausch, K. Y. Chen, L. S. Wu, and J. H. Lin, "Comparison of substance P concentration in acupuncture points in different tissues in dogs," *The American Journal of Chinese Medicine*, vol. 26, no. 1, pp. 13–18, 1998.
- [30] K.-D. Xu, T. Liang, K. Wang, and D.-A. Tian, "Effect of preelectroacupuncture on p38 and c-Fos expression in the spinal dorsal horn of rats suffering from visceral pain," *Chinese Medical Journal*, vol. 123, no. 9, pp. 1176–1181, 2010.
- [31] H.-J. Park, H.-S. Lee, H.-J. Lee et al., "Decrease of the electroacupuncture-induced analgesic effects in nuclear factor-kappa B1 knockout mice," *Neuroscience Letters*, vol. 319, no. 3, pp. 141– 144, 2002.
- [32] S. L. Nori, M. L. Rocco, F. Florenzano, M. T. Ciotti, L. Aloe, and L. Manni, "Increased nerve growth factor signaling in sensory neurons of early diabetic rats is corrected by electroacupuncture," Evidence-Based Complementary and Alternative Medicine, vol. 2013, Article ID 652735, 15 pages, 2013.

- [33] L. Manni, M. Albanesi, M. Guaragna, S. Barbaro Paparo, and L. Aloe, "Neurotrophins and acupuncture," *Autonomic Neuroscience: Basic and Clinical*, vol. 157, no. 1-2, pp. 9–17, 2010.
- [34] L. Manni, F. Florenzano, and L. Aloe, "Electroacupuncture counteracts the development of thermal hyperalgesia and the alteration of nerve growth factor and sensory neuromodulators induced by streptozotocin in adult rats," *Diabetologia*, vol. 54, no. 7, pp. 1900–1908, 2011.
- [35] A. Viggiano, N. Zagaria, M. B. Passavanti et al., "New and low-cost auto-algometry for screening hypertension-associated hypoalgesia," *Pain Practice*, vol. 9, no. 4, pp. 260–265, 2009.
- [36] R. Polianskis, T. Graven-Nielsen, and L. Arendt-Nielsen, "Spatial and temporal aspects of deep tissue pain assessed by cuff algometry," *Pain*, vol. 100, no. 1-2, pp. 19–26, 2002.
- [37] A. A. Fischer, "Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold," *Pain*, vol. 30, no. 1, pp. 115–126, 1987.
- [38] J. A. Hogeweg, M. J. Langereis, A. T. Bernards, J. A. Faber, and P. J. Helders, "Algometry. Measuring pain threshold, method and characteristics in healthy subjects," *Scandinavian Journal of Rehabilitation Medicine*, vol. 24, no. 2, pp. 99–103, 1992.
- [39] C. H. Gibbs, K. Karpinia, J. E. Moorhead, J. W. Maruniak, and P. J. Heins, "An algometer for intraoral pain tolerance measurements," *Journal of Neuroscience Methods*, vol. 88, no. 2, pp. 135– 139, 1999.
- [40] H. MacPherson, A. White, M. Cummings, K. Jobst, K. Rose, and R. Niemtzow, "Standards for reporting interventions in controlled trials of acupuncture: the STRICTA recommendations," *Acupuncture in Medicine*, vol. 20, no. 1, pp. 22–25, 2002.
- [41] E. Kosek, J. Ekholm, and R. Nordemar, "A comparison of pressure pain thresholds in different tissues and body regions," *Scandinavian Journal of Rehabilitation Medicine*, vol. 25, no. 3, pp. 117–124, 1993.
- [42] T. Kiso, Y. Nagakura, T. Toya et al., "Neurometer measurement of current stimulus threshold in rats," *The Journal of Pharmacol*ogy and Experimental Therapeutics, vol. 297, no. 1, pp. 352–356, 2001
- [43] F. J. Zijlstra, I. van den Berg-de Lange, F. J. P. M. Huygen, and J. Klein, "Anti-inflammatory actions of acupuncture," *Mediators of Inflammation*, vol. 12, no. 2, pp. 59–69, 2003.
- [44] H.-W. Kim, D.-H. Roh, S.-Y. Yoon et al., "The anti-inflammatory effects of low- and high-frequency electroacupuncture are mediated byperipheral opioids in a mouse air pouch inflammation model," *Journal of Alternative and Complementary Medicine*, vol. 12, no. 1, pp. 39–44, 2006.
- [45] C. H. Yeh, L. C. Chien, Y. C. Chiang, D. Ren, and L. K. Suen, "Auricular point acupressure as an adjunct analgesic treatment for cancer patients: a feasibility study," *Pain Management Nursing*, 2014.
- [46] J. Rodríguez-Mansilla, M. V. González-López-Arza, E. Varela-Donoso, J. Montanero-Fernández, B. González Sánchez, and E. M. Garrido-Ardila, "The effects of ear acupressure, massage therapy and no therapy on symptoms of dementia: a randomized controlled trial," Clinical Rehabilitation, 2014.
- [47] H. M. Chen, H. H. Wang, M. H. Chiu, and H. M. Hu, "Effects of acupressure on menstrual distress and low back pain in dysmenorrheic young adult women: an experimental study," *Pain Management Nursing*, 2014.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 769546, 9 pages http://dx.doi.org/10.1155/2015/769546

Research Article

Bioceramic Resonance Effect on Meridian Channels: A Pilot Study

Ting-Kai Leung, ^{1,2,3,4} Wing P. Chan, ² Chen-Jei Tai, ^{3,5} Ting-Pin Cho, ⁶ Jen-Chang Yang, ⁷ and Po-Tsung Lee⁸

Correspondence should be addressed to Ting-Kai Leung; hk8648@tmu.edu.tw

Received 11 September 2014; Revised 16 February 2015; Accepted 16 February 2015

Academic Editor: Gerhard Litscher

Copyright © 2015 Ting-Kai Leung et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Bioceramic is a kind of material which emits nonionizing radiation and luminescence, induced by visible light. Bioceramic also facilitates the breakup of large clusters of water molecules by weakening hydrogen bonds. Hydrogen bond weakening, which allows water molecules to act in diverse ways under different conditions, is one of the key mechanisms underlying the effects of Bioceramic on biophysical and physical-chemical processes. Herein, we used sound to amplify the effect of Bioceramic and further developed an experimental device for use in humans. Thirteen patients who suffered from various chronic and acute illnesses that severely affected their sleep patterns and life quality were enrolled in a trial of Bioceramic resonance (i.e., rhythmic 100-dB sound waves with frequency set at 10 Hz) applied to the skin surface of the anterior chest. According to preliminary data, a "Propagated Sensation along Meridians" (PSM) was experienced in all Bioceramic resonance-treated patients but not in any of the nine control patients. The device was believed to enhance microcirculation through a series of biomolecular and physiological processes and to subject the specific meridian channels of Traditional Chinese Medicine (TCM) to coherent vibration. This noninvasive technique may offer an alternative to needle acupuncture and other traditional medical practices with clinical benefits.

1. Introduction

Bioceramic is material, modified from high-performance far infrared ray (FIR) emitting material, and possesses the characteristics of emitting nonionized radiation spectrum and visible light-induced luminescence [1–4]. In preclinical and clinical studies, we showed that Bioceramic-emitted light improves microcirculation, glucose control, and skin conductance at the acupuncture points of Traditional Chinese Medicine [1–4]. Photoluminescence is a special type

of luminescence. Photoluminescence is light emitted from material in response to light energy absorption and the interaction between electromagnetic radiation and matter [5–7]. Photoluminescence of Bioceramic (PLB) is the combination of Bioceramic and visible light ray [6, 7], when a visible light source (e.g., light-emitting diodes (LEDs)) without necessary additional thermal effect can propagate the effect of Bioceramic on living animal and human being (Figure 1). As far as we know, our publications are the first to report the phenomenon of photoluminescence of Bioceramic

¹Department of Radiology, Taipei Hospital, Ministry of Health and Welfare, No. 127 Su Yuan Road, Hsinchuang, New Taipei City 242-13, Taiwan

²Department of Radiology, Wan Fang Hospital, Taipei Medical University, No. 111, Sec. 3, Xinglong Road, Taipei 116, Taiwan

³ Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, No. 250, Wu-Hsing Street, Taipei 110, Taiwan

⁴Department of Radiology, Shanghai East Hospital, 1800 Yuntai Road, Pudong New Area, Shanghai 200123, China

⁵Department of Traditional Chinese Medicine, Taipei Medical University Hospital, No. 252, Wu Hsing Street, Taipei 110, Taiwan

⁶Metal Industries Research & Development Centre, 1001 Kaonan Highway, Kaohsiung 811, Taiwan

⁷School of Dentistry, College of Oral Medicine, Taipei Medical University, Taipei 110, Taiwan

⁸Department of Photonics and Institute of Electro-Optical Engineering, National Chiao Tung University, 1001 Ta Hsueh Road, Hsinchu 300, Taiwan

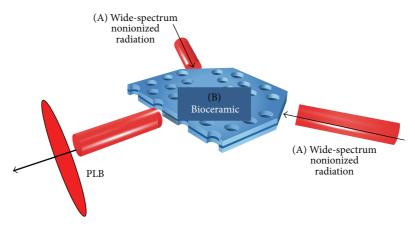


FIGURE 1: Conceptual picture of photoluminescence (PL) emission from the Bioceramic material (B) in response to excitation by visible light (A).

(PLB) material emission, which can produce its effect at long distance via visible light rays [1-4]. PLB emission can enhance microcirculation and "Propagated Sensation along Meridians" (PSM) of acupuncture as described previously but in less than 20% of cases [4]. To examine the possible health promotion effects of Bioceramic technology, we reviewed the publications of Professor Wei-Kung Wang and his colleagues. Wang et al. stated that each pulse wave in the arterial system can be broken down into many harmonic frequencies based on an individual's heart beat frequencies. Based on Wang's deduction, the source of the twelve meridian channels is the individual's heart beat and harmonic frequencies. Acupuncture points and meridian channels are thought to be closely related to the microcirculation [7-10] (explained below). Besides visible light, we also using sound frequency to construct Bioceramic resonance device. According to our new observations and the so far unpublished data, the sound waves have long-distance effects because they can move long distances and also bend around corners.

To choose the suitable frequency for our experiment, we reviewed previous articles and studies on the effects of different frequencies. A study by Rasmussen found that frequencies from 1 to 20 Hz are the most effective [11]. We selected 10 Hz (mean value of 1 to 20 Hz) as the first frequency setting to test our Bioceramic resonance device for this study.

In this study, we describe the newest design of our Bioceramic device and the effect of resonance on the meridian channels of the human body and discuss the possible applications.

2. Materials and Methods

The Bioceramic powder used in this study (obtained from Bioenergy Laboratories, Bioenergy Development Ltd., Taoyuan, Taiwan) was composed of microsized particles containing several ingredients, mainly elemental components [1–4]. The average emissivity of the ceramic powder was 0.98 at wavelengths of $6\sim14\,\mu\mathrm{m}$ (determined using a CI SR5000 spectroradiometer), indicating an extremely high far infrared ray emission rate (Figure 1). This ceramic powder

can induce many physical, chemical, and biological effects at room temperature without the need for direct contact [1–4].

2.1. Photoluminescent Bioceramic (PLB) Material and Bioceramic Irradiation Combined with Sound Waves of Frequency (10 Hz). Photoluminescent substances are materials that absorb light energy and then release that energy in the form of light. Photoluminescence obeys the laws governing the interaction between electromagnetic (EM) radiation and matter. Bioceramic material absorbs a portion of the EM spectrum (including near, middle, and far infrared wavelengths) and emits lower energy wavelengths, providing for our purpose a useable visible light source. In the present study, these light sources were visible light-emitting diodes (LEDs), emitting light energy in the range of wavelengths between 480 nm and 780 nm. The level of illumination was strictly controlled at 500 lux, thus avoiding thermal effects on the skin of the participants. In addition, a rhythmic 100dB sound with frequency 10 Hz was projected through a Bioceramic membrane (consisting of 10% Bioceramic material mixed with silicone rubber) onto the skin surface of the anterior chest wall to achieve resonance with the tissues of the whole human body. The concept of emission from a Photoluminescent Bioceramic (PLB) material acting in concert with rhythmic sound waves is shown in Figure 2.

2.1.1. Experimental Methods to Test the Effect of the Bioceramic Device on Hydrogen Bonding. Procedures used to determine the key effect and mechanism of the Bioceramic device are as follows.

(a) Fourier Transform Infrared Spectroscopy (FT-IR). FT-IR is one of the most precise methods used to study H-bonds. Control double distilled water (DDW) and Bioceramic-irradiated DDW treated for 1h were prepared for infrared measurement. Aliquots were sealed between a pair of CaF₂ windows (Beckman FH-01) with a thin Teflon spacer approximately 150 $\mu \rm m$ in thickness. The infrared spectrum was recorded at 25°C at a resolution of 2 cm $^{-1}$ using a Nicolet Magna 550 spectrometer equipped with a dTGS detector. An

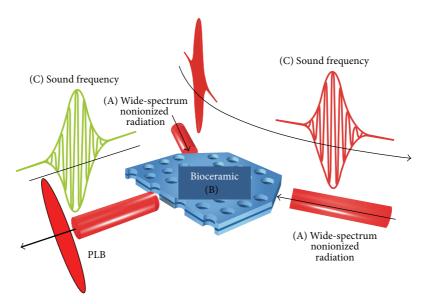


FIGURE 2: The combination of PL emission and acoustic radiation (sound waves) (C).

average of 32 scans were carried out and merged for each sample. (Detection of an effect on hydrogen bonding requires a large number of scans and high resolution of 2 cm⁻¹.) The data were then calculated from the absorption spectrum in the far infrared ray region (3400 cm⁻¹).

(b) Coating of the Bioceramic by Sputter Deposition. Bioceramic with purity of 100% was sputtered onto the target quartz surface. Sputtering was performed using a closed field unbalanced magnetron sputtering system supported by four vertical cathodes at intervals of 90° (developed by Metal Industries Research & Development Centre, Kaohsiung, Taiwan). The target dimensions (quartz) were $300 \text{ mm} \times 100 \text{ mm}$ × 10 mm. The sputtering current was 1 Amp. (370 Watt., 370 Volt.). The power was supplied by an ENI RPG-100 pulse generator with DC pulse, frequency of 50 kHz, and pulse width of 1056 ns. The Argon (Ar) flow rate was maintained at 30 standard cubic centimeters per minute (sccm) with working pressure at 3×10^{-3} Torr. The coating architecture was single layer and no buffer layer. The surface coating thickness was 22 nm for optimal outlook translucency. The light pump used the photoluminescence spectra (PL Spectrum), with detection band of $<1 \mu m$. After absorbing visible light, the Bioceramic material emitted a slightly lower energy light signal. The three different photon energy sources included (1) a 488-nm visible light laser (blue), (2) 532-nm visible light laser (green), and (3) 633-nm visible light laser (red). The light was projected onto the translucent quartz surface coated with Bioceramic material.

2.1.2. Construction of the Bioceramic Resonance Device and Trial of the Device in Humans

Candidates. Thirteen candidates (six females and seven males) consented to participate in this clinical trial. All were adults with different health issues. The study protocol was

approved by the Human Subjects Committee at the Taipei Hospital (Ministry of Health and Welfare), New Taipei City, Taiwan (approval number: TH-IR-0014-0001). The patients all suffered from insomnia in conjunction with other symptoms, such as dyspepsia, migraine, anxiety, low back pain with radiculopathy, poststroke paralysis of the extremities, and leg swelling due to deep vein thrombosis. As aforementioned, since sound can enhance the effect of the Bioceramic device (Figure 2), we developed instrument of Bioceramic Resonance (BR) for human trials, capable of producing a sound frequency resonance effect. The vibration source was at about 50 cm from the skin surface of anterior chest wall and the average sound level was 100 dB. The candidates received Bioceramic resonance with rhythmic sound frequency set at 10 Hz. Clinical observation and subjective descriptions (such as time and duration of PSM experiences over the 1hour experimental period) were recorded at posttreatment interviews to assess possible changes in sensation throughout

On the other hand, nine candidates with insomnia received the usual light and 10-Hz sound frequency but without Bioceramic resonance.

3. Results

3.1. Bioceramic Irradiation Affects Hydrogen Bonding. Absorbance of light in the far infrared ray (FIR) region (3400 cm⁻¹) by Bioceramic-irradiated DDW was significantly below that of control DDW. This result indicates a hydrogen bond weakening effect of Bioceramic irradiation on DDW (Figure 3). The projection of photons with wavelengths 488 (blue; Figures 4(a) and 4(b)), 532-nm (green) (Figures 5(a) and 5(b)), and 633 nm (red; Figures 6(a) and 6(b)) across the translucent quartz coated with Bioceramic material resulted in a definite pre- to postexcitation difference in the energy of the emitted photoluminescence signal.

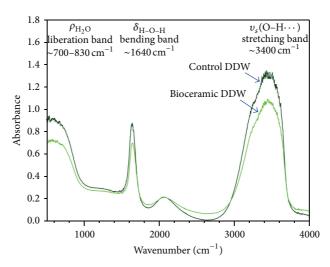


FIGURE 3: Area under the absorbance curve of Bioceramic-irradiated DDW in the FIR region (3400 cm⁻¹) was significantly decreased, compared to that of the control nonirradiated DDW.

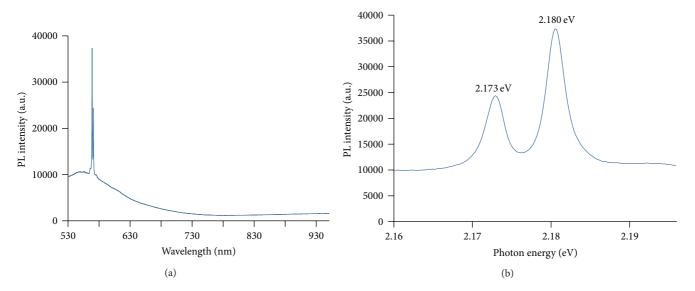


FIGURE 4: The c-FIR material coated quartz surface absorbed visible laser light (488 nm) and emitted slightly lower energy light signals. The decrease from input to output photon energy (in eV) was 2.541 to 2.173 and 2.180, respectively.

3.2. Energies of the Emitted Photons. The energy differences between the peaks of photon emission after Bioceramic material absorption of the three different wavelengths of the visible light were 0.361 eV and 0.368 eV below that of the original excitatory light sources (Table 1; Figure 7).

3.3. Clinical Observations Relevant to Bioceramic Resonance. The thirteen individuals exposed to Bioceramic irradiation with 10-Hz rhythmic sound vibrations (but not the nine controls exposed to the usual light and 10-Hz rhythmic sounds, without Bioceramic irradiation) reported experiencing a "Propagated Sensation along Meridians" (PSM). PSM as described in our previous study was reported in response to using PLB on acupuncture points, but the proportion of participants experiencing PSM was lower than 20% [9].

Bioceramic treatment elicited PSM on the skin's surface in lines that correspond to meridian lines on the skin's surface or the twelve main meridian channels according to Traditional Chinese Medicine (TCM) (Table 2; Figures 8(a) and 8(b)) [1, 9].

4. Discussion

4.1. Reasons for the Effect of Bioceramic Irradiation on Water Properties. We investigated the weakening of the hydrogen bonds of water after Bioceramic irradiation and the resulting effects on physical, biological, and medical properties of water. Fourier transform infrared spectroscopy (FT-IR) was used herein to explore the Bioceramic irradiation-induced

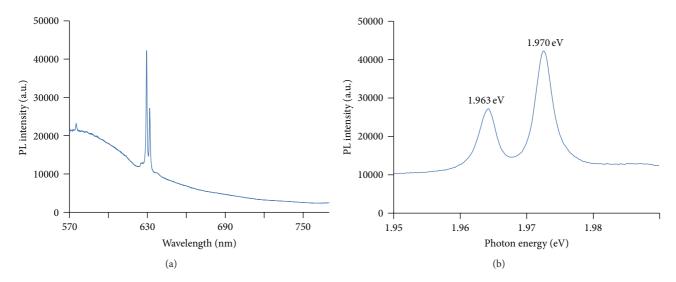


FIGURE 5: After absorbing visible laser light (532 nm), the coated surface emitted slightly lower energy light signals. The decrease from input to output photon energy (in eV) was 2.331 to 1.963 and 1.970, respectively.

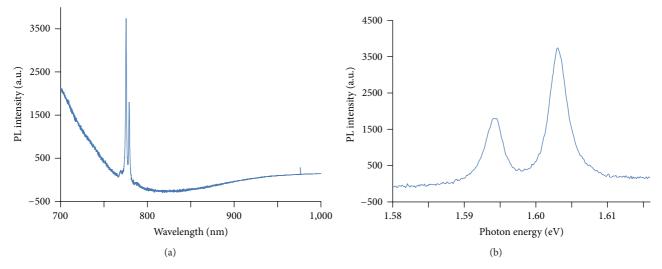


FIGURE 6: After absorbing visible laser light (633 nm), the coated surface emitted slightly lower energy light signals. The decrease from input to output photon energy (in eV) was 1.960 to 1.592 and 1.599, respectively.

change in hydrogen bonding; in addition, capillary viscometers, gas chromatographs (GC), differential scanning calorimetry (DSC), contact angle analysis, Franz cells, highperformance liquid chromatography (HPLC), and capillary electrophoresis analysis have been used to evaluate other physical characteristics, such as viscosity, volatility, temperature of water crystallization, surface tension, diffusion, solubility of solid particles, and changes in the pH of acetic acid [1-4]. The Bioceramic irradiation caused the decrease in viscosity and surface tension (contact angles) of water, but the increase in the solubility of solid particles in water, temperature of water crystallization, and acidity of acetic acid. The weakening of water hydrogen bonds corresponds to the increase in microcirculation described in our previous reports. At the three excitation wavelengths, the energy differences between the pumping photons and the emitted

photons were 0.361 eV (corresponding to wavenumber at 2910 cm⁻¹) (Figure 3 and Table 1) and 0.368 eV (corresponding to wavenumber at 2960 cm⁻¹; Figure 3 and Table 1), which lie within the absorption spectrum of FT-IR. The energy of this characteristic irradiation might lead to the break-up of large water clusters in DDW (hydrogen bond strength 5–30 kJ/mole), reduction in the volume charge density, and formation of effective dipoles that could lead to a decrease in absorbance signals [12–14].

Water possesses important properties required for lifegiving processes [15, 16]. Three or four strong hydrogen bonds are needed to form clusters of water molecules, and it is this feature of hydrogen bonding that is responsible for the special properties of water. Weakening of hydrogen bonds allows water to act in diverse ways under different conditions [17]. Hydrogen bond weakening is the basis for the biophysical

	PL energy	First excited photon energy (E1)	Second excited photon energy (<i>E</i> 2)	$\Delta E1 \text{ (eV)} = E - E1$	$\Delta E2 \text{ (eV)} = E - E2$
488 nm laser	2.541 eV	2.180 eV	2.173 eV	0.361 eV	0.368 eV
532 nm laser	2.331 eV	1.970 eV	1.963 eV	0.361 eV	0.368 eV
633 nm laser	1.960 eV	1.599 eV	1.592 eV	0.361 eV	0.368 eV

Table 1: Calculation of energy differences between the absorbed and emitted infrared photons.

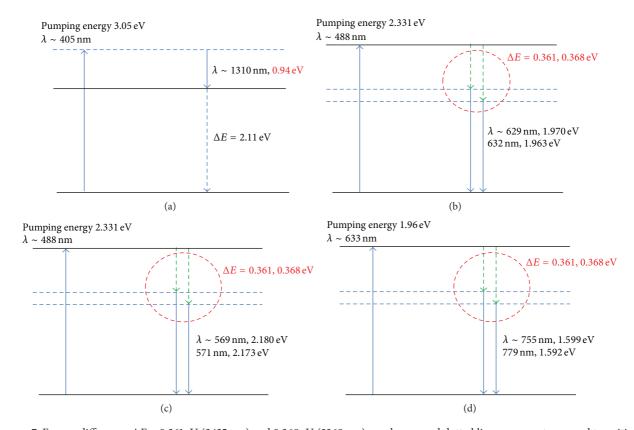


Figure 7: Energy difference: $\Delta E = 0.361\,\mathrm{eV}$ (3435 nm) and 0.368 eV (3369 nm) are shown, and dotted lines represent assumed transitions.

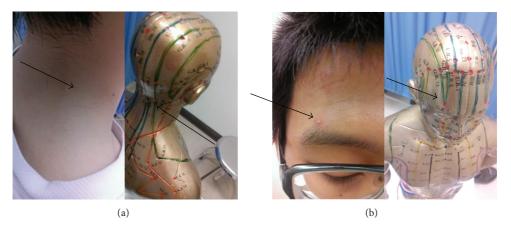


FIGURE 8: Subjective description of PSM by a candidate (arrows on left sides) who virtually traced the GB, one of the twelve main meridian channels of TCM (arrows on right sides).

Table 2: Candidate characteristics and clinical observations after Bioceramic resonance treatment.

Chief complaints	Sex	Age	Location(s) of PSM	Duration of PSM after Bioceramic resonance treatment	Observations during the one-hour period following treatment
Dyspepsia	Yangming Stomach Channel at bilateral sides of the throat, chest, abdomen, and lower extremities		Within one minute	No further change	
Poor appetite	Yangming Stomach Channel appetite F 32 at bilateral sides of the throat, chest, and abdomen		About five minutes	No further change	
Posttraumatic head injury right side), complicated by F 55 ntermittent migraine Shaoyang Gallbladder Channel at right side of head, posterior neck, and upper lateral chest		About two minutes	No further change		
Insomnia	М	61	Jueyin Pericardium Channel at bilateral ventral sides of hands and arms	About ten minutes	No further change
Taiyang Bladder Channel and Shaoyang Gallbladder		About five minutes	No further change		
Migraine	M	62	Shaoyang Sanjiao Channel of the left upper arm	About six minutes	No further change
Anxiety and insomnia	М	36	Shaoyang Sanjiao Channel at the bilateral sides of lateral scalp of head	About 10 minutes	No further change
Benign facial tremor, left	F	52	Shaoyang Gallbladder Channel of the bilateral upper arms	About 10 minutes	No further change
Low back pain with bilateral posterior leg radiculopathy	M	45	Taiyang Bladder Channel of the buttock and bilateral thighs and legs	About 5 minutes	No further change
Old hemorrhagic stroke with facial weakness and paralysis of the right upper and lower arm	М	60	Shaoyang Gallbladder Channel of the right posterior neck	About 20 minutes	No further change
Insomnia	F	40	Taiyang Bladder Channel of the occipital head	About 10 minutes	No further change
Insomnia	F	45	Shaoyang Sanjiao Channel of the right hand to arm	About 5 minutes	No further change
Deep vein thrombosis of the bilateral lower legs Posttraumatic injury of the right great toe with poor wound healing		49	Jueyin Liver Channel at the dorsomedial side of the right foot	About 15 minutes	No further change

and chemical effects of Bioceramic irradiation reported in our previous publications [1-4].

4.2. Lessons from Human Trial Studies That Can Be Applied to Therapy. Since all participants who received Bioceramic Resonance experienced "Propagated Sensation along Meridians" (PSM), our results seem to suggest that Bioceramic irradiation stimulates the twelve main meridian channels according to Traditional Chinese Medicine (TCM) (Table 2 and Figures 8(a) and 8(b)) [1, 4]. PSM becomes apparent

from one to about twenty minutes after Bioceramic Resonance is initiated and as it moves along the meridians of an acupuncture point. PSM is propagated along the meridian channels during acupuncture by two assumed mechanisms: (1) neuromodulation [18–20] and (2) histamine release due to degranulation of mast cells, which leads to capillary dilation, increase in blood perfusion, and interstitial fluid [20]. Although the existence of meridian channels as described in the ancient Chinese medical textbook (The Yellow Emperor's Inner Classic) published over 2500 years ago is scientifically

unproven, our Bioceramic resonance device will allow the gathering of more concrete and objective evidence of PSM. To explain the PSM response to Bioceramic irradiation, we reviewed the past literature [8, 9] on the origin of meridian channels. Previous studies used Fourier transform analysis to decompose the frequency range of signals (such as pulsatile pressure due to heartbeat and rate of radial or femoral artery blood flow that change over time) into eleven harmonic sound frequencies.

The equation is as shown below:

$$P(t) = \sum_{n=1}^{11} (b_n \sin(nNt))$$
 (1)

(*P*: pressure; *t*: time; *n*: number of harmonic sound frequencies; b_n : pressure of the number "n"; *N*: original heartbeat frequency; P(t): pressure change in time; $\sum_{n=1}^{11}$: adding from 1st to 11th harmonic sound frequency; nN: frequency of the number "n").

Based on Wang's deduction, the energy of a twelfth frequency is the sum of the energies of the eleven harmonic frequencies. According to series of publications by Wang et al., the harmonic rhythmic sound frequencies of the heartbeat are the main frequency components of the propagated pressure wave and correspond to the twelve meridian channels of TCM. Acupuncture points and meridian channels are thought to be closely related to microcirculation [7-10]. On the other hand, rhythmic low frequency sound waves are characterized by longer wavelengths, weaker attenuation, and greater depth of penetration than high frequency sound waves. It was reported that rhythmic low frequency sound travels more efficiently through human tissues. While acupuncture is being administered, a rhythmic sound of 2-15 Hz could produce vibrations that resonate with the vibrations of human tissues or organs [21]. In other words, meridian channels have different harmonic frequencies all based on the individual's heartbeat frequency. Another hypothesis by Zhang et al. suggests that meridian channels course through subcutaneous tissues with fluid flowing within them [1, 22], and Bioceramic irradiation weakens hydrogen bond strength in the fluid thereby enhancing microcirculation. To answer the question of why sensation is propagated along meridians, we propose that rhythmic sound waves (10 Hz) and their different harmonic frequencies produce vibrations that resonate with the vibrations of the meridian channels of TCM and that the combined effects of Bioceramic irradiation and photoluminescence on hydrogen bond weakening enhance microcirculation, which resonate with harmonic frequencies of the individual's heartbeat. We suggest that tissues of interstitial fluid channels that fail to resonate with heartbeat harmonic frequencies will be enforced by Bioceramic effect and may enhance mast cell degranulation and histamine release along the specific meridian channels. It is further causing capillary dilation, increased blood and interstitial fluid circulation, and simultaneous continuous nerve signals to regulate the nervous system or neuromodulation. We propose that this train of nerve impulses is the basis for PSM that is provoked by Bioceramic resonance. Even though the above hypothesis needs further elaboration,

rhythmic sound frequency resonance begins a new era in TCM and its therapeutic concepts. The Bioceramic resonance technique faces two major challenges to its acceptance by mainstream medical science. First, the pathways of meridian channels must be demonstrated anatomically and second the correspondence of different meridian channels to specific vibration frequencies must be demonstrated anatomically [22]. We hope that more support, constructive criticism, and comments will be forthcoming to facilitate more successful future studies.

5. Conclusion

The Bioceramic resonance device combines nonionizing radiation with rhythmic sound frequencies (10 Hz) to provoke hydrogen bond weakening and facilitate microcirculation improvement. This combination resulted in effective coherent vibrations within human tissue that elicited PSM along TCM meridian lines in our thirteen candidates. The noninvasive Bioceramic resonance technique is potentially an alternative method to other Traditional Chinese methods (such as needle acupuncture or moxibustion). More experiments should be performed in the expectation that this method will improve treatment of many illnesses.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This study was supported by a grant from the Taipei Hospital, Ministry of Health and Welfare (Project no. 201403). The authors are grateful for the assistance of Dr. Mimmo Gasberri, Mr. Meng-Lin Li, and Mr. Ping-Tai Lin.

- [1] C. W. Chen, C. J. Tai, C. S. Choy et al., "Wave-induced flow in meridians demonstrated using photoluminescent BIO-CERAMIC material on acupuncture points," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 739293, 11 pages, 2013.
- [2] S. L. Lin, C. S. Choy, W. P. Chan, and T. K. Leung, "Photoluminescence of BIOCERAMIC materials (PLB) as a complementary and alternative therapy for diabetes," *Journal of Diabetes and Metabolism*, vol. 4, no. 10, pp. 321–325, 2013.
- [3] S. L. Lin, W. P. Chan, C. S. Choy, and T. K. Leung, "Translating laboratory research of BIOCERAMIC material, application on computer mouse and bracelet, to ameliorate computer work-related musculoskeletal disorders," *Translational Medicine*, vol. 4, article 122, 2013.
- [4] T. K. Leung, M. Gasbarri, J. T. Chen, and W. P. Chan, "Application of Photoluminescent BIOCERAMIC Material (PLB) for differentchronic illnesses by selecting 'trigger points' and 'propagated sensation along meridians' (PSM) phenomenon," Chinese Journal of Integrative Medicine. In press.

- [5] S. Kwee and P. Raskmark, "Changes in cell proliferation due to environmental non-ionizing radiation 1. ELF electromagnetic fields," *Bioelectrochemistry and Bioenergetics*, vol. 36, no. 2, pp. 109–114, 1995.
- [6] G. D. Gilliland, "Photoluminescence spectroscopy of crystalline semiconductors," *Materials Science and Engineering: R: Reports*, vol. 18, no. 3–6, pp. 99–399, 1977.
- [7] W. K. Wang, T. L. Hsu, H. C. Chang, and Y. Y. Wang, "Effect of acupuncture at Tai-Tsih (K-3) on the pulse spectrum," *American Journal of Chinese Medicine*, vol. 24, pp. 305–313, 1996.
- [8] Y. Y. L. Wang, T. L. Hsu, M. Y. Jan, and W. K. Wang, "Review: theory and applications of the harmonic analysis of arterial pressure pulse waves," *Journal of Medical and Biolology Engineering*, vol. 3, pp. 125–131, 2010.
- [9] Y. Y. L. Wang, W. K. Sze, J. G. Bau et al., "The ventricular-arterial coupling system can be analyzed by the eigenwave modes of the whole arterial system," *Applied Physics Letter*, vol. 92, Article ID 153901, 2008.
- [10] Y. Y. Lin Wang, M. Y. Jan, C. S. Shyu, C. A. Chiang, and W. K. Wang, "The natural frequencies of the arterial system and their relation to the heart rate," *IEEE Transactions on Biomedical Engineering*, vol. 51, no. 1, pp. 193–195, 2004.
- [11] G. Rasmussen, "Human body vibration exposure and its measurement," *Journal of the Acoustical Society of America*, vol. 73, p. 2229, 1983.
- [12] H. Yu, S. Lycett, C. Roberts, and R. Murray, "Time resolved study of self-assembled InAs quantum dots," *Applied Physics Letter*, vol. 69, pp. 4087–4089, 1996.
- [13] L. Turi, W. S. Sheu, and P. J. Rossky, "Characterization of excess electrons in water-cluster anions by quantum simulations," *Science*, vol. 309, pp. 914–917, 2005.
- [14] X. J. Wang, B. Wang, L. Wang et al., "Extraordinary infrared photoluminescence efficiency of Er_{0.1}Yb_{1.9}SiO₅ films on SiO₂/Si substrates," *Applied Physics Letters*, vol. 98, Article ID 071903, 2011.
- [15] M. F. Chaplin, "A proposal for the structuring of water," *Biophysical Chemistry*, vol. 83, no. 3, pp. 211–221, 2000.
- [16] C. J. Fecko, J. J. Loparo, S. T. Roberts, and A. Tokmakoff, "A local hydrogen bonding dynamics and collective reorganization in water: ultrafast infrared spectroscopy of HOD/D(2)O," *The Journal of Chemical Physics*, vol. 122, Article ID 54506, 2005.
- [17] V. Buch, "Molecular structure and OH-stretch spectra of liquid water surface," *Journal of Physical Chemistry B*, vol. 109, pp. 17771–17774, 2005.
- [18] W.-B. Zhang, Y. Zhao, and F. Kjell, "Understanding propagated sensation along meridians by volume transmission in peripheral tissue," *Chinese Journal of Integrative Medicine*, vol. 19, no. 5, pp. 330–339, 2013.
- [19] M. S. Lee, Y. C. Kim, S. R. Moon, B. C. Shin, and D. M. Jeong, "Hydrodynamic analysis of waveforms induced by vibrational stimuli at meridian and non-meridian points," *The American Journal of Chinese Medicine*, vol. 32, no. 6, pp. 977–984, 2004.
- [20] S. Lo, X. Geng, and D. Gann, "Evidence for the existence of stable-water-clusters at room temperature and normal pressure," *Physics Letter A*, vol. 373, no. 42, pp. 3872–3876, 2009.
- [21] X. M. Wang, "Analysis on the mechanism of acupuncture rhythmic sound energy in treatment of diseases," *Zhongguo Zhen Jiu*, vol. 29, pp. 223–226, 2009.
- [22] W.-B. Zhang, Y.-Y. Tian, H. Li et al., "A discovery of low hydraulic resistance channel along meridians," *Journal of Acupuncture & Meridian Studies*, vol. 1, no. 1, pp. 20–28, 2008.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 273909, 7 pages http://dx.doi.org/10.1155/2015/273909

Research Article

Effects of Jae-Seng Acupuncture Treatment on the Improvement of Nasolabial Folds and Eye Wrinkles

Jin Hyong Cho,^{1,2} Ho Jin Lee,¹ Kyu Jin Chung,¹ Byung Chun Park,¹ Mun Seog Chang,¹ and Seong Kyu Park¹

¹Department of Prescriptionology, College of Korean Medicine, Kyung Hee University, Seoul 130-701, Republic of Korea ²O-Hang Center, Kwangdong Hospital of Traditional Korean Medicine, 612 Bongeunsa-ro, Gangnam-gu, Seoul 135-881, Republic of Korea

Correspondence should be addressed to Mun Seog Chang; mschang@khu.ac.kr and Seong Kyu Park; comskp@khu.ac.kr

Received 10 October 2014; Revised 19 January 2015; Accepted 19 January 2015

Academic Editor: Lu Wang

Copyright © 2015 Jin Hyong Cho et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The microneedle therapy system (MTS), a mechanical method involving making minute multiple holes in the skin, reportedly improves skin condition, such as by reducing flushing and melanin. A newly attempted bloodletting therapy, Jae-Seng Acupuncture, has several advantages over traditional mechanical punching methods because it allows the practitioner to regulate the depth and direction of needle stimulations and to choose whether to stimulate the muscle layers. This study was conducted to determine the efficacy of Jae-Seng Acupuncture in the treatment of nasolabial folds and eye wrinkles. The nasolabial folds and eye wrinkles of 107 patients ranging in age from their 20s to their 70s were subjected to DermaVision, a digital skin image analyzer, before the treatment and one to six months after treatment. Additionally, stimulation of the meridians, such as Taeyang, Tongjaryo, Chongmyong, Sungup, Sabaek, Yonghyang, Chichang, Taeyong, was performed to improve the function of the stomach, large intestine. Analyses of the images indicate that Jae-Seng Acupuncture improved nasolabial folds and eye wrinkles, suggesting that this technique is a safe and effective method for the improvement of facial skin conditions.

1. Introduction

As the standard of living has been increasing, the demand for beauty and healthy skin has been growing within the medical area and can affect social activities. Therefore, studies on the maintenance of homeostasis and prevention of skin aging have been conducted, and alternative methods such as traditional acupuncture therapy have been explored [1].

The microneedle therapy system (MTS) is a representative approach for improving skin parameters such as wrinkles, elasticity, moisture ratio, and smoothness [2]. MTS may induce collagen synthesis by using needling to make microwounds that can stimulate fibroblast, dermal neovascularization with no change in pigmentation as observed in percutaneous collagen induction therapy [3]. Additionally, for incisional repair, platelet-derived growth factor (PDGF-BB homodimer) appears to enhance the inflammatory phase of wound healing to induce intracellular procollagen type

I (PC-I) synthesis indirectly, whereas transforming growth factor-beta 1 (TGF-beta 1) enhances PC-I synthesis directly, accounting for their different durations of activities within healing wounds [4].

Building on this technique, Jae-Seng Acupuncture which means acupuncture for cell regeneration in Korean is applied by hand to make 1.0 to 3.0 mm incisions in the dermis of the skin to improve blood circulation and stimulate collagen and elastin secretion. In addition to yielding the positive effects of MTS, Jae-Seng Acupuncture is applicable to various facial regions that are difficult to access using instruments, such as the rounded side of noses and the area surrounding the eyes. Stimulating face meridians followed by Jae-Seng Acupuncture treatment improved elasticity and reduced number of pores, flushing and wrinkles of the face. This study was conducted to determine the efficacy of Jae-Seng Acupuncture in the treatment of nasolabial folds (NLs) and eye wrinkles (EWs).

Age in years			Validity		
Age III years		Frequency	Percentage	Valid percentage	Accumulative percentage
20s		5	4.7	4.7	4.7
30s		28	26.2	26.2	30.8
40s		36	33.6	33.6	64.5
50s		28	26.2	26.2	90.7
60s		6	5.6	5.6	96.3
70s		4	3.7	3.7	100.0
	Total	107	100.0	100.0	_

TABLE 1: Comparison by age.

2. Materials and Methods

Emla cream 5% (lidocaine 25 mg/g, prilocaine 25 mg/g; Astrazeneca Korea, Seoul, Republic of Korea) was used as an anesthetic. A 30 G \times 1/2 needle manufactured by the International Hongchim Association connected to an 80 mm folder was used for Jae-Seng Acupuncture treatment.

2.1. Image Measurement and Analysis. To examine the effects of Jae-Seng Acupuncture treatment on NLs and EWs, 107 patients ranging in age from their 20s to their 70s (Table 1) were examined one to six months after the treatment. To relieve pain, the anesthetic cream was applied on the face for 30 min. DermaVision (OptoBioMed, Wonju, Korea) was used to analyze images of wrinkles, as reported previously [5, 6]. For EW treatment, the needle was injected repeatedly to the dermis at a depth of 1-2 mm in the same direction as the wrinkles to stimulate the orbicularis oculi muscle, and the temporalis muscle was stimulated by injecting the needle in a parallel direction with the skin layer at a 2 cm depth. Stimulation of the meridians such as Taeyang, Tongjaryo, Chongmyong, Sungup was performed by injecting the needle at a 2 to 3 mm depth in the vertical direction for corresponding points. For NL treatment, the needle was injected repeatedly to the dermis at a 2 to 3 mm depth in the vertical direction of the NLs, as shown in Figure 1. Next, muscles such as the levator labii superioris alaeque nasi (LLSAN), levator labii superioris (LLS), zygomaticus major, and zygomaticus minor were stimulated by injecting the needle at a 1 to 1.5 cm depth in the vertical direction. In addition, stimulation of the meridians such as Sabaek, Yonghyang, Chichang, Taeyong was performed by injecting the needle at a 1 to 1.5 cm depth in the vertical direction. For the last acupuncture session, the subcision was carried out to cut off the adhesion of wrinkles followed by calming the face with a cooling pack for 20 min. To measure results, parallel polarization images were taken by DermaVision before and after the Jae-Seng Acupuncture treatment. Figure 1 shows the facial locations where Jae-Seng Acupuncture was used.

2.2. Statistical Analysis. Image data were analyzed between each group using paired-sample *t*-testing for NLs and EWs. One-way analysis of variance (ANOVA) was used to analyze differences within the group before and after the Jae-Seng Acupuncture treatment. A *P* value less than 0.05 and LSD (least significant difference) were considered to indicate statistical significance.

3. Results

3.1. DermaVision Analysis. DermaVision images were analyzed to compare the effects of Jae-Seng Acupuncture before and after the treatment. Results were calculated automatically as a percentage before (left) and after (right) treatment and are shown in the left panel for EWs and right panel for NLs (Figures 2(a)-2(j)). Among female patients in their 20s, EWs and NLs were improved from 42.6% to 31.5% and from 39.4% to 36.0%, respectively (Figure 2(a)). Among female patients in their early 30s, EWs and NLs were improved from 41.2% to 35.0% and from 35.9% to 32.8%, respectively (Figure 2(b)). The effects of the therapy were observed in all patient groups as follows: 40.2% to 33.9% and 41.5% to 34.0% in females in their mid-30s; 44.1% to 38.9% and 39.5% to 34.2% in females in their late 30s; 34.4% to 27.1% and 39.0% to 38.0% in females in their 40s; 38.4% to 34.1% and 38.5% to 33.4% in females in their early 50s; 45.1% to 38.9% and 34.5% to 33.4% in females in their mid-50s; 41.5% to 37.3% and 41.6% to 39.5% in females in their 60s; 42.2% to 32.1% and 40.5% to 30.7% in females in their 70s; and 38.1% to 36.5% and 39.2% to 36.4% in males in their 30s.

3.2. Paired-Samples t-Test. Right NLs before and after Jae-Seng Acupuncture treatment differed significantly (P < 0.001; see Table 2). The average difference before and after Jae-Seng Acupuncture treatment in right NLs was 2.63, indicating a reduction after treatment. Matching 2~4 (see Table 2) revealed similar tendencies to those observed in right NLs. Averages reductions ranged from 2.5 to 3.6, indicating improvements in NLs and EWs after Jae-Seng Acupuncture treatment.

3.3. Correlation Coefficient of Matching Samples. The correlation coefficient of right NLs before and after Jae-Seng Acupuncture treatment was 91.1%, indicating statistical significance at the 95% significance level (Table 3). The frequencies and correlations of changes in wrinkles ranged from 83 to 91% among the four groups, demonstrating a positive correlation after treatment.

3.4. Mean Difference of Treatment according to Age. One-way ANOVA was carried out to analyze the effects of Jae-Seng Acupuncture treatment on patients of different ages. For right NLs, the mean averages according to age were in the order of 70s > 50s > 40s > 60s > 30s > 20s (Figure 3). For left NLs, the

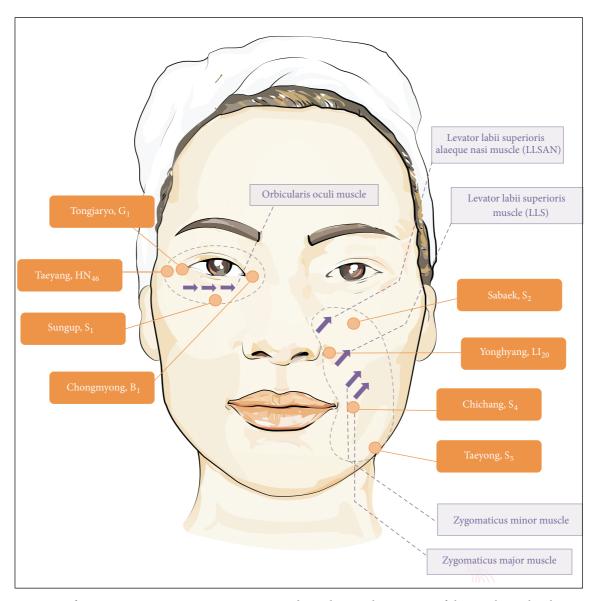


FIGURE 1: Locations of Jae-Seng Acupuncture treatment. Arrows indicate the stimulation points of the muscles in this therapy, and each meridian point is also presented. The procedure is described in Section 2.

Table 2: Paired-sample t-test.

	Average S.D.	S.E.	95%	t value	D.O.F.	P value		
	Average S.D.		J.L.	Lower limit	Upper limit			
Matching 1 ^a	2.6355	2.5487	.2464	2.1470	3.1240	10.697	106	.000
Matching 2 ^b	2.5393	2.5896	.2503	2.0429	3.0356	10.143	106	.000
Matching 3 ^c	3.5673	3.0722	.2970	2.9785	4.1561	12.011	106	.000
Matching 4 ^d	3.6738	3.2593	.3151	3.0491	4.2985	11.660	106	.000

^aNLB (R) versus NLA (R);

NL: nasolabial fold, EW: eye wrinkle, B: before, A: after, R: right, L: left, S.D.: standard deviation, S.E.: standard error of the average, C.I.: confidence interval for the difference, and D.O.F.: degree of freedom.

^bNLB (L) versus NLA (L);

^cEWB (R) versus EWA (R);

^dEWB (L) versus EWA (L).

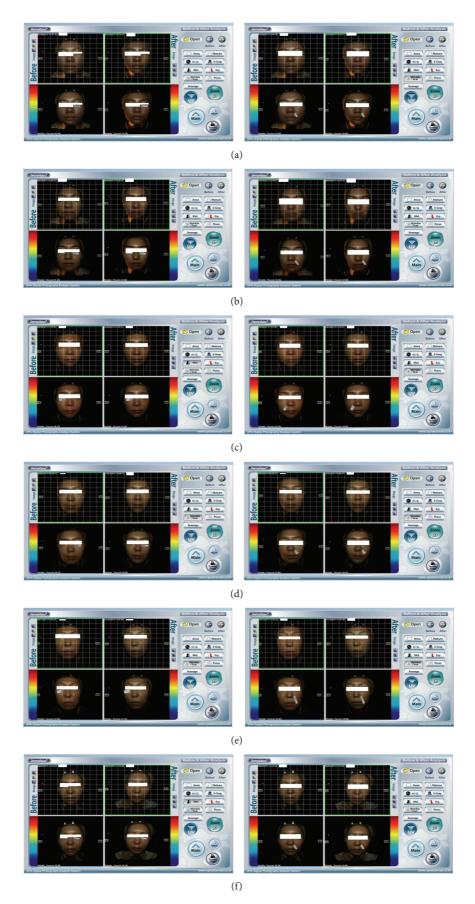


FIGURE 2: Continued.

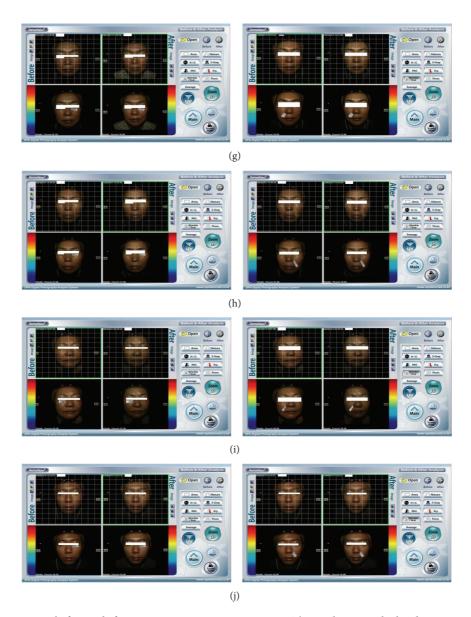


FIGURE 2: DermaVision images before and after Jae-Seng Acupuncture treatment. The results were calculated automatically as the percentage before (left) and after (right) treatment and are shown in the left panel for eye wrinkles and right panel for nasolabial folds, respectively. The figure shows the calculation, with the designated area shown as white boxes for eye wrinkles and nasolabial folds. Female, 20s (a); female, early 30s (b); female, mid-30s (c); female, late 30s (d); female, 40s (e); female, early 50s (f); female, mid-50s (g); female, 60s (h); female, 70s (i); and male, 30s (j) are shown.

mean averages according to age were in the order of 20s > 70s > 60s > 50s > 40s > 30s. For right EWs, the mean averages according to age were in the order of 70s > 60s > 50s > 40s > 30s > 20s, while for left EWs the mean averages according to age were in the order of 20s > 70s > 60s > 50s > 40s > 30s.

4. Discussion

People are increasingly more interested in taking care of their appearance, and many choose to have cosmetic surgery [7]. Dermatological care is one of the most frequently used therapies to improve skin conditions including acne, scars, pigmentation, and wrinkles. Chemical and laser decortications

have been widely performed, but they involve relatively long recovery times and are often accompanied by flushing, infection, and scarring [8, 9].

MTS was developed to create microscopic channels, puncturing the skin by rolling 192 needles sized 0.25~2.0 mm over the skin's surface. Automatic MTS can induce procollagen I expression and increase the weight and density of the dermis [10]. Jae-Seng Acupuncture also involves making punctures on the surface of the skin, but it involves making incisions of 0.25~2.0 mm in depth on the meridians of the face, allowing bloodletting to remove the extravasated blood, and stimulating blood circulation to activate collagen and elastin synthesis in wound healing. Incisions and bloodletting

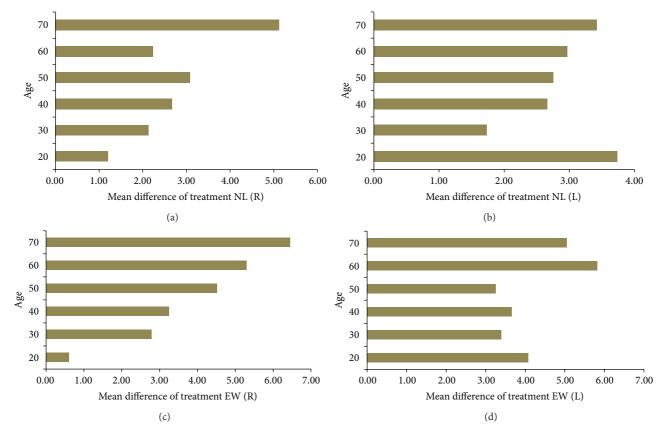


FIGURE 3: Mean difference of treatment for both nasolabial folds and eye wrinkles. The effects of the Jae-Seng Acupuncture treatment were calculated and are shown according to age. Mean difference for NL (R): (a), NL (L): (b), EW (R): (c), and EW (L): (d).

TABLE 3: Matching sample correlation coefficient.

	N	Correlation coefficient	P value
Matching 1 ^a	107	.911	.000
Matching 2 ^b	107	.911	.000
Matching 3 ^c	107	.880	.000
Matching 4 ^d	107	.828	.000

^aNLB (R) versus NLA (R);

NL: nasolabial fold, EW: eye wrinkle, B: before, A: after, R: right, and L: left.

of meridian points have long been used to relieve inflammation and edema by removing abscesses and allowing blood to circulate smoothly [11, 12].

Jae-Seng Acupuncture has advantages over MTS because it is performed by hand. It can be applied to the sensitive, narrow, and thin-layer facial regions that are difficult to access using instruments. Therefore, this procedure can be extended to areas such as the rounded sides of noses and the area surrounding the eyes, with different depths to the epidermis, dermis, and muscle layer. Taken together, the results presented herein indicate that stimulation of the meridians such as Sabaek, Yonghyang, Chichang, Taeyong and Sungup to improve the function of the stomach, large intestine may affect the regeneration of skin in a positive way.

A previous study of how plastic acupuncture can improve appearance focused on improving wrinkles, melanin, flushing, and water content in 18 cases [13]. In the present study, 107 cases were analyzed before and after Jae-Seng Acupuncture treatment to examine its effects on NLs and EWs. Statistical analyses showed that Jae-Seng Acupuncture treatment improved both NLs and EWs in all of the classified age groups, and the effects lasted longer than 6 months. However, this procedure needs to be further investigated because bruises and rubefaction of the skin were frequently observed for 3 to 7 days after Jae-Seng Acupuncture treatment, and more patients in their 20s, 60s, and 70s need to be examined.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

- [1] H.-C. Choi and C.-H. Oh, "Evaluation of skin furrows in the ageing process using an image analysis system," *Korean Journal of Dermatology*, vol. 35, no. 2, pp. 292–302, 1997.
- [2] J.-H. Suk and S.-H. Li, "The effect of MTS (micro needle therapy system) treatment on women's light wrinkles and elasticity improvement," *Korean Journal of Aesthetic Society*, vol. 8, no. 3, pp. 21–32, 2010.

^bNLB (L) versus NLA (L);

^cEWB (R) versus EWA (R);

dEWB (L) versus EWA (L).

- [3] M. C. Aust, D. Fernandes, P. Kolokythas, H. M. Kaplan, and P. M. Vogt, "Percutaneous collagen induction therapy: an alternative treatment for scars, wrinkles, and skin laxity," *Plastic* and *Reconstructive Surgery*, vol. 121, no. 4, pp. 1421–1429, 2008.
- [4] G. F. Pierce, D. Brown, and T. A. Mustoe, "Quantitative analysis of inflammatory cell influx, procollagen type I synthesis, and collagen cross-linking in incisional wounds: influence of PDGF-BB and TGF-beta1 therapy," *The Journal of Laboratory and Clinical Medicine*, vol. 117, no. 5, pp. 373–382, 1991.
- [5] H. Kang, B. Jung, and J. S. Nelson, "Polarization color imaging system for on-line quantitative evaluation of facial skin lesions," *Dermatologic Surgery*, vol. 33, no. 11, pp. 1350–1356, 2007.
- [6] Y.-W. Bae, T. Son, J. Stuart Nelson, J.-H. Kim, E. H. Choi, and B. Jung, "Dermatological feasibility of multimodal facial color imaging modality for cross-evaluation of facial actinic keratosis," Skin Research and Technology, vol. 17, no. 1, pp. 4–10, 2011.
- [7] J.-K. Heo, J.-M. Lee, C.-H. Lee, J.-B. Jang, K.-S. Lee, and J.-H. Cho, "A review of recent studies on cosmetic acupuncture," *The Journal of Oriental Obstetrics & Gynecology*, vol. 23, no. 4, pp. 146–154, 2010.
- [8] B. M. Hantash, B. Renton, R. Laurence Berkowitz, B. C. Stridde, and J. Newman, "Pilot clinical study of a novel minimally invasive bipolar microneedle radiofrequency device," *Lasers in Surgery and Medicine*, vol. 41, no. 2, pp. 87–95, 2009.
- [9] S. Kim and K.-H. Cho, "Clinical trial of dual treatment with an ablative fractional laser and a nonablative laser for the treatment of acne scars in Asian patients," *Dermatologic Surgery*, vol. 35, no. 7, pp. 1089–1098, 2009.
- [10] J.-H. Kim, H.-Y. Park, M. Jung, and E. H. Choi, "Dermal proliferative effect and safety of automicroneedle therapy system (AMTS)," *Korean Journal of Dermatology*, vol. 48, no. 11, pp. 955–965, 2010.
- [11] The Association of Korean College of Oriental Medicine and Department of Acupuncture and Moxibustion, Acupuncture and Moxibustion, Jipmoondang Publishing, 2008.
- [12] K.-E. Hong, G.-H. Lee, and J.-H. Cho, "Hong-Acupuncture therapy," *Journal of Oriental Medicine*, vol. 31, no. 1, pp. 35–49, 2008.
- [13] J.-H. Cho, I.-S. Kim, and S.-Y. Baek, "Effects of plastic acupuncture on wrinkles, melanin, flush and water content," *The Journal of Korea Medical Institute of Dermatology and Aesthetics*, vol. 5, no. 1, pp. 24–34, 2012.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 268471, 6 pages http://dx.doi.org/10.1155/2015/268471

Research Article

Effects of GUASHA on Heart Rate Variability in Healthy Male Volunteers under Normal Condition and Weightlifters after Weightlifting Training Sessions

Xingze Wang,^{1,2,3} Uraiwan Chatchawan,^{1,4} Saowanee Nakmareong,⁴ Atit Silsirivanit,⁵ Yingying Wang,⁶ Dongbei Xie,² Jinsheng Yang,⁶ and Wichai Eungpinichpong^{1,3}

Correspondence should be addressed to Jinsheng Yang; zml@ibucm.com and Wichai Eungpinichpong; wiceun@yahoo.com

Received 12 June 2014; Revised 1 August 2014; Accepted 2 August 2014

Academic Editor: Gerhard Litscher

Copyright © 2015 Xingze Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objectives. This paper aims at exploring the effects of GUASHA on heart rate variability between healthy volunteers under normal condition and weightlifters after training sessions. *Methods*. Ten healthy male volunteers under normal condition and 15 male weightlifters after weightlifting training sessions were recruited into two groups. Electrocardiography was recorded before and immediately after 20-minute GUASHA. HRV was calculated in both the time domain and the frequency domain. *Results*. Stress index was reduced, while standard deviation of N-N intervals (SDNN), proportion derived by dividing the number of interval differences of successive N-N intervals greater than 50 ms, and root mean square of successive differences (RMSSD) were enhanced after GUASHA therapy in the two groups. The changes in SDNN and RMSSD were higher in the healthy men group than in the weightlifters group. In addition, low frequency was decreased whereas high frequency was significantly increased in healthy men after the GUASHA session. *Conclusions*. GUASHA therapy facilitates the parasympathetic nervous activity and modulates the balance between parasympathetic and sympathetic activities in both healthy men under normal condition and weightlifters after training sessions as indicated. Although the changes of the HRV parameters were similar in both groups, the responsiveness was more pronounced in healthy men than in male weightlifters.

1. Introduction

GUASHA is a traditional Chinese therapy in which skin is scraped repeatedly by using a blunt spoon-like object on certain areas of the body. It is performed along the meridians with different kinds of tools and manipulation techniques to cause petechiae and ecchymosis for treatment and health care. "GUA" means to scrape or rub; "SHA" means petechiae and ecchymosis as well as the feeling of satisfaction. The physiological mechanism of GUASHA in both healthy

people and patients is that it increases surface microperfusion [1]. GUASHA has an immune anti-inflammatory effect due to upregulating the heme oxygenase-1 [2], prolonging the endurance time [3], enhancing the amount of white blood cells and neutrophils [4], and reducing muscle pain and chronic fatigue syndrome [5, 6].

Heart rate variability (HRV) is used as a marker of fatigue [7]. HRV is the tiny variation of beat-to-beat of the heart. It refers to various computed outcomes used to quantify the time intervals between heart beats as well as

¹Research Center in Back, Neck, Other Joint Pain and Human Performance, Khon Kaen University, Khon Kaen 40002, Thailand

²Faculty of Physical Education, Gannan Normal University, Ganzhou 341000, China

³Research and Training Center for Enhancing Quality of Life of Working-Age People, Khon Kaen University, Khon Kaen 40002, Thailand

⁴Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

⁵Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

⁶Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing 100700, China

beat-to-beat changes in one single interval. Physiological studies show that high variability of the interbeat interval generally corresponds to the enhanced parasympathetic nervous activity whereas low variability of the interbeat interval generally corresponds to the strengthened sympathetic nervous activity [8]. HRV can be changed by acupuncture therapy [9-11]. Some of the other therapies such as moxibustion, tuina, cupping, and GUASHA [12] have similar effects with acupuncture. However, few studies have reported the effects of GUASHA therapy on HRV. We hypothesized that GUASHA can reduce the exercise fatigue of the athletes, such as weightlifters. Objective of the present study was to investigate the possibility that HRV can be used to detect changes in autonomic nervous activity after GUASHA therapy in healthy male volunteers under normal condition and male weightlifters after weightlifting training sessions.

2. Materials and Design

The same manipulation was conducted to test HRV during a session in healthy male volunteers and male weightlifters by a research group including one GUASHA therapist, a neurologist, and a research methodologist/statistician. The ethic committee of Khon Kaen University approved the research protocol. Written informed consent was obtained from all the participants before the study. This study was conducted in the Division of rehabilitation, Faculty of Physical Education, Gannan Normal University, China.

- 2.1. Environment and Procedure. Each of the participants underwent a process of HRV measurements and scraping as shown in Figure I. Measurements were made in a quiet room with about 50% humidity and average temperature of $27 \pm 1^{\circ}$ C, without direct sunlight, without infrared radiation, and without indoor-outdoor ventilation. Before measurements, the subjects were instructed to rest more than 10 minutes in this quiet and relaxing atmosphere. Subjects were further instructed to be in a sitting position wearing an ear sensor and to breathe at a frequency of 1 breath/4 s (0.25 Hz) in synchrony with the sound of an electric metronome at comfortable volume levels.
- 2.2. Subjects. All subjects were college students or active athletes who underwent a physical examination to determine that they had no health problems or injuries. The inclusion criteria were no smoking, no alcohol, and no history of hormone therapy. Exclusion criteria were with joint or muscle dysfunction, smoking, or drinking alcohol. Data were collected in China from 25 male volunteers, in whom there were 10 university students and 15 weightlifters. The baseline features were as follows: the average age was 21.6 ± 3.4 years, the average weight was 54.2 ± 31.8 kg, the average height was 172.8 ± 8.1 cm, and the average body mass index was 24.6 ± 4.2 . For the male students, they have never joined professional training. Futhermore, their exercises were aimed to improve health fitness, such as, exercises were performed 3 sessions per week, more than 30 minutes per session, and reach 85% of maximum heart rate. For the male weightlifters, the average



FIGURE 1: Trial flowchart.

duration of training experiences was 4.2 ± 0.7 years, the average active athletic level was 2.0 ± 0.5 (note that the titles of athletes in China included international masters of sports (1++), masters of sports (1+), first grade (1), second grade (2), third grade (3), and young athletes (4)). Definition of normal condition and weightlifting training sessions is as follows: (a) normal life in healthy male university student involves having classes in the morning and afternoon and doing exercises on Monday, Wednesday, and Friday afternoon with middle intensity load for half an hour; (b) normal weightlifting training sessions in male weightlifters involve training from Monday to Saturday, on Wednesday with 85% 1RM, on Friday with 90% 1RM, and on Saturday 90-95% 1RM on snatch or clean and jerk. All the participants were required to get up before 8:00 am on the day of experiment. The subjects live with the same lifestyle based on the previous life before and during the experiment day.

Recording of HRV. HRV was measured on Monday morning in that all the volunteers were in equal and basal physical conditions. Data was recorded (version 4.2, biofeedback 2000 x-pert software, made in Austria) from the chest wall for 5 minutes before and after GUASHA. The sampling frequency was 100 Hz. The red electrode cable was attached to the left chest in the area of the fifth rib and the blue one to the right chest; the reference can be attached to the Adam's apple. Various temporal indications can be calculated including stress index (SI), standard deviation of N-N intervals (SDNN), proportion derived by dividing the number of interval differences of successive N-N intervals greater than 50 ms (pNN50), root mean square of successive differences (RMSSD), low frequency (LF), high frequency (HF), and the ratio of LF/HF which is a direct index of HRV.

- 2.3. GUASHA Intervention. The tool of GUASHA was the Buffalo Horn scraper and a skin lubricant to decrease friction. The therapist has been trained and certified by the Ministry of Human Resources and Social Security, China. The head, neck, and back were scraped with 45 degrees between the scraper and skin in the direction from up to down and center to edge. The number of times of GUASHA: head (60), neck (60), back (whole 40, up 40, middle 40, low 20). Total GUASHA time was 20 minutes and it took place between 9:00–11:30 am. Pressure of GUASHA by the GUASHA therapists was mild (487 \pm 21.4 g) and moderate (626 \pm 10.6 g), based on the measurements using AlgoMed System. "SHA" describes stasis within the tissue as well as the petechiae raised from GUASHA signifying liberation of that stasis [13].
- 2.4. Data Analysis. Data were presented as mean \pm standard deviation (SD). Within group, paired sample t test was used

Item	Туре	Before	After
SI	Healthy $(n = 10)$	36.03 ± 28.81	29.31 ± 21.57
31	Weightlifters ($n = 15$)	35.06 ± 16.41	27.57 ± 15.78
SDNN (ms)	Healthy $(n = 10)$	152.82 ± 90.37	159.05 ± 91.72
SDININ (IIIS)	Weightlifters ($n = 15$)	99.46 ± 53.75	110.32 ± 56.96
RMSSD (ms)	Healthy $(n = 10)$	149.37 ± 90.59	162.03 ± 95.54
KIVIOSID (IIIS)	Weightlifters ($n = 15$)	99.61 ± 60.14	112.22 ± 65.13
pNN50 (%)	Healthy $(n = 10)$	45.011 ± 16.03	51.71 ± 13.86
p11130 (70)	Weightlifters $(n = 15)$	42.51 ± 13.46	49.72 ± 11.71

TABLE 1: Changes of time domain before and after GUASHA therapy.

TABLE 2: Changes of frequency domain before and after GUASHA therapy.

Item	Туре	Before	After
LF (Hz)	Healthy $(n = 10)$	$0.074 \pm 0.041 \mathrm{Hz}$	$0.064 \pm 0.024 \mathrm{Hz}$
LI (IIZ)	Weightlifters $(n = 15)$	$0.076 \pm 0.023 \mathrm{Hz}$	$0.065 \pm 0.023 \mathrm{Hz}$
HF (Hz)	Healthy $(n = 10)$	$0.23 \pm 0.036 \mathrm{Hz}$	$0.25 \pm 0.053 \mathrm{Hz}$
пг (пz)	Weightlifters $(n = 15)$	$0.253 \pm 0.052 \mathrm{Hz}$	$0.249 \pm 0.042 \mathrm{Hz}$
LF/HF	Healthy $(n = 10)$	0.54 ± 0.13	0.51 ± 0.17
LF/HF	Weightlifters $(n = 15)$	0.612 ± 0.237	0.515 ± 0.26

to compare the results, and independent sample t test was used to analyze the difference between groups. Statistical analysis was performed using SPSS 17.0 Software. To achieve the statistical significant, 80% power and an alpha level of 0.05 were used.

3. Results

3.1. The Effects of GUASHA Therapy on Time Domain. The changes in time domain of HRV include SI, SDNN, RMSSD, and pNN50. Table 1 showed the values before and after GUASHA therapy. The results revealed that the SI was significantly reduced, while SDNN, RMSSD, and pNN50 were improved in both groups. When the two groups were compared, SDDN and RMSSD were higher in the healthy group while pNN50 and SI kept the same trend during the GUASHA therapy, Figure 2.

3.2. The Effects of GUASHA Therapy on Frequency Domain. Figure 3 shows the changes in frequency domain of HRV. These values were significantly different before and after GUASHA (P < 0.05). These values were induced due to GUASHA therapy, Table 2. It revealed that LF and HF significantly improved in the healthy males group, while LF/HF were significantly reduced in both groups. When comparing the two groups, HF was higher in the healthy group than in the weightlifters group for baseline level (P < 0.01, independent t test), whereas LF, LF/HF kept the same trend during the GUASHA therapy in the two groups.

4. Discussions

4.1. The Effects of GUASHA Therapy on Time Domain. The recording of HRV in healthy people was used to modulate

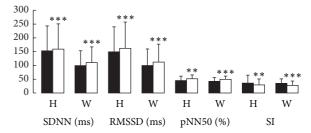


FIGURE 2: The changes in the time domain of HRV before and after GUASHA in the healthy males under normal condition and weightlifters under weightlifting training condition. The black bar means before GUASHA. The white bar means after GUASHA treatment. H means healthy males; W means male weightlifters. SDNN means standard deviation of N-N intervals; SI means stress index; pNN50 means proportion derived by dividing the number of interval differences of successive N-N intervals greater than 50 ms; RMSSD means root means square of successive differences. The units in *y*-axis are different in accordance with units in the brackets of the *x*-axis items, ** P < 0.01. *** P < 0.001 means the time domain of the subjects before GUASHA versus after GUASHA.

and monitor health care in previous studies [14–17]. Time domain including SI, SDNN, RMSSD, and PNN50 analyzes the changes in heart rate over time or intervals between successive normal cardiac cycles [18]. SI responds sensitively to changes in the vegetative balance between the sympathetic and parasympathetic nervous system. SDNN describes the total regulation of the autonomic nervous system to cardiac function. RMSSD indicates how much the heart rate varies from one heart beat to the next. pNN50 is an indication of parasympathetic activity.

Farinatti et al. studied that the change of time domain, including SDNN, RMSSD, and pNN50, increased after stretch session such that their values enhanced after the

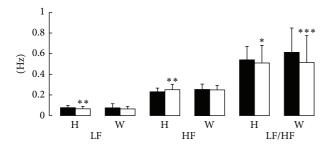


FIGURE 3: The changes in the frequency domain of HRV before and after GUASHA in healthy males under normal condition and male weightlifters under weightlifting training condition. LF and HF significantly improved in the healthy males group, while LF/HF were significantly reduced in both groups. The black bar means the value before GUASHA treatment. The white bar means the value after GUASHA treatment. H refers to healthy males; W means male weightlifters; LF is short for low frequency; HF is short for high frequency. $^*P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$ versus before treatment.

stretch session [19]. Another research demonstrated the same trend after mild physical exercise on change of time domain [20], whereas our study also demonstrated the same results which were that the SDNN, pNN50, and RMSSD enhanced significantly after GUASHA treatment. Nevertheless, there was a difference between both groups in time domain such that the values of SDNN and RMSSD in healthy group were more than those in weightlifters in our study. The reason may be different parasympathetic nervous activities due to the weightlifters having been trained for 4 years in this study. The effect of habitual weightlifting training influences baseline parasympathetic tone in HRV. Furthermore, the value of the weightlifters was lower than that of the healthy males, as players' physical fatigue was higher than that of average people. The previous studies showed some difference in HRV between the healthy group and the weightlifters [21, 22].

Another study demonstrated that the effects of exercise training on HRV which enhanced in HRV due to appropriate exercise on health promotion, such as, increasing the SDNN and RMSSD after exercise and training [23]. RMSSD showed an increase after GUASHA therapy, expressing the strengthened activity of the parasympathetic function by GUASHA in this study; however, the difference between healthy males and players may be in that RMSSD was not in the same active level in the parasympathetic nervous system between these two groups. SI was lower in the two groups after GUASHA. The reasons of the same changes may be in that the weightlifters were also healthy people. Also, the same meridians were used in both acupuncture and GUASHA therapies [12].

The GUASHA therapy is beneficial for health care and treatment because it effectively improves microcirculation [1] and skin temperature [24], and it upregulates heme oxygenase-1 [2] and reduces muscle pain and chronic fatigue syndrome [5, 6]. The previous study demonstrated that GUASHA could reduce fatigue [4, 6]. The cutaneous regions have a defensive function and are an external indicator of the functional status of zang-fu organs in TCM [25], and skin can metabolize hormones and produce derivatives with a

potentially systemic activity based on modern medicine [26–31]. The change of time domain indicated that some meridians may be stimulated in cutaneous regions and perhaps the biochemical, neurological, and endocrine changes were induced by physical therapy (acupuncture, moxibustion, GUASHA, cupping, and tuina).

4.2. The Effects of GUASHA Therapy on Frequency Domain. Frequency domain analysis including HF, LF, and the ratio of LF/HF describes the periodic oscillations of the heart rate signal decomposed at different frequencies and provides information on the amount of relative intensity in the heart's sinus rhythm [32]. LF represents parasympathetic and sympathetic influences, and fluctuations in this band are periodic oscillations of the arterial blood pressure as a result of rhythmic contraction of blood vessels that offer resistance to blood flow. HF band reflects how the heart rate adapts to the respiration rhythm. It is an important factor in parasympathetic activity. The ratio of LF/HF is regarded as the proportion of sympathetic and parasympathetic activity.

Chalencon et al. demonstrated the relevance of frequency domain change in HRV as a valuable tool to assess the physiological training-induced responses and to optimize athletic performance; moreover, using performance or HF as the systems' output is as the systems output provided the same information on the fatigue status of the athlete [33]. Chen et al. demonstrated that parasympathetic power indicated by HF in HRV can reflect the recovery status of the weightlifter after training, such that the HF value declined due to weightlifting training [34]. Vigorous training can suppress parasympathetic power by lowering increasing HF, whereas sympathetic power is increased by LF in HRV. So, HF power is contributed to parasympathetic nervous activity. However, HF was enhanced to display the high level of parasympathetic activity after GUASHA only in the healthy males, possibly indicating that the players belong to a special group of people whose range is limited. It was found that the effect of GUASHA therapy is beneficial for healthy people relating to parasympathetic activity function.

Our study shows that LF declined significantly after GUASHA therapy in the healthy males; however, LF has a trend of decline in weightlifters. These indicate the higher level balance between the parasympathetic and sympathetic nervous systems. LF power in normalized unit is considered as a marker of sympathetic nervous activity. Another study demonstrated that LF in HRV enhanced after weightlifting training [34]. Previous study showed that the ratio of LF/HF enhanced due to weightlifting training [21]. Increased HRV has been found when a decrease in LF/HF ratio occurs and is indicative of increased parasympathetic activity. Our study showed that LF/HF ratio declined significantly in both groups. As a result, the ratio of LF/HF declined, expressing that the parasympathetic nervous system was activated due to the GUASHA therapy in both groups.

Many mechanisms by which GUASHA may affect the skin and homeostasis have been suggested. A study on effect of mechanical pressure on the skin demonstrate that the pressure could activate fibroblastic proliferation depended on the amount and form of the applied pressure [35]. However, the "SHA" resulting from the repeated mechanical pressure (with stroke) was thought to be extravasation of blood from the peripheral capillaries [36]. These biological responses may be induced by leakage [37]. Furthermore, the GUASHA could regulate the endocrine and increase HO-1 [2, 38], releasing corticotropin hormone due to the cutaneous response to the stress [39]. The surface of the body offers evidence of internal dysfunction, and it is possible to influence the interior by the application of reflexively powerful stimuli from the skin surface. Koizumi found that stimulation of the skin in the abdomen produced profound inhibition of intestinal movement [40]. This phenomenon showed that the internal organs cannot react directly to painful stimulus, instead by producing spasm and paraesthesia in the reflexively related muscle wall, often augmented by hyperaesthesia of the overlying skin. Autonomic nervous system was stimulated due to GUASHA in cutaneous regions

5. Conclusions

GUASHA therapy could facilitate the parasympathetic nervous activity and modulate the balance between parasympathetic and sympathetic activities in both the healthy men and the weightlifters as indicated by the changes in HRV parameters. Although the changes of the HRV parameters were similar in both groups, the responsiveness was more obvious in the healthy males than in the weightlifters.

Conflict of Interests

There is no conflict of interests in this paper.

Acknowledgments

This scientific investigation was supported by Dr. Wichai Eungpinichpong. Corresponding author, Dr. Wichai Eungpinichpong, designed the GUASHA intervention. Xingze Wang performed the experiment. Dr. Uraiwan Chatchawan analyzed the data. Saowanee Nakmareong constructed the paper. Atit Silsirivanit drew the figures, Dongbei Xie analyzed the data, and Ms Jackie Hall edited the paper. And the authors thank Dr. Xinyan Gao in the Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences for her contribution giving guidance to their experiment and language polishing in writing this paper.

- [1] A. Nielsen, N. T. M. Knoblauch, G. J. Dobos, A. Michalsen, and T. J. Kaptchuk, "The effect of Gua Sha treatment on the microcirculation of surface tissue: a pilot study in healthy subjects," *Explore*, vol. 3, no. 5, pp. 456–466, 2007.
- [2] K. K. Kwong, L. Kloetzer, K. K. Wong et al., "Bioluminescence imaging of heme oxygenase-1 upregulation in the Gua Sha procedure," *Journal of Visualized Experiments*, no. 30, Article ID e1385, 2009.

- [3] F. Musial, A. Michalsen, and G. Dobos, "Functional chronic pain syndromes and naturopathic treatments: neurobiological foundations," *Forschende Komplementarmedizin*, vol. 15, no. 2, pp. 97–103, 2008.
- [4] X. Z. Wang, W. Eungpinichpong, J. S. Yang et al., "Effect of scraping therapy on weightlifting ability," *Journal of Traditional Chinese Medicine*, vol. 34, no. 1, pp. 52–56, 2014.
- [5] M. Braun, M. Schwickert, A. Nielsen et al., "Effectiveness of traditional Chinese "Gua Sha" therapy in patients with chronic neck pain: a randomized controlled trial," *Pain Medicine*, vol. 12, no. 3, pp. 362–369, 2011.
- [6] Z. Feng, Y. Pang, and F. Ye, "TCM non-medicinal therapy for regulation and treatment of chronic fatigue syndrome," *Journal* of Acupuncture and Tuina Science, vol. 6, no. 6, pp. 376–380, 2008.
- [7] Z. Li, C. Wang, A. F. T. Mak, and D. H. K. Chow, "Effects of acupuncture on heart rate variability in normal subjects under fatigue and non-fatigue state," *European Journal of Applied Physiology*, vol. 94, no. 5-6, pp. 633–640, 2005.
- [8] Registry of Nursing Research Conference Abstracts, WIN—Western Institute of Nursing, Heart Rate Variability as a Biomarker of Arousal in Insomnia, 2012, http://www.nursing-library.org/vhl/handle/10755/211708.
- [9] O. B. Fasmer, H. Liao, Y. Huang et al., "A naturalistic study of the effect of acupuncture on heart-rate variability," *Journal of Acupuncture and Meridian Studies*, vol. 5, no. 1, pp. 15–20, 2012.
- [10] S. Lee, M. S. Lee, J. Choi, S. Jeong, and E. Ernst, "Acupuncture and heart rate variability: a systematic review," *Autonomic Neuroscience: Basic and Clinical*, vol. 155, no. 1-2, pp. 5–13, 2010.
- [11] B. Anderson, A. Nielsen, D. McKee, A. Jeffres, and B. Kligler, "Acupuncture and heart rate variability: a systems level approach to understanding mechanism," *Explore*, vol. 8, no. 2, pp. 99–106, 2012.
- [12] L. Fan and L. Yin, "Hypothesis, modern researches and clinical applications of cutaneous regions in traditional Chinese medicine," *Journal of Acupuncture and Tuina Science*, vol. 12, no. 2, pp. 125–132, 2014.
- [13] A. Nielsen, "Gua Sha: a clinical overview," *Jornal of Chinese Medicine Times*, vol. 3, no. 4, 2008.
- [14] K. L. Rennie, H. Hemingway, M. Kumari, E. Brunner, M. Malik, and M. Marmot, "Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants," *The American Journal of Epidemiology*, vol. 158, no. 2, pp. 135–143, 2003.
- [15] E. G. Vaschillo, B. Vaschillo, and P. M. Lehrer, "Characteristics of resonance in heart rate variability stimulated by biofeedback," *Applied Psychophysiology Biofeedback*, vol. 31, no. 2, pp. 129–142, 2006.
- [16] S. Guzzetti, E. Borroni, P. E. Garbelli et al., "Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation," *Circulation*, vol. 112, no. 4, pp. 465–470, 2005.
- [17] B. De La Cruz Torres, C. L. López, and J. N. Orellana, "Analysis of heart rate variability at rest and during aerobic exercise: a study in healthy people and cardiac patients," *British Journal of Sports Medicine*, vol. 42, no. 9, pp. 715–720, 2008.
- [18] R. E. Kleiger, P. K. Stein, M. S. Bosner, and J. N. Rottman, "Time domain measurements of heart rate variability," *Cardiology Clinics*, vol. 10, no. 3, pp. 487–498, 1992.
- [19] P. T. V. Farinatti, C. Brandão, P. P. S. Soares, and A. F. A. Duarte, "Acute effects of stretching exercise on the heart rate variability in subjects with low flexibility levels," *Journal of Strength and Conditioning Research*, vol. 25, no. 6, pp. 1579–1585, 2011.

- [20] G. Raczak, G. D. Pinna, M. T. La Rovere et al., "Cardiovagal response to acute mild exercise in young healthy subjects," *Circulation Journal*, vol. 69, no. 8, pp. 976–980, 2005.
- [21] E. V. Oreshnikov, V. F. Tihonov, and T. V. Agafonkina, "Heart rate variability in weightlifters," *Human Physiology*, vol. 35, no. 4, pp. 517–519, 2009.
- [22] D. M. Sacknoff, G. W. Gleim, N. Stachenfeld, and N. L. Coplan, "Effect of athletic training on heart rate variability," *American Heart Journal*, vol. 127, no. 5, pp. 1275–1278, 1994.
- [23] M. V. Kamath, M. A. Watanabe, and A. R. M. Upton, Eds., Heart Rate Variability (HRV) Signal Analysis: Clinical Applications, CRC Press, 2012.
- [24] Q. Xu, J. Yang, B. Zhu, L. Yang, Y. Wang, and X. Gao, "The effects of scraping therapy on local temperature and blood perfusion volume in healthy subjects," *Evidence-Based Complementary* and Alternative Medicine, vol. 2012, Article ID 490292, 6 pages, 2012.
- [25] F. Lozano, "Basic theories of traditional Chinese medicine," in *Acupuncture for Pain Management*, chapter 2, pp. 13–43, Springer, New York, NY, USA, 2014.
- [26] C. C. Zouboulis, "The skin as an endocrine organ," *Dermato-Endocrinology*, vol. 1, no. 5, pp. 250–252, 2009.
- [27] A. Slominski and J. Wortsman, "Neuroendocrinology of the skin," *Endocrine Reviews*, vol. 21, no. 5, pp. 457–487, 2000.
- [28] C. C. Zouboulis, "Human skin: an independent peripheral endocrine organ," *Hormone Research*, vol. 54, no. 5-6, pp. 230– 242, 2000.
- [29] C. C. Zouboulis, "The human skin as a hormone target and an endocrine gland," *Hormones (Athens)*, vol. 3, pp. 9–26, 2004.
- [30] A. Slominski, J. Wortsman, R. Paus, P. M. Elias, D. J. Tobin, and K. R. Feingold, "Skin as an endocrine organ: implications for its function," *Drug Discovery Today: Disease Mechanisms*, vol. 5, no. 2, pp. e137–e144, 2008.
- [31] A. Slominski, B. Zbytek, G. Nikolakis et al., "Steroidogenesis in the skin: implications for local immune functions," *The Journal* of Steroid Biochemistry and Molecular Biology, vol. 137, pp. 107– 123, 2013.
- [32] Z. Ori, G. Monir, J. Weiss, X. Sayhouni, and D. H. Singer, "Heart rate variability: frequency domain analysis," *Cardiology Clinics*, vol. 10, no. 3, pp. 499–533, 1992.
- [33] S. Chalencon, T. Busso, J. Lacour et al., "A model for the training effects in swimming demonstrates a strong relationship between parasympathetic activityperformance and index of fatigue," *PLoS ONE*, vol. 7, no. 12, Article ID e52636, 2012.
- [34] J. L. Chen, D. P. Yeh, J. P. Lee et al., "Parasympathetic nervous activity mirrors recovery status in weightlifting performance after training," *Journal of Strength and Conditioning Research*, vol. 25, no. 6, pp. 1546–1552, 2011.
- [35] W. I. Hammer, "The effect of mechanical load on degenerated soft tissue," *Journal of Bodywork and Movement Therapies*, vol. 12, no. 3, pp. 246–256, 2008.
- [36] X. Zhang and W. Hao, Holographic Meridian Scraping Therapy, Foreign Languages Press, 2000.
- [37] U. R. Acharya, K. P. Joseph, N. Kannathal, C. M. Lim, and J. S. Suri, "Heart rate variability: a review," *Medical and Biological Engineering and Computing*, vol. 44, no. 12, pp. 1031–1051, 2006.
- [38] K. Wang, Y. Jiang, Q. J. Zhang et al., "Changes Guasha of bilirubin,SOD,IL-1,IL-6 and WBC count before and after treatment in rats," *Journal of Beijing University of Traditional Chinese Medicine*, vol. 32, no. 9, 2009.

- [39] A. Slominski, J. Wortsman, T. Luger, R. Paus, and S. Solomon, "Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress," *Physiological Reviews*, vol. 80, no. 3, pp. 979–1020, 2000.
- [40] K. Koizumi, "Autonomic system reactions caused by excitation of somatic afferents: study of cutaneo-intestinal reflex," in *The Neurobiologic Mechanisms in Manipulative Therapy*, pp. 219– 227, Springer, New York, NY, USA, 1978.
- [41] R.-D. Treede, R. A. Meyer, S. N. Raja, and J. N. Campbell, "Peripheral and central mechanisms of cutaneous hyperalgesia," *Progress in Neurobiology*, vol. 38, no. 4, pp. 397–421, 1992.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 641792, 4 pages http://dx.doi.org/10.1155/2015/641792

Research Article

A Pilot Study: Warm Stimulation on Guangming (GB37) to Relief Asthenopia

Tao Huang

Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing 100700, China

Correspondence should be addressed to Tao Huang; dr_huangtao@sina.com

Received 10 October 2014; Accepted 6 November 2014

Academic Editor: Gerhard Litscher

Copyright © 2015 Tao Huang. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Infrared thermometry was performed in 15 female asthenopia patients (average \pm SD: 54.88 \pm 7.30 years) prior to, during, and after stimulation using electrothermal Bian-stone at the Guangming (GB37) acupoints. The results of this controlled pilot study (control points at the Yongquan (KII) and Tianshu (ST25) points) showed significant ($P \le 0.05$) increases in eyes' temperature. At the same time, no changes were found at the control points. Furthermore, after warm stimulation on Guangming (GB37) acupoints, the clinical symptoms were getting better than the control points. The symptoms' score was decreased significantly too ($P \le 0.05$). It was demonstrated that there is some relationship between Guangming (GB37) point and eyes, and warm stimulation on Guangming (GB37) could relief uncomfortable of asthenopia.

1. Introduction

Asthenopia is very common seen in later-middle age women and with the symptoms like eye fatigue, ache, dryness and heaviness in the eye, itching, red eyes, blurred vision, tearing, and so on. In TCM textbook, there are report that acupuncture Guangming (GB37) could cure "blue blind" and could adjust liver and gallbladder meridian [1].

In the former studies, electrothermal Bian-stone was used to observe the influence of blood flux of brain by warm stimulation on local points and could increase the flux of blood at local area [2, 3]. The goal of this experiment is to investigate the clinical effects and change of eyes' temperature on the asthenopia patients to find out the interrelationship between eyes and distant acupoints.

2. Materials and Methods

2.1. Electrothermal Bian-Stone. The electrothermal Bian-stone apparatus is made by using a special Sibinfu stone with the ultrasound, far-infrared, and microcrystal properties and by using the modern electrothermal and microcomputer temperature control technology [4]. It was proved to have the similar function as traditional moxibustion [5]. Compared

with traditional moxibustion, it can offer adjustable and constant temperature and without the pollution of moxa smoking and noxious odour. DRB-2E electrothermal Bianstone moxibustion apparatus is produced by Beijing Healthcare Company, China, with 2 small probes which could be fixed on the acupoint. The temperature of probe was chosen 37°C (see Figure 1). The treatment time was 30 minutes.

- 2.2. Asthenopia Patients' Inclusion Criteria. 15 asthenopia patients (mean±SD: age 54.88±7.30 years; range 45–65 years; all female) were studied. All of them fill in the asthenopia questionnaire including 8 common clinical symptoms like dryness, foreign body sensation, itching, and heaviness in the eye, tearing, redness, blurred vision, and photophobia. They were informed of the nature of the investigation as far as the study design allowed. The study was approved by the local ethics committee and all persons gave written informed consent.
- 2.3. Measuring of Eye's Temperature Using FLIR i7. Each patient accepted 2 times treatments and measurements in different day. Room temperature was constant at 26°C. Participants lay face up on a bed with DRB-2E electrothermal Bian-stone (Healthcare Company, Beijing, China) probes





FIGURE 1: Electrothermal Bian-stone instrument and its stone probe.





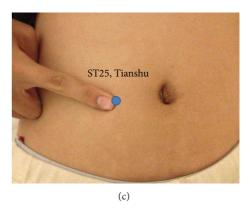


FIGURE 2: (a) Location of Guangming (GB37): 5 cun upper the prominence of the medial malleolus. (b) Location of Yongquan (KI1): 1/3 forth of fossa of foot. (c) Location of Tianshu (ST25): 2 cun beside the navel.

Table 1: The change of eyes' temperature before, during, and after warm stimulation ($x \pm s$).

	The temperature of both eyes (°C), $N = 15$					
	Guangming (GB37)	Control points				
Before treatment	35.72 ± 0.70	36.04 ± 0.59				
During treatment	$36.52 \pm 0.34^*$	36.12 ± 0.47				
10 mins after removing the stone probes	$36.30 \pm 0.37^*$	36.05 ± 0.55				

 $P \le 0.05$.

Table 2: The change of asthenopia symptoms score $(x \pm s)$.

	The change of symptom score, $N = 15$				
	Guangming (GB37)	Control points			
Before treatment	59.67 ± 12.50	57.04 ± 8.90			
After treatment	$35.67 \pm 6.51^{**}$	54.67 ± 10.02			
de de					

^{**}P < 0.01.

on both Guangming (GB37) acupoints, Yongquan (KI), or Tianshu (ST25) as the control points at random (see Figures 2(a)–2(c)). Using the thermal infrared imager FLIR i7 (FLIR Company, Portland, USA) measured the patients' eyes before, during 10 to 30 minutes, and 10 minutes after removing the stone probes.

2.4. Statistical Analysis. Data of temperature of eyes were transferred into measurement by FIIR QuickReport 1.2 SP1 (FLIR company, Portland, USA). Symptom score and the

measurement data were all analyzed using Friedman repeated measures ANOVA on ranks and Tukey's test was used for analysis post hoc. The level of significance was defined as P < 0.05.

3. Results

3.1. Change of the Eyes' Temperature. The eyes' temperature of Guangming (GB37) increased significantly after accepting the warm stimulation and decreased significantly after removing the warm stone probes too. But in control group, neither matter Yongquan (KII) nor Tianshu (ST25), the change of eyes' temperature was not significant (see Table 1).

Figures 3(a)-3(c) and Figures 4(a)-4(c) displayed the representative images.

3.2. The Improvement of Clinical Symptoms. Almost patients reported that the symptoms like dryness, itching, and blurred vision got better and felt bright eyed immediately. But the redness had no change. Although the long-term therapeutic effect cannot be proved, the symptoms score was also improved (see Table 2).

4. Discussion

As a high-tech moxibustion instrument, electrothermal Bianstone could offer adjustable and constant temperature, with the effects of warming and activating the channels, dispelling cold, and promoting blood flow.

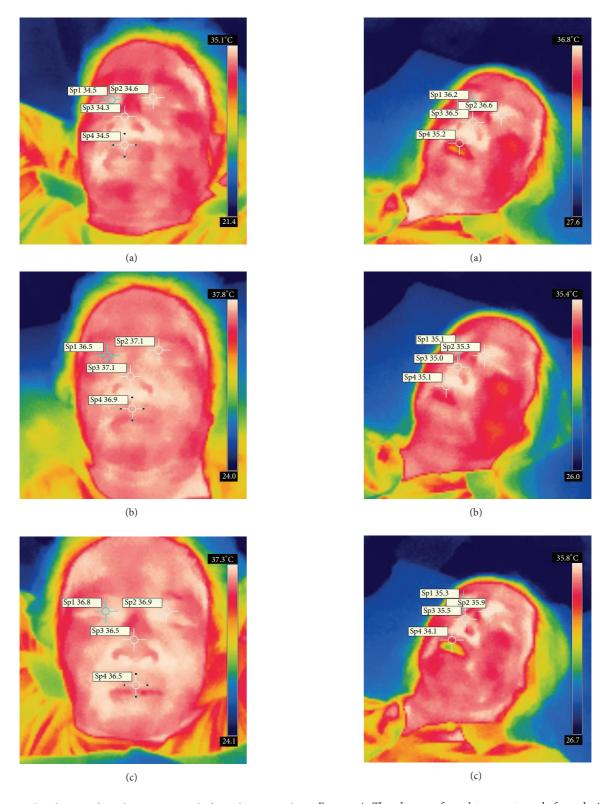


FIGURE 3: The change of eyes' temperature, before, during, and 10 minutes after removing the warm stimulation on Guangming (GB37).

FIGURE 4: The change of eyes' temperature, before, during, and 10 minutes after removing the warm stimulation on control point Yongquan (KI1).

Guangming (GB37) is Luo-connecting point of gallbladder meridian/channel and connects liver and GB meridian/channel. In the earliest acupuncture literature *Classic of Acupuncture and Moxibustion (Zhenjiujiayijing)*, there was not any record about using Guangming (GB37) to treat eye's diseases [6]. But some scholar of later period thought that it could cure eye diseases including glaucoma and cataract [7]. Because liver opens into eyes, it seem as make sense in TCM. What is the relationship between Guangming (GB37) and eyes? This experiment attempts to answer this question. Warm stimulation given on Guangming (GB37) could increase the temperature of patients' eye significantly and improved the clinical symptoms in short time. Same stimulation on control points had no effect.

5. Conclusion

Acupoint Guangming (GB37) could specifically work in the eyes, and the function channel might be Chinese liver and gallbladder channels. Warm stimulation on Guangming (GB37) could relief the asthenopia. The correct and long term effect is worth further study.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The scientific activities were carried out within the project "Integration and Normative Research of Appropriate Chinese-Western Medical Technology for Rural Communities" (no. 2013BAI05B09) supported by The People's Republic of China Ministry of Science and Technology. The measurements were partly performed by Mr. Hui Zhao, Zhenhao Dong, and M.S. Yunlei Cao. The author wants to thank Professor Weibo Zhang for providing the equipment of electrothermal Bian-stone instrument DRB-2E.

- [1] Y. F. Luo, *Acupoints Theory*, Shanghai Publishing House of Science and Technique, 1996.
- [2] G. Litscher, L. Wang, T. Huang, and W. Zhang, "Violet laser acupuncture–part 3: pilot study of potential effects on temperature distribution," *Journal of Acupuncture and Meridian Studies*, vol. 4, no. 3, pp. 164–167, 2011.
- [3] T. Huang, G. Litscher, L. Wang, and W. B. Zhang, "Electrothermal bian-stone on GV14 affect cerebral artery blood flow velocity: pilot study," *Chinese Journal of Basic Medicine in Traditional Chinese Medicine*, vol. 18, no. 3, pp. 312–313, 2012.
- [4] W. B. Zhang, "The originator of Chinese external therapy: Bianstone therapy," *China Acupuncture & Moxibustion*, vol. 23, pp. 299–300, 2000.

- [5] T. Huang, R.-H. Wang, X. Huang et al., "Comparison of the effects of traditional box-moxibustion and eletrothermal bianstone moxibustion on volume of blood flow in the skin," *Journal of Traditional Chinese Medicine*, vol. 31, no. 1, pp. 44–45, 2011.
- [6] M. Huangfu, *Classic of Acupuncture and Moxibustion*, Chinese Medical Science and Technology Press, 1990.
- [7] K. S. Zheng, Zheng's Complete Edition of Acupuncture, vol. 164, People's Medical Publishing House, 2000.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 529675, 9 pages http://dx.doi.org/10.1155/2015/529675

Research Article

The Effects of Acupuncture at Real or Sham Acupoints on the Intrinsic Brain Activity in Mild Cognitive Impairment Patients

Baohui Jia,^{1,2,3} Zhishun Liu,¹ Baoquan Min,² Zhenchang Wang,⁴ Aihong Zhou,² Yong Li,⁴ Haifa Qiao,^{3,5} and Jianping Jia²

Correspondence should be addressed to Haifa Qiao; haifa.qiao@med.fsu.edu and Jianping Jia; jiajp@vip.126.com

Received 12 September 2014; Accepted 14 November 2014

Academic Editor: Gerhard Litscher

Copyright © 2015 Baohui Jia et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Accumulating neuroimaging studies in humans have shown that acupuncture can modulate a widely distributed brain network in mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. Acupuncture at different acupoints could exert different modulatory effects on the brain network. However, whether acupuncture at real or sham acupoints can produce different effects on the brain network in MCI or AD patients remains unclear. Using resting-state fMRI, we reported that acupuncture at Taixi (KI3) induced amplitude of low-frequency fluctuation (ALFF) change of different brain regions in MCI patients from those shown in the healthy controls. In MCI patients, acupuncture at KI3 increased or decreased ALFF in the different regions from those activated by acupuncture in the healthy controls. Acupuncture at the sham acupoint in MCI patients activated the different brain regions from those in healthy controls. Therefore, we concluded that acupuncture displays more significant effect on neuronal activities of the above brain regions in MCI patients than that in healthy controls. Acupuncture at KI3 exhibits different effects on the neuronal activities of the brain regions from acupuncture at sham acupoint, although the difference is only shown at several regions due to the close distance between the above points.

1. Introduction

Mild cognitive impairment (MCI) is defined as a slight impairment in cognitive function (typically memory) with otherwise normal function in the performance of activities of daily living. It is now widely accepted that MCI is a transitional phase between normal function and Alzheimer's disease (AD), during which cognitive impairment is progressing [1, 2]. Most recent findings suggest that sensitive neuroimaging and network analysis may play a special role in understanding the pathophysiological mechanism of MCI and AD. Several resting-state fMRI studies have investigated the neuronal integrity in the brain of the AD or MCI patients by different methods. Using resting functional magnetic resonance imaging (fMRI), Biswal et al. [3] were

the first to demonstrate that spontaneous low-frequency fluctuations (LFFs; <0.08 Hz) of the blood oxygen level dependent (BOLD) signal during rest were of physiological importance. It suggested that regional spontaneous BOLD fluctuations likely reflect spontaneous neuronal activity [3–5]. Recently, this technique has been used to investigate the intrinsic or spontaneous brain activity in subjects with AD or MCI [6–15].

Previous studies have identified that acupuncture, as a therapy of traditional Chinese medicine (TCM), remains promising to treat neurological diseases including chronic pain, drug addiction, stroke, and dementia [16–18]. Now neuroimaging, in particular fMRI, is a versatile tool which has been applied to investigate the mechanisms of acupuncture. Accumulating neuroimaging studies in humans have shown

 $^{^1}$ Department of Acupuncture, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

²Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China

³Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, FL 32306, USA

⁴Department of Radiology, Tongren Hospital of Capital Medical University, Beijing 100730, China

⁵Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing 100700, China

that acupuncture can modulate a widely distributed brain network [19–29]. Acupuncture could activate the temporal lobe (such as hippocampus, insula), some regions of the parietal lobe, and cerebellum in AD patients [30]. These regions are consistent with impaired brain areas in AD patients, which are closely correlated with the cognitive function (memory, reason, language, executive, etc.). This study also provides the preliminary neurophysiological evidence for the potential effect of acupuncture on AD [31]. On the other hand, acupuncture at different acupoints could exert different modulatory effects on the brain network [20]. However, whether acupuncture at real or sham acupoints can produce different effects on the brain network in MCI or AD patients still remains elusive.

Here we used resting-state fMRI to investigate the effects of acupuncture at KI3 or sham acupoint which is 25 mm above Taixi (KI3) on brain regions in MCI patients. Our analyses established that acupuncture at KI3 or sham acupoint could produce effects on some brain regions which are components of default cognitive network in MCI patients, and the statistical difference was only exhibited in several regions.

2. Materials and Methods

2.1. Participants. Twenty-three right-handed subjects participated in this study. 8 MCI patients (2 males and 6 females, average age: 74.1 ± 7.8 years) and 15 elder healthy controls (8 males and 7 females, mean age: 73.7 ± 7.3 years) were recruited from Xuanwu Hospital affiliated to Capital Medical University, Beijing. All the patients received medical interview, physical examination, blood tests, brain magnetic resonance imaging (MRI), and neuropsychological assessment, including Mini-Mental State Examination (MMSE) [32], Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and clinical dementia rating (CDR) [33], modified Hachinski ischemic scale (HIS) [34], activity of daily living scales (ADL), and Hamilton depression scale (HDS), and met the following criteria: (a) impaired memory performance on a normalized objective verbal memory delayed-recall test; (b) normal or near-normal performance on global cognitive tests; (c) MMSE score >24; (d) intact activities of daily living; (e) global rating of 0.5 on the CDR scale, with a score of at least 0.5 on the memory domain; and (f) absence of dementia. The controls were identified as healthy through a regular health examination, MMSE, a clinical memory scale (CMS), HDS, and MRI and met the following criteria: (a) no neurological or psychiatric disorders such as stroke, depression, and epilepsy; (b) no neurological deficiencies such as visual or hearing loss; (c) no abnormal findings such as infarction or focal lesion in conventional brain MR imaging; (d) no cognitive complaints; (e) MMSE score of 28 or higher; (f) CDR score of 0. Participants with contraindications for MRI such as pacemaker, cardiac defibrillator, implanted material with electric or magnetic system, vascular clips or mechanical heart valve, cochlear implant, or claustrophobia were excluded. In addition, patients with a history of stroke, trauma, psychiatric disorders, drug/alcohol

abuse, severe hypertension, diabetes, anemia, systematic diseases, and intellectual disability were also not included. Informed consent was obtained from each subject or his (her) guardian. This study was approved by the Medical Research Ethics Committee of Xuan Wu Hospital.

2.2. Data Acquisition. Data acquisition was performed on a GE 1.5-T Magnetom Sonata system using a standard head coil. Foam padding and headphones were used to limit head motion and reduce scanner noise. Structural images were acquired using a sagittal magnetization-prepared rapid gradient echo (MPRAGE) three-dimensional T1-weighted sequence (repetition time (TR) = 1970 ms, echo time (TE) =3.9 ms, inversion time (TI) = 1100 ms, flip angle (FA) = 20°, and field of view (FOV) = 220×220). Subjects were instructed to keep their body frozen and eyes closed but not think of anything and fall asleep in particular during rest fMRI scanning. Functional images were collected by using an echo-planar imaging (EPI) sequence sensitive to BOLD contrast (TR = 2000 ms, TE = 30 ms, FA = 90° , and FOV = 220×220). Whole-brain volumes were acquired with 24 contiguous 5-mm thick transverse slices, with a 1 mm gap and in-plane resolution = 64×64 , 180 volumes. Through a simple questionnaire after the scan, we knew that all the subjects were awake with their eyes closed during the fMRI scanning session.

2.3. Data Preprocessing. Image preprocessing was carried out using the Statistical Parametric Mapping (SPM5) package (http://www.fil.ion.ucl.ac.uk/spm). The first five volumes were discarded to allow for T1 equilibration effects and the adaptation of the subjects to the circumstances, and then all functional images were corrected for different intravolume acquisition times between slices using the sinc interpolation and for the intervolume geometrical displacement due to head movement using a six-parameter (rigid body) spatial transformation [35]. After the corrections, the images were normalized into the stereotaxic space [36] using an optimum 12-parameter affine transformation and nonlinear deformations [37] and then resampled to 3 mm isotropic voxels. Finally, all normalized data were further temporally band-pass-filtered (0.01-0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noises. One male healthy control (male) was excluded because of excessive movement (>2 mm of translation or 2° of rotation in any direction).

The functional datasets of all patients and healthy controls were preprocessed using the following main steps. (a) Slice timing: the differences of slice acquisition times of each individual were corrected using slice timing. (b) Realigning: the temporal processed volumes of each subject were realigned to the first volume to remove the head motion. All participants had less than 3 mm of translation in x-, y-, or z-axis and 3° of rotation in each axis. (c) Spatial normalization: the realigned volumes were spatially standardized into the MNI (Montreal Neurological Institute) space by normalizing with the EPI template via their corresponding mean image. Then, all the normalized images were resliced by $3.0 * 3.0 * 3.0 * mm^3$

TABLE 1: Characteristics of the MCI patients and normal controls.

Characteristics	MCI	Controls	P value
	(n = 7)	(n = 15)	1 varae
Age (years)	74.1 ± 7.8	70.2 ± 7.1	0.571
Education (years)	12.5 ± 3.1	11.4 ± 4.2	0.787
MMSE	27.0 ± 2.3	29.2 ± 1.3	P < 0.001
ADAS-cog	6.7 ± 2.9	2.5 ± 1.7	P < 0.001

MMSE: Mini-Mental State Examination (max = 30); ADAS: Alzheimer's Disease Assessment Scale.

voxels. (d) Smoothing: Analysis of Functional Neuroimages (AFNI) software (http://afni.nimh.nih.gov) was used to filter linear drift. The normalized functional series were smoothed with a Gaussian kernel of 6 mm full width at half-maximum (FWHM).

- 2.4. Acupuncture. In this study, we selected KI3 which is one of the most frequently used acupoints for the treatment of impaired memory and locates in the depression between the tip of the medial malleolus and Achilles' tendon [38], as a real acupoint, and a point which is 25 mm directly above KI3 as a sham control. The acupuncture needles (0.25 \times 40 mm, Suzhou Hwato Medical Instruments, China) were inserted bilaterally, vertically to a depth of about 20 mm and rotated right then left, at a frequency of 2 Hz for 60 s. During fMRI scanning, the needles were kept in the points.
- 2.5. Statistical Analysis. Using global assessment of random effect, the data of each group was linked and then analyzed statistically. One-sample t-test was used between resting state (baseline) and resting state with acupuncture at true or sham acupoints in each group. Two-sample t-test was performed between different groups (P < 0.01 (multiple correction)). The connected voxels greater than 30 were considered to be activated brain regions. The mean activated image was transformed to Talairach axis and superimposed three-dimension Talairach template in AFNI software [36] for the final localization of the activated region.

3. Results

- 3.1. Demographic and Neuropsychological Characteristics. Demographic and neuropsychological characteristics were shown in Table 1. There were no significant differences between groups in gender, age, and years of education. ADScog score in MCI is significantly different compared with that in control, whereas no significant difference was found in MMSE score between groups.
- 3.2. Amplitude of Low-Frequency Fluctuation (ALFF) Analysis within Group. Firstly we performed one-sample *t*-test to explore the ALFF patterns within group on the individual ALFF maps for each group. As shown in Figure 1, visual inspection indicated that frontal, parietal, and temporal lobes exhibited the increased ALFF values which are parallel with the distribution of default brain networks within each group.

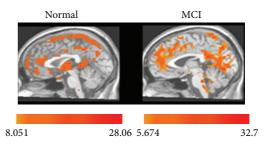


FIGURE 1: Mean ALFF maps in normal controls and MCI patients in the resting state. Color bar represents *t* value which increases with the darker color. The number under the color bar is the range of *t* value.

Narrowly, the increased regions include prefrontal lobe, posterior cingulate cortex, and precuneus. Figure 2 and Table 2 showed the two-sample unpaired *t*-test of ALFF between the MCI patients and the healthy controls. In the resting state, ALFF value in MCI group was decreased significantly in the left medial frontal gyrus and was significantly increased in the right inferior temporal gyrus and posterior cingulate, comparing to the healthy group.

- 3.3. ALFF Analysis within Each Group in the Resting State Combined with Acupuncture at the Real Point. Secondly, we explored the activated regions by acupuncture at real or sham acupoint in each group. As shown in Figures 3(a) and 3(b), regardless of acupuncture at real or sham acupoint, prefrontal, parietal, and temporal lobes displayed increased ALFF values within either MCI group or healthy controls in the resting state.
- 3.4. ALFF Analysis between Groups in the Resting State Combined with Acupuncture at the Real or Sham Acupoint. Subsequently we used two-sample unpaired *t*-test to analyze the difference between groups in the real or sham acupoint. As shown in Figure 4 and Table 3, in MCI patients, the regions showing decreased ALFF are postcentral gyrus, right medial frontal gyrus, cerebellar tonsil culmen, brainstem culmen, and left cuneus displaying increased ALFF in the resting state combined with acupuncture at the real point, comparing to the healthy controls. As shown in Figure 5 and Table 4, in MCI patients, acupuncture at sham acupoint caused tiny difference in the regions showing decreased ALFF between groups and only the left medial frontal gyrus and right superior frontal gyrus decreased ALFF value comparing to the healthy controls, suggesting that, in resting state, acupuncture at real and sham acupoints could activate different brain regions in both MCI and healthy groups.
- 3.5. ALFF Analysis between Resting State with and without Acupuncture at the Real Acupoint in MCI Patients. To explore the effect of acupuncture at the real acupoint on the ALFF in MCI patients, we performed the two-sample paired *t*-test to compare the ALFF between resting state without and with acupuncture. As shown in Figure 6 and Table 5, in MCI patients, acupuncture at KI3 in

TABLE 2: The brain areas that show significant difference in ALFF compared with the MCI patients with normal controls in the resting state.

Volume	Anatomical area	BA	Н	x	у	z	Peak t value	Peak P value
3672	Medial frontal gyrus	BA6	L	4.5	22.5	68.5	-6.144	5.0×10^{-4}
1539	Inferior temporal gyrus		R	-58.5	13.5	-21.5	5.1157	2.6×10^{-4}
1242	Posterior cingulate		R	-22.5	58.5	20.5	5.0297	2.9×10^{-4}

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

Table 3: The brain areas that show significant difference in ALFF in MCI patients compared with normal controls in the resting state combined with acupuncture at KI3.

Volume	Anatomical area	BA	Н	х	у	z	Peak t value	Peak P value
1107	Culmen		R	10.5	-40.5	-12.5	4.3581	9.3×10^{-4}
972	Medial frontal gyrus anterior cingulate	10	R	10.5	37.5	-12.5	4.0723	1.6×10^{-3}
918	Paracentral lobule		L	-4.5	-22.5	77.5	-5.436	1.5×10^{-4}
891	Cerebellar tonsil Culmen		R	19.5	-34.5	-27.5	6.7392	2.1×10^{-5}
675	Cuneus	23 18	L	-13.5	-73.5	8.5	4.7565	$\textbf{4.7}\times\textbf{10}^{-\textbf{4}}$

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

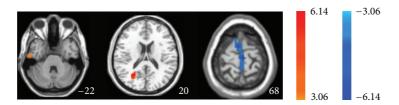


FIGURE 2: Unpaired t-test shows statistical difference map of ALFF between MCI patients and normal controls in the resting state.

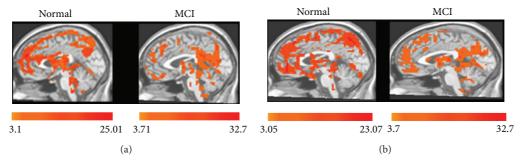


FIGURE 3: Mean ALFF maps in the resting state combined with acupuncture at real or sham acupoint in normal controls and MCI patients. (a) Mean ALFF maps within normal controls and MCI patients in the resting state combined with acupuncture at KI3. (b) Mean ALFF maps within normal controls and MCI patients in the resting state combined with acupuncture at sham acupoint.



FIGURE 4: Unpaired *t*-test exhibits statistical difference map of ALFF between MCI patients and normal controls in resting state combined with acupuncture at KI3.

Table 4: The brain areas that show significant difference in ALFF in MCI patients compared with normal controls in the resting state combined with acupuncture at sham acupoint.

Volume	Anatomical area	BA	Н	х	у	z	Peak t value	Peak P value
1053	Medial frontal gyrus	6	L	-4.5	-25.5	74.5	-4.1004	1.5×10^{-3}
972	Superior frontal gyrus Medial frontal gyrus	6	R	1.5	-4.5	68.5	-4.1896	1.3×10^{-3}

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

TABLE 5: The brain areas of ALFF signal change significantly in MCI patients with acupuncture at KI3 compared with no acupuncture in the resting state.

Volume	Anatomical area	BA	Н	x	у	z	Peak t value	Peak P value
1134	Parahippocampal gyrus	28	L	-13.5	-13.5	-9.5	5.644	1.3×10^{-3}
972	Middle frontal gyrus		R	28.5	7.5	32.5	6.9909	4.2×10^{-4}
891	Cingulate gyrus		L	-25.5	1.5	29.5	7.117	3.9×10^{-4}
702	Cingulate gyrus Middle frontal gyrus	6	L	-25.5	-10.5	38.5	7.0511	4.1×10^{-4}
621	Subthalamic nucleus (thalamus)		R	10.5	-16.5	-3.5	9.6493	7.1×10^{-5}

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

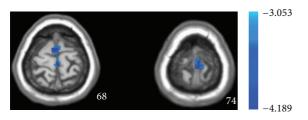


FIGURE 5: Unpaired *t*-test shows significant difference map of ALFF between MCI patients and normal controls in resting state combined with acupuncture at sham acupoint.

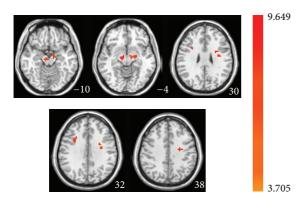


FIGURE 6: Two-sample paired *t*-test shows statistical difference map of ALFF in MCI patients between acupuncture at KI3 and no acupuncture in the resting state.

the resting state increased ALFF in the left parahippocampal gyrus, cingulate gyrus, middle frontal gyrus, right middle frontal gyrus, and subthalamic gyrus. In the healthy controls, acupuncture at the KI3 in the resting state increased ALFF in the right parahippocampal gyrus and reduced it in the right paracentral lobule and cuneus (see Figure S1 and

Table S1 of the Supplementary Material available online at http://dx.doi.org/10.1155/2015/529675).

3.6. ALFF Analysis between Resting State with and without Acupuncture at the Sham Acupoint in MCI Patients. Figure 7 and Table 6 showed the effect of acupuncture at the sham acupoint on the ALFF between resting states without and with acupuncture in MCI patients. Comparing to the resting state without acupuncture, acupuncture at the sham acupoint in the resting state enhanced ALFF in the left precentral gyrus, both right and left medial frontal gyrus, and decreased in the right superior temporal gyrus. In healthy controls, acupuncture at the sham acupoint in the resting state reduced the ALFF in the right cuneus, paracentral lobule but activated it in the right medial frontal gyrus, left anterior cingulate, and parahippocampal gyrus (Figure S2 and Table S2) comparing to the resting state without acupuncture. These data suggest that comparing to the resting state without acupuncture, acupuncture at the sham acupoint in MCI patients activated the different brain regions from those in healthy controls.

3.7. ALFF Analysis between Acupuncture at the Real and the Sham Acupoints in the Resting State. Here a question was raised: what is the difference between acupuncture at the real and the sham acupoints? To answer this question, we conducted a two-sample paired t-test. As shown in Figure 8 and Table 7, in MCI patients, acupuncture at the KI3 increased ALFF in the right superior temporal gyrus, cingulate gyrus and decreased it in the middle front gyrus comparing to acupuncture at the sham acupoint in the resting state. In healthy controls, acupuncture at the real acupoint only decreased the ALFF in the left anterior cingulate comparing to acupuncture at the sham acupoint in the resting state (Figure S3 and Table S3). These data suggest that in the resting state acupuncture at KI3 can produce different

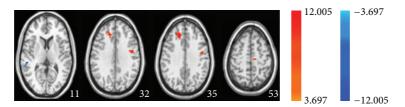


FIGURE 7: Two-sample paired t-test displays statistical difference map of ALFF in MCI patients between acupuncture at sham point and no acupuncture in the resting state.

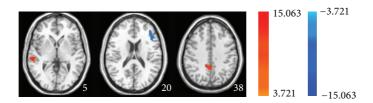


FIGURE 8: Two-sample paired t-test exhibits statistical difference map of ALFF in MCI patients between acupuncture at KI3 acupuncture and acupuncture at sham acupoint in the resting state.

effects on certain brain regions from acupuncture at the sham acupoint, especially in MCI patients.

4. Discussion

In the current study, we performed fMRI to detect the effects of acupuncture at KI3 and the sham acupoints on the restingstate brain activity in MCI patients and healthy controls and discovered that during the resting state brain activities in MCI patients were different from those of healthy subjects. In resting state combined with acupuncture, although acupuncture at KI3 or sham acupoint could not induce significant ALFF value change within either MCI group or healthy control, acupuncture at the real acupoint induced ALFF change of different brain regions in MCI patients from those shown in the healthy controls; acupuncture at sham acupoint also caused difference in MCI patients comparing to the healthy controls, suggesting that, in resting state, acupuncture at KI3 and sham acupoints could activate different brain regions in both MCI and healthy groups. We also found that, in MCI patients, acupuncture at KI3 in the resting state increased or decreased ALFF in the different regions from those activated by acupuncture in the healthy controls. In resting state, acupuncture at the sham acupoint in MCI patients activated the different brain regions from those in heath controls. Acupuncture at the KI3 can produce different effects on a few of brain regions in the resting state from acupuncture at the sham acupoint, especially in MCI patients.

The frontal and temporal regions were considered as important components of human default-mode networks [28–30] and have been shown to exhibit AD- and MCI-related structural and functional abnormalities [29]. By measuring the amplitude of the spontaneous activities (ALFF), several researchers have shown altered baseline brain activity in children with attention deficit hyperactivity disorder [39] and trauma survivors shortly after traumatic events [40]. Two

recent resting fMRI studies also utilized ALFF to investigate the brain's spontaneous activity under eyes-open and eyesclosed conditions and found that the activities within the visual cortex and default-mode regions were significantly different between the two conditions [41, 42]. These recent studies indicate that the ALFF is physiologically meaningful for measuring intrinsic or spontaneous neuronal activity of the brain. In the present study, we found that in the resting state the ALFF of medial frontal gyrus decreased, but inferior temporal gyrus and posterior cingulate increased, suggesting that the default model network was changed in MCI patients. The increase in inferior temporal gyrus is consistent with previous studies which showed increased temporal activation in MCI and at-risk subjects relative to healthy controls [29, 43-46], but in our study the fact that the increase in the posterior cingulate is different from the previous report [15] maybe contributed to the different diagnosis criteria. The decreased ALFF in the medial frontal gyrus implies that the activities of neurons in this region were reduced in the early stage of MCI, and the excitability of its project fibers to the posterior regions was downregulated; the activities of the inferior temporal gyrus and posterior cingulate are compensatorily increased to keep the excitability of network and reinforce the relationship between the front gyrus and medium/posterior brain regions. However, in patients with AD, the neuronal activities are reduced due to the disruption of the compensatory increase in the posterior cingulate in resting state and thereby the brain regions associated with cognitive function like parahippocampus are affected [47].

It is generally agreed that acupuncture plays a homeostatic role and may have a greater effect on patients with a pathological imbalance compared to the healthy controls [48, 49]. Hence, imaging its effect on the brain networks in patients may further help to elucidate the mechanisms by which acupuncture achieves its therapeutic effects. KI3 is one of the most important acupoints for dementia. Previous studies demonstrated that acupuncture at KI3 with a depth

TABLE 6: The brain areas of ALFF signal change significantly in MCI patients with acupuncture at sham acupoint compared with no acupuncture in the resting state.

Volume	Anatomical area	BA	Н	х	у	z	Peak t value	Peak P value
864	Superior temporal gyrus	41	R	49.5	-31.5	11.5	-6.4773	6.5×10^{-4}
864	Precentral gyrus	6	L	-46.5	-7.5	32.5	10.425	4.4×10^{-5}
648	Medial frontal gyrus		R	13.5	34.5	35.5	12.005	2.0×10^{-5}
594	Medial frontal gyrus	6	L	-10.5	-19.5	53.5	6.0288	9.5×10^{-4}

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

Table 7: The brain areas of ALFF signal change significantly in MCI patients with acupuncture at KI3 compared with acupuncture at sham acupoint in the resting state.

Volume	Anatomical area	BA	П	· · · · · · · · · · · · · · · · · · ·	41	~	Peak t value	Peak P value
volume	Allatollilcal area	DA	11	λ	у	~	reak i value	reak r value
1593	Middle frontal gyrus	46	L	-43.5	19.5	20.5	-6.3792	7.0×10^{-4}
864	Superior temporal gyrus	22	R	55.5	-28.5	5.5	15.064	5.4×10^{-6}
594	Cingulate gyrus	31	R	7.5	-43.5	38.5	8.1928	1.8×10^{-4}

BA: Brodmann area; H: hemisphere; x: x-axis; y: y-axis; z: z-axis; L: left; and R: right.

of 1-2 cm enhanced the correlations related to the temporal regions in the poststimulus resting brain in MCI patients [31]. In the present study, we also found that acupuncture at KI3 could change more ALFF in MCI patients than that in healthy subjects. In MCI patients, acupuncture at KI3 increased ALFF in left parahippocampus, cingulate, and middle temporal gyrus of both sides and decreased it in precuneus. Those brain regions are components of the default model network. In MCI patients, acupuncture enhances the neuronal activity in the brain regions associated with cognitive function like parahippocampal gyrus and inhibits compensatory increase of activity in temporal regions like precuneus. The enhancement or inhibition of neuronal activities in above brain regions maintains the physiological homeostasis of default model network [7]. Interestingly, in healthy subjects, acupuncture did not significantly change neuronal activities in resting state. We speculated that in the healthy subjects the homeostasis of the neuronal activities in different brain regions is maintained well. In another study regarding the effect of acupuncture on ALFF in AD patients, we also found that acupuncture did not significantly affect the neuronal activities of the default network in rest state (data not shown). The efficiency of acupuncture on the default network may be reduced by the loss of neurons of brain regions associated with cognitive function. These data also give a hint that the early stage may be a "window of opportunity" to prevent dementia aggravation by acupuncture.

In the current study, we did not find the specific regularity from the difference between resting states with and without acupuncture at real or sham acupoint. Acupuncture, as a mechanic stimulation, may activate or inhibit one or one more brain region directly or may evoke or inhibit one brain region which affects other regions. This may be why we can see that the increase or decrease of neuronal activities induced by acupuncture at KI3 in some regions is similar to those induced by acupuncture at sham acupoint.

Specific effect of acupoints is an interesting issue which is helpful for the elucidation of the mechanism response for acupuncture. To verify the hypothesis that a specific region can be activated by acupuncture at an acupoint, we compared the activated brain regions by acupuncture at KI3 or sham acupoint and found that although acupuncture at either KI3 or sham acupoint can induce the increase or decrease of ALFF in the same brain region, but in some brain regions, a few of brain regions show different effects between acupuncture at KI3 and sham acupoint. Our results support the hypothesis that different acupoints can produce the different effects on some brain regions. Similar anatomical characteristics of KI3 and sham acupoint may be the reason that only few brain regions show different effects. To further elucidate the specific effect of acupoint, future studies should be directed to examine the effects of real and sham acupoints where anatomical characteristics are different significantly.

In general, we concluded that acupuncture at KI3 and sham acupoint improved the neuronal activities of the certain cognitive-related regions including medial frontal gyrus, inferior temporal gyrus, and posterior cingulate, which are components of default network. Acupuncture displays more significant effect on neuronal activities of the above brain regions in MCI patients than that in healthy controls. In MCI patients, acupuncture at KI3 presents different effects on the neuronal activities in middle frontal gyrus, superior temporal gyrus, and cingulate gyrus from those of acupuncture at sham acupoint and also exhibits different effects on a few of brain regions.

Conflict of Interests

No conflict of interests, financial or otherwise, is declared by the authors.

Authors' Contribution

Baohui Jia and Jianping Jia designed the conception; Baohui Jia, Zhishun Liu, Baoquan Min, and Aihong Zhou conducted the trials; Zhenchang Wang and Yong Li analyzed data; Baohui Jia and Haifa Qiao interpreted the results and

prepared figures; Haifa Qiao and Baohui Jia drafted the paper; Haifa Qiao, Baohui Jia, and Jianping Jia edited and revised the paper; and Baohui Jia, Zhishun Liu, Baoquan Min, Zhenchang Wang, Aihong Zhou, Yong Li, Haifa Qiao, and Jianping Jia approved the final version of the paper.

Acknowledgments

This work was supported by the National Natural Science Foundation of China grant (no. 81273831) and Intramural Program of Institute of Acupuncture and Moxibustion (no. ZZ12006) to Haifa Qiao. The authors thank Dr. Yufeng Zang for data analysis.

- [1] R. C. Petersen, "Mild cognitive impairment as a diagnostic entity," *Journal of Internal Medicine*, vol. 256, no. 3, pp. 183–194, 2004.
- [2] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment: clinical characterization and outcome," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308, 1999.
- [3] B. Biswal, F. Z. Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI," *Magnetic Resonance in Medicine*, vol. 34, no. 4, pp. 537–541, 1995.
- [4] P. Fransson, "Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis," *Human Brain Mapping*, vol. 26, no. 1, pp. 15–29, 2005.
- [5] V. Kiviniemi, J. Jauhiainen, O. Tervonen et al., "Slow vasomotor fluctuation in fMRI of anesthetized child brain," *Magnetic Resonance in Medicine*, vol. 44, pp. 373–378, 2000.
- [6] F. Bai, Z. Zhang, H. Yu et al., "Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study," *Neuroscience Letters*, vol. 438, no. 1, pp. 111– 115, 2008
- [7] M. D. Greicius, G. Srivastava, A. L. Reiss, and V. Menon, "Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI," Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 13, pp. 4637–4642, 2004.
- [8] Y. He, L. Wang, Y. Zang et al., "Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study," *NeuroImage*, vol. 35, no. 2, pp. 488–500, 2007.
- [9] S.-J. Li, Z. Li, G. Wu, M.-J. Zhang, M. Franczak, and P. G. Antuono, "Alzheimer disease: evaluation of a functional MR imaging index as a marker," *Radiology*, vol. 225, no. 1, pp. 253–259, 2002.
- [10] V. Maxim, L. Şendur, J. Fadili et al., "Fractional Gaussian noise, functional MRI and Alzheimer's disease," *NeuroImage*, vol. 25, no. 1, pp. 141–158, 2005.
- [11] C. Sorg, V. Riedl, M. Mühlau et al., "Selective changes of restingstate networks in individuals at risk for Alzheimer's disease," Proceedings of the National Academy of Sciences of the United States of America, vol. 104, no. 47, pp. 18760–18765, 2007.
- [12] L. Wang, Y. Zang, Y. He et al., "Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence

- from resting state fMRI," NeuroImage, vol. 31, no. 2, pp. 496–504, 2006.
- [13] K. Wang, M. Liang, L. Wang et al., "Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study," Human Brain Mapping, vol. 28, no. 10, pp. 967–978, 2007.
- [14] H.-Y. Zhang, S.-J. Wang, J. Xing et al., "Detection of PCC functional connectivity characteristics in resting-state fMRI in mild Alzheimer's disease," *Behavioural Brain Research*, vol. 197, no. 1, pp. 103–108, 2009.
- [15] Z. Wang, C. Yan, C. Zhao et al., "Spatial patterns of intrinsic brain activity in mild cognitive impairment and alzheimer's disease: a resting-state functional MRI study," *Human Brain Mapping*, vol. 32, no. 10, pp. 1720–1740, 2011.
- [16] L. Lu, Y. Liu, W. Zhu, J. Shi, W. Ling, and T. R. Kosten, "Traditional medicine in the treatment of drug addiction," *The American Journal of Drug and Alcohol Abuse*, vol. 35, no. 1, pp. 1–11, 2009.
- [17] G. Li and E. S. Yang, "An fMRI study of acupuncture-induced brain activation of aphasia stroke patients," *Complementary Therapies in Medicine*, vol. 19, no. 1, pp. S49–S59, 2011.
- [18] X.-Y. Zhong, X.-X. Su, J. Liu, and G.-Q. Zhu, "Clinical effects of acupuncture combined with nimodipine for treatment of vascular dementia in 30 cases," *Journal of Traditional Chinese Medicine*, vol. 29, no. 3, pp. 174–176, 2009.
- [19] Y. Feng, L. Bai, Y. Ren et al., "Investigation of the large-scale functional brain networks modulated by acupuncture," *Magnetic Resonance Imaging*, vol. 29, no. 7, pp. 958–965, 2011.
- [20] C. Zhong, L. Bai, R. Dai et al., "Modulatory effects of acupuncture on resting-state networks: a functional MRI study combining independent component analysis and multivariate granger causality analysis," *Journal of Magnetic Resonance Imaging*, vol. 35, no. 3, pp. 572–581, 2012.
- [21] L. Bai, W. Qin, J. Tian et al., "Acupuncture modulates spontaneous activities in the anticorrelated resting brain networks," *Brain Research*, vol. 1279, pp. 37–49, 2009.
- [22] L. Bai, W. Qin, J. Tian, J. Dai, and W. Yang, "Detection of dynamic brain networks modulated by acupuncture using a graph theory model," *Progress in Natural Science*, vol. 19, no. 7, pp. 827–835, 2009.
- [23] R. P. Dhond, C. Yeh, K. Park, N. Kettner, and V. Napadow, "Acupuncture modulates resting state connectivity in default and sensorimotor brain networks," *Pain*, vol. 136, no. 3, pp. 407–418, 2008.
- [24] B. Yan, K. Li, J. Xu et al., "Acupoint-specific fMRI patterns in human brain," *Neuroscience Letters*, vol. 383, no. 3, pp. 236–240, 2005.
- [25] L. Bai, J. Tian, C. Zhong et al., "Acupuncture modulates temporal neural responses in wide brain networks: evidence from fMRI study," *Molecular Pain*, vol. 6, article 73, 2010.
- [26] K. K. Hui, J. Liu, N. Makris et al., "Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects," *Human Brain Mapping*, vol. 9, pp. 13–25, 2000.
- [27] M. T. Wu, J. C. Hsieh, J. Xiong et al., "Central nervous pathway for acupunture stimulation: localization of processing with functional MR imaging of the brain—Preliminary experience," *Radiology*, vol. 212, no. 1, pp. 133–141, 1999.
- [28] G. Zhang, H. Yin, Y.-L. Zhou et al., "Capturing amplitude changes of low-frequency fluctuations in functional magnetic resonance imaging signal: a pilot acupuncture study on NeiGuan (PC6)," *Journal of Alternative and Complementary Medicine*, vol. 18, no. 4, pp. 387–393, 2012.

- [29] Z. Wang, B. Nie, D. Li et al., "Effect of acupuncture in mild cognitive impairment and Alzheimer disease: a functional MRI study," *PLoS ONE*, vol. 7, no. 8, Article ID e42730, 2012.
- [30] Y. Zhou and J. Jia, "Effect of acupuncture given at the HT 7, ST 36, ST 40 and KI 3 acupoints on various parts of the brains of Alzheimer's disease patients," *Acupuncture & Electro-Therapeutics Research*, vol. 33, no. 1-2, pp. 9–17, 2008.
- [31] Y. Feng, L. Bai, Y. Ren et al., "FMRI connectivity analysis of acupuncture effects on the whole brain network in mild cognitive impairment patients," *Magnetic Resonance Imaging*, vol. 30, no. 5, pp. 672–682, 2012.
- [32] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, pp. 189–198, 1975.
- [33] L. Berg, "Clinical Dementia Rating (CDR)," Psychopharmacology Bulletin, vol. 24, no. 4, pp. 637–639, 1988.
- [34] W. G. Rosen, R. D. Terry, P. A. Fuld, R. Katzman, and A. Peck, "Pathological verification of ischemic score in differentiation of dementias," *Annals of Neurology*, vol. 7, no. 5, pp. 486–488, 1980.
- [35] K. J. Friston, J. Ashburner, C. D. Frith, J.-B. Poline, J. D. Heather, and R. S. J. Frackowiak, "Spatial registration and normalization of images," *Human Brain Mapping*, vol. 3, no. 3, pp. 165–189, 1995.
- [36] J. Talairach and P. Tournoux, Co-Planar Stereotaxic Atlas of the Human Brain, Thieme Medical Publishers, New York, NY, USA, 1st edition, 1988.
- [37] J. Ashburner and K. J. Friston, "Nonlinear spatial normalization using basis functions," *Human Brain Mapping*, vol. 7, pp. 254– 266, 1999.
- [38] X. N. Cheng, Chinese Acupuncture and Moxibustion, Foreign Language Press, Beijing, China, 1999.
- [39] Y. F. Zang, Y. He, C. Z. Zhu et al., "Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI," *Brain & Development*, vol. 29, no. 2, pp. 83–91, 2007.
- [40] S. Lui, X. Huang, L. Chen et al., "High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China," Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 36, pp. 15412–15417, 2009.
- [41] C. Yan, D. Liu, Y. He et al., "Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load," *PLoS ONE*, vol. 4, no. 5, Article ID e5743, 2009.
- [42] H. Yang, X.-Y. Long, Y. Yang et al., "Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI," *NeuroImage*, vol. 36, no. 1, pp. 144–152, 2007.
- [43] S. Y. Bookheimer, M. H. Strojwas, M. S. Cohen et al., "Patterns of brain activation in people at risk for Alzheimer's disease," *The New England Journal of Medicine*, vol. 343, no. 7, pp. 450–456, 2000.
- [44] B. C. Dickerson, D. H. Salat, J. F. Bates et al., "Medial temporal lobe function and structure in mild cognitive impairment," *Annals of Neurology*, vol. 56, no. 1, pp. 27–35, 2004.
- [45] B. C. Dickerson and R. A. Sperling, "Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies," *Neuropsychologia*, vol. 46, no. 6, pp. 1624–1635, 2008.
- [46] A. Hämäläinen, M. Pihlajamäki, H. Tanila et al., "Increased fMRI responses during encoding in mild cognitive impairment," *Neurobiology of Aging*, vol. 28, no. 12, pp. 1889–1903, 2007.

- [47] W. Jagust, R. Thisted, M. D. Devous Sr. et al., "SPECT perfusion imaging in the diagnosis of alzheimer's disease: a clinicalpathologic study," *Neurology*, vol. 56, no. 7, pp. 950–956, 2001.
- [48] L. Zhu, New Acupuncture, People's Press, Beijing, China, 1954.
- [49] T. J. Kaptchuk, "Acupuncture: theory, efficacy, and practice," Annals of Internal Medicine, vol. 136, no. 5, pp. 374–383, 2002.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 687196, 8 pages http://dx.doi.org/10.1155/2015/687196

Research Article

Therapeutic Effects of Oligonol, Acupuncture, and Quantum Light Therapy in Chronic Nonbacterial Prostatitis

İlhan Öztekin, ¹ Hakan Akdere, ² Nuray Can, ³ Tevfik Aktoz, ² Ersan Arda, ² and Fatma Nesrin Turan ⁴

- ¹ Departments of Anesthesiology & Algology, Medical Faculty, Trakya University, Balkan Campus, 22030 Edirne, Turkey
- ² Department of Urology, Medical Faculty, Trakya University, Balkan Campus, 22030 Edirne, Turkey
- ³ Department of Pathology, Medical Faculty, Trakya University, Balkan Campus, 22030 Edirne, Turkey

Correspondence should be addressed to İlhan Öztekin; ioztekin@hotmail.com

Received 28 June 2014; Revised 27 August 2014; Accepted 28 August 2014

Academic Editor: Lu Wang

Copyright © 2015 İlhan Öztekin et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This research aimed to compare anti-inflammatory effects of oligonol, acupuncture, and quantum light therapy in rat models of estrogen-induced prostatitis. Adult male Wistar albino rats were grouped as follows: Group I, control (n=10); Group II, chronic prostatitis (n=10); Group III, oligonol (n=10); Group IV, acupuncture (n=10); Group V, quantum (n=10); Group VI, oligonol plus quantum (n=10); Group VII, acupuncture plus oligonol (n=10). Chronic prostatitis (CP) was induced by the administration of 17-beta-estradiol (E2) and dihydrotestosterone (DHT). Oligonol was given for 6 weeks at a dose of 60 mg/day. Acupuncture needles were inserted at CV 3/4 and bilaterally B 32/35 points with 1-hour manual stimulation. Quantum therapy was administered in 5-minute sessions three times weekly for 6 weeks. Lateral lobes of prostates were dissected for histopathologic evaluation. Although all of the treatment modalities tested in this study showed anti-inflammatory effects in the treatment of CP in male rats, a synergistic effect was observed for oligonol plus quantum light combination. Monotherapy with oligonol showed a superior anti-inflammatory efficacy as compared to quantum light and acupuncture monotherapies.

1. Introduction

Nearly 50% of all men experience prostatitis like symptoms at least once during their lifetime [1, 2]. The cause and pathogenesis of nonbacterial prostatitis is obscure, and its chronic course is associated with therapeutic challenges [1, 2]. Lewis and Wistar rats represent appropriate animal models for experimental CP studies due to the fact that their aging is associated with spontaneous development of nonbacterial prostatitis [3]. Administration of estradiol (E2) causes increased frequency and severity of prostatitis in adult male Wistar rats [4, 5]. Naslund et al. established the emergence of the same histological findings in spontaneous prostatitis and E2-induced prostatitis in Wistar rats. In a number of different studies, spontaneous nonbacterial prostatitis in rats has been

shown to exhibit histological features that are very similar to those in human CP [6, 7].

Polyphenol hydroxyl group, a secondary metabolite substance present in green tea, inhibits inflammation upon being activated with the effect of several antioxidant enzymes. It has been shown to play an important potential role in the prevention of several degenerative conditions such as heart disease and cancer [8–10]. Shoskes et al. showed at least 25% improvement in the symptom scores in 67% of category III CP patients receiving 5-bioflavonoid quercetin. Oligonol, an oligomerized polyphenol (Amino Up Chemical Co., Sapporo, Japan), consists of high concentrations of lower oligomers such as monomers, dimers, trimers, and tetramers that are obtained through the depolymerization of catechintype polyphenol [11]. In the study by Kim et al., oligonol has

⁴ Department of Biostatistics, Medical Faculty, Trakya University, Balkan Campus, 22030 Edirne, Turkey

been found to be efficacious in the prevention of chronic abacterial prostatitis in rats [1].

Quantum light therapy, which is increasingly more commonly used, has its roots in the early 1990s. It can be defined as the collection of data sources, pathways, and methods based on the use of electromagnetic waves, quantum processes, and the informative wave characteristics of the organism. Its effects occur at a cellular and molecular level and they are dispersed throughout the organism via a chain reaction. The wide range of therapeutic effects of the quantum devices is explained based on their ability to allow a communication between electromagnetic information and proteometabolic processes, as well as a special concordance with the organism [12].

The following electromagnetic beams are chosen for use in quantum therapy devices: low intensity, coherent, and super pulsed laser beams with a wavelength of 905 nanometer; wideband pulsed infrared beams with wavelengths between 890 and 960 nanometer; pulsed visible red light with wavelengths between 640 and 740 nanometer; constant magnetic field with an intensity of 35 millitesla [12].

Super pulsed coherent laser beams penetrate deep into tissue (12-13 cm) with strong stimulant effects on blood circulation, cell membrane, and intracellular metabolism. It also activates neurohumoral factors and immunocompetent systems and regulates the endocrine system. Low level laser therapy (LLLT) has a positive effect on the inflammatory process and tissue regeneration [12–17].

The pulsed noncoherent infrared beams possess a wider spectral band with lower penetration abilities, affecting a variety of reflexogen regions, and exhibit a strong regulatory effect on the healthy central nervous and vegetative nervous systems [12].

Pulsed red light, with even lower penetration characteristics than with infrared light, reduces the intensity of inflammation in articular structures, particularly in porous tissues [12, 18].

A constant magnetic field has been designed to serve as an energy barrier against environmental noxious factors including air. It facilitates the penetration of laser beams, allowing the reduction of radiation required to achieve the same level of effect with laser monotherapy [12, 19].

Acupuncture is based on the insertion of sterile needles in acupoints according to certain canal and meridian systems, which were originally defined by the early practitioners of the traditional Chinese medicine (TCM). The needles are rotated manually and stimulated electrically or thermally [20, 21]. Although physiological mechanisms of acupuncture are unknown, several hypotheses exist. For example, acupuncture treatment is thought to regulate the pain control mechanisms within the central nervous system (CNS) through the release of specific neurotransmitters, such as endorphins [21–24].

Acupuncture is generally used for the alleviation of chronic painful conditions [25–29]. Beneficial effects on urinary symptoms and quality of life in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) have been reported [30].

The aim of this study was to compare anti-inflammatory effects of oligonol, acupuncture, and quantum light therapy (magnetic infrared laser) in rat models of estrogen-induced nonbacterial prostatitis.

2. Materials and Methods

2.1. Chemical Reactants. Oligonol manufactured by Quality of Life Labs (NY, USA) by polymerization of polyphenols found in lychee fruit and green tea extract was used in the study. 17-beta-estradiol (E2), testosterone (T), dihydrotestosterone (DHT), and hematoxylin and eosin were provided by Sigma Aldrich (Steinheim, Germany).

2.2. Animals and Treatment. The adult male Wistar albino rats (age > 3 months) were obtained from the Animal Experiment Laboratory, Trakya University (Edirne, Turkey). They were accommodated under controlled temperature and humidity conditions with successive 12-hour cycles of darkness and light. The Local Ethics Committee for Animal Experimentation, Trakya University, approved the treatment protocols. In order to induce lateral prostatic lobe inflammation, a modified estrogen protocol originally proposed by Robinette [31] and Naslund et al. [4] was used. A total of 9 treatment groups with 10 rats in each group were established as follows: Group I, normal controls; Group II, chronic prostatitis; Group III, oligonol; Group IV, acupuncture; Group V, quantum; Group VI, oligonol plus quantum; Group VII, acupuncture plus oligonol; Group VIII, quantum plus acupuncture; Group IX, acupuncture plus quantum plus oligonol. The experimental protocol is shown in Table 1. The normal control group received no treatment. Subcutaneous E2 administration was performed for 4 weeks in animals in the chronic prostatitis group and in other treatment groups, with the additional DHT for two weeks after day 15. E2 and DHT were dissolved in sesame oil and were given subcutaneously at a dose of 250 microgram/kg/day. In oligonol groups, oligonol at a dose of 60 mg/kg/day was given for 6 weeks via oral feeding tube after being diluted with drinking water. The same oligonol protocol was used in combination treatments involving oligonol use. Before each session in the acupuncture groups, ketamine (50 mg/kg, i.m.) and xylazine (5 mg/kg, i.m.) were given for anesthesia. Steel needles $(0.20 \times$ 13 mm) produced by Hua Long Co. (China) were applied for a total duration of 6 weeks at conceptual vessels (CV) 3 and 4 and bilaterally urinary bladder (Bl) 32 and 34 points under the guidance of rat anatomy atlas [32] and atlas of acupuncture [33] by an acupuncturist for three days a week, with 1-hour daily sessions and manual stimulation every 10 minutes. The same acupuncture protocol was used in combination groups involving acupuncture treatment. CV 3 and 4 points are on the anterior midline of the abdomen, 4/5 and 3/5 of the way down from the umbilicus to the superior edge of the pubic bone. B 32 point is on the region of the sacrum, on the 2nd sacral foramen. B 34 point is on the region of the sacrum, medial, on the 4th sacral foramen [33].

TABLE 1: Structure of the experiment.

Groups		n	Drug treatment	Agents administrated to induce inflammation
Group I	Normal control	10	_	_
Group II	Chronic prostatitis	10	_	E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group III	Oligonol	9	Oligonol 60 mg/kg (p.o.)	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group IV	Acupuncture	7	_	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group V	Quantum	7	_	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group VI	Oligonol + quantum	8	Oligonol 60 mg/kg (p.o.)	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group VII	Acupuncture + oligonol	9	Oligonol 60 mg/kg (p.o.)	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group VIII	Quantum + acupuncture	8	_	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)
Group IX	Quantum + oligonol + acupuncture	9	Oligonol 60 mg/kg (p.o.)	10 E2 0.25 mg/kg (s.c.) + DHT 0.25 mg/kg (s.c.)

E2, 17-beta-estradiol; DHT, dihydrotestosterone; s.c., subcutaneous injection; p.o., oral administration.

In the quantum therapy groups, a RIKTA-04/4 Magnetic Infrared Laser Treatment device (JSC MILTA-PKP GIT, Moscow, Russia) was used together with the above mentioned anesthesia protocol under the guidance of a rat anatomy atlas [32] in the following manner with 5-minute daily sessions for 3 days a week for a total duration of 6 weeks: through an emitter with a laser pulse strength of 12 W and active application area of 4 cm² to suprapubic, urinary bladder, anterior penile, and femoral artery (bilateral) regions and through a Douche Emitter with a laser pulse strength of 30 W and active circular application area of 20 cm² to mid-perineum region between testicles and anus (including prostate area) (Table 2). The same protocol was also used in combination treatments involving quantum therapy.

2.3. Body/Prostate Weight and Histopathology. Body weight measurements were performed in all groups at days 1, 20, and 40. After the prostate gland weight was measured without bladder or seminal vesicles, both lateral lobes of prostates were dissected and used for histopathologic evaluation. Samples were fixed in neutral 10% formalin solution for 24 hours at room temperature, dehydrated in ethanol, cleared in xylene, and embedded in paraffin. Hematoxylin and eosin stained 4 micron sections were obtained for histological examination. Double pathologist blinded assessments for pathological evaluations were performed. Prostatitis was considered if inflammatory cell infiltration in epithelial cells of single acini was present. The inflammation was scored according to its intensity and distribution through the prostatic tissue (Figure 1). In this study, a four-tiered scale system applied by Bernoulli et al. was used: grade 0 = no contact between inflammatory cells and epithelium; grade 1 = some contact; grade 2 = periglandular infiltrates adjacent to partially destroyed epithelium; and grade 3 = the number

TABLE 2: Parameters of the quantum light therapy used.

Wavelength of impulsive infrared laser radiation: 890–910 nanometers

Wavelength of pulsating broadband infrared radiation: 860–960 nanometers

Wavelength of pulsating broadband red radiation: 40-740 nanometers

Frequency setting: 50 Hz

Frequency of red light radiation: 2 Hz Magnetic induction: 35 \pm 10 mTl

Time of radiation: 5 min.

Power supply: alternating current

Frequency: 50/60 Hz

Power consumed from an electric network: 20 W Power: 12 W emitter and 30 W emitter (perineum)

Beam area at the skin: 4 cm²

Anatomical location: suprapubic, urinary bladder, anterior penile, and femoral artery (bilateral)

regions and mid-perineum region between testicles and anus (including prostate area)

Number of treatments: 18 procedures

Interval between treatments: 3 days a week for a total duration of 6 weeks

of these acini was more than 25% (Figure 2). The numbers of inflamed acini were counted for the entire prostate area using the same sample sections.

2.4. Statistical Analyses. All data were presented as mean \pm SD. The distributions of all continuous variables for normal distribution were tested using the Kolmogorov-Smirnov one

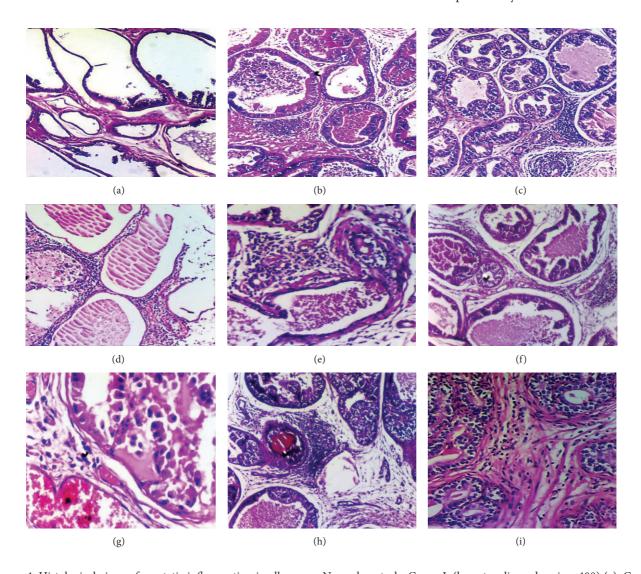


FIGURE 1: Histological views of prostatic inflammation in all groups. Normal controls; Group I, (hematoxylin and eosin, $\times 100$) (a); Group II, chronic prostatitis (hematoxylin and eosin, $\times 100$) (b); Group III, oligonol (hematoxylin and eosin, $\times 100$) (c); Group IV, acupuncture (hematoxylin and eosin, $\times 100$) (d); Group V, quantum (hematoxylin and eosin, $\times 200$) (e); Group VI, oligonol plus quantum (hematoxylin and eosin, $\times 100$) (f); Group VII, acupuncture plus oligonol (hematoxylin and eosin, $\times 200$) (g); Group VIII, quantum plus acupuncture (hematoxylin and eosin, $\times 100$) (h); Group IX, acupuncture plus quantum plus oligonol (hematoxylin and eosin, $\times 200$) (i).

sample test. The comparison between and within groups was performed using repeated measures of ANOVA; the comparison of the groups was performed using one way ANOVA and binary (post hoc) comparisons Tukey b and Dunnett T3 tests. The comparison within groups was evaluated using paired *t*-test. Analyses were performed using the SPSS 20.0 Statistical Package Program. *P* values < 0.05 were considered statistically significant.

3. Results

The total numbers of rats remaining in the study groups at the end of the 6-week experimental protocol are shown in Table 3. 3.1. Body Weight and Prostate Weight. An increase in body weight was observed in all groups, as evidenced by the body weight measurements at days 1, 20, and 40. Despite the absence of a significant difference between the groups in body weight from days 1 to 20, a significant increase at day 40 was noted in Group I compared to Groups VI, VII, and IX (P = 0.032, P = 0.007, and P = 0.009, resp.). In oligonol groups, significantly fewer increases in body weight at day 40 were found as compared to the normal control group (Table 3). However, no significant differences in terms of body weight increase were noted between the normal control group and others. The normal control group showed significantly higher prostate weight compared to the other groups (P = 0.0001) (P = 0.016, 0.017, 0.009, 0.021, 0.047, 0.017, 0.0010, and 0.028, resp.) (Table 3) (Figure 3). A total of 13 rats in all groups died

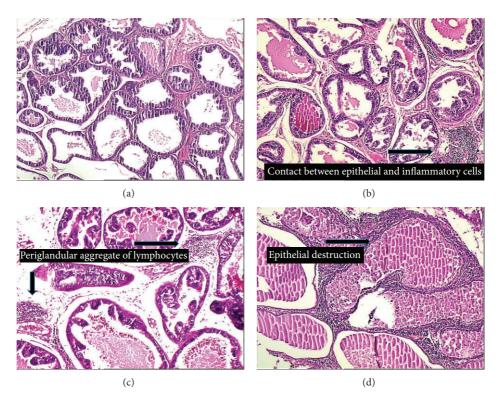


FIGURE 2: Histological views of prostatic inflammation. Control group without any inflammation, grade 0 (hematoxylin and eosin, ×100) (a). Some contact between epithelial cells and inflammatory cells (black arrow), grade 1 (hematoxylin and eosin, ×100) (b). Periglandular infiltrates adjacent to partially destroyed epithelium (black arrows), grade 2 (hematoxylin and eosin, ×100) (c). The inflammation was intensive (black arrow) and the number of inflamed acini was more than 25%, grade 3 (hematoxylin and eosin, ×100) (d).

after anaesthesia (Table 3). Side effects, such as lethargy and mortality, were observed in one rat in response to oligonol.

3.2. Histopathology. In the normal control group, there was almost a normal appearance (median prostatitis score: 1) of the glandular epithelium and stroma with a few leukocyte infiltrations into the lumina and stroma that refers to a grade between 0 and 1 in all rats. Extensive infiltrations of inflammatory cells in the lumina, mononuclear cells in the stroma of the gland, and epithelial degeneration were observed in Group II suggesting CP. Of the 10 rats in this group, 4 rats showed grade 3 and 3 showed grade 2 inflammations.

According to the prostatitis score, there were significant differences between the groups (P = 0.023): between Group I and Groups II, VIII; between Group II and Groups III, VI (resp., P = 0.009, 0.034, 0.017, and 0.024). In Group VIII (8 rats in total), 2 rats showed grade 3 and 3 showed grade 2; the other 3 rats showed grade 1 inflammations. In Group III (9 rats in total), 1 rat showed grade 2 and 8 showed grade 1 inflammations. In Group VI (8 rats in total), 1 rat showed grade 2 and 7 showed grade 1 inflammations (Figure 1).

Oligonol and oligonol plus quantum groups were showed to have stronger anti-inflammatory effects than in the other groups (Table 3).

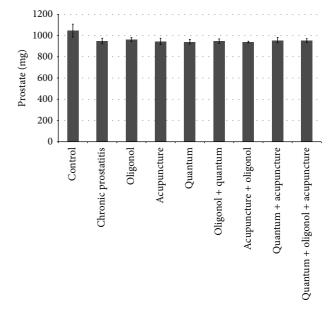


FIGURE 3: Prostate weight groups on day 40.

4. Discussion

Injection of E2 into rats results in prostatic inflammation. Whereas combination of E2 with testosterone prevents tissue

		BW day 1 (gr)	BW day 20 (gr)	BW day 40 (gr)	Prostate weight (mg)	Prostatitis score
Groups		Mean ± SD Median (min–max)	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	Mean ± SD Median (min-max)	Median (min-max)
Group I	Normal control (<i>n</i> : 10)	314.40 ± 20.57 312.50 (289-350)	371.00 ± 29.06 364.00 (325-408)	412.60 ± 16.44 419.50 (380–430)	1,046.80 ± 61.08 1,030.50 (979–1130)	1 (0-2)
Group II	Chronic prostatitis (n:10)	311.80 ± 15.29 317.00 (287-330)	345.20 ± 27.98 342.50 (315-392)	367.80 ± 35.89 373.00 (321-420)	950.00 ± 25.98 950.50 (920–985)	2 (1–3)
Group III	Oligonol (n: 9)	319.67 ± 10.44 324.00 (302-330)	362.78 ± 23.02 373.00 (322-378)	380.33 ± 14.47 385.00 (354-394)	964.00 ± 17.41 974.00 (939–980)	1 (1-2)
Group IV	Acupuncture (n: 7)	316.86 ± 15.04 321.00 (294-332)	372.43 ± 23.41 381.00 (335-394)	406.71 ± 14.04 409.00 (390–425)	947.86 ± 28.75 934.00 (926–992)	2 (1-2)
Group V	Quantum (n: 7)	310.00 ± 14.00 308.00 (294-331)	341.86 ± 29.01 326.00 (321–389)	381.43 ± 25.25 384.00 (350–417)	942.71 ± 2.09 935.00 (928–991)	1 (1–3)
Group VI	Oligonol + quantum (<i>n</i> : 8)	313.50 ± 9.77 314.00 (298-325)	344.12 ± 19.74 343.00 (323–386)	383.88 ± 14.15 388.00 (368–417)	950.25 ± 19.61 945.00 (928–975)	1 (1-2)
Group VII	Acupuncture + oligonol (<i>n</i> : 9)	311.22 ± 8.87 309.00 (301–326)	349.22 ± 27.79 331.00 (323–387)	380.11 ± 13.82 372.00 (364–399)	940.78 ± 8.03 940.00 (930–953)	1 (1–3)
Group VIII	Quantum + acupuncture (n: 8)	308.88 ± 9.43 307.50 (294-321)	358.75 ± 27.35 356.00 (329-392)	386.00 ± 21.82 380.50 (358–416)	956.38 ± 25.15 939.50 (935–989)	2 (1-3)
Group IX	Quantum + oligonol + acupuncture	312.44 ± 14.40	367.67 ± 32.35	388.33 ± 15.50	953.56 ± 17.27	1 (1–3)

TABLE 3: Body weight, prostate weight, and prostatitis score of the groups.

SD: standard deviation; median (min-max): (minimum-maximum) values; BW: body weight; gr: gram; mg: milligram.

atrophy and inflammation, DHT allows the persistence of E2-induced inflammation while preventing tissue atrophy [34]. In this study, E2 and DHT (250 micrograms/kg/day) doses proposed by Naslund et al. [4] were used to induce chronic prostatitis (CP).

We have to use the suitable doses of oligonol, estradiol, and DHT that would be affected by body weight changes in this experimental model. Kim and colleagues [1] mentioned that the estradiol + DHT and oligonol treated groups showed significantly reduced prostate weight compared to the normal control group (P < 0.001). Additionally, no significant difference in prostate weight was noted between the estradiol + DHT and oligonol treated groups (P = 0.125).

In oligonol groups, significantly fewer increases in body weight at day 40 were found as compared to the normal control group. CP and other treatment groups showed significantly reduced prostate weight compared to the normal control group. The reduced prostate weight was most likely due to decreased secretion production. E2 given with DHT could restore wet prostate weight which does not include the secretion weight and could decrease secretion production as well [1]. The 4-point inflammation grading system, used by Bernoulli and colleagues, was applied in evaluating the severity of inflammation of lateral prostate lobes [35]. The severity of inflammation was assessed according to the aggressiveness of inflammation and by counting the number

of inflamed acini from grade 0 to grade 3. Wistar rats represent appropriate animal models for experimental CP studies since aging is associated with spontaneous development of nonbacterial prostatitis in these species [3]. So, median prostatitis score for the control group was 1 with a range between 0 and 2. On microscopic examinations, the oligonol and oligonol plus quantum groups showed an effectively reduced inflammation of the prostate and degeneration of the glandular epithelium compared to the other treatment groups. It has been proposed that oligonol shows beneficial effects in the treatment of nonbacterial CP through the regulation of antioxidative mechanisms, proinflammatory cytokines, and IKBa phosphorylation [1]. Antioxidant effects of oligonol have been previously demonstrated in a number of studies [1, 3, 36]. In a study by Kim et al. [1], an association between the development of nonbacterial prostatitis and significantly reduced activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the prostate tissue has been shown. The same authors have also reported a greater effect of oligonol on GPx activation. The marked similarity between human CP and E2-induced CP in rats may help explain beneficial therapeutic and preventive effects of oligonol on patients with CP/CPPS IIIA [1].

As previously proposed by Vladimirov et al. [37], experimental evidence exists to explain the stimulatory effects of the low intensity laser and noncoherent beams with free

radical mechanisms. They have also pointed out a proven association between the primary mechanisms of the stimulatory effects of light and the secondary mechanisms defining the sanitation effects (bactericidal effect, cellular proliferation, and regulation of microcirculation). In addition, laser beams used for the quantum therapy have been reported to induce an ordered series of nonspecific regulatory reactions with revitalizing, rejuvenating, anesthetic, and antiphlogistic effects [12]. For example, Kogan and colleagues have reported significant superiority of magnetolaser over standard pharmaceutical treatments in terms of the improvement in pain, urinary symptoms, and quality of life scores in the treatment of inflammatory chronic nonbacterial prostatitis [38] that are in line with these research experimental findings. We can say that quantum light therapy is a new approach to CP's treatment as an inexpensive and reasonable alternative treatment that has no apparent side effects.

A good body of evidence suggests that acupuncture therapy helps with anti-inflammatory and analgesic effects [39, 40]. In addition, a report has proposed that the pain in CP/CPPS may be of neuropathic character and acupuncture has neuromodulatory effects [41]. In this study, the acupuncture points most frequently preferred for the treatment of CP/CPPS, that is, CV 3 and 4 bilaterally B1 32 and 34, were used [39] under the guidance of a Rat Atlas and Acupuncture Atlas [32, 33] by an acupuncturist. The mechanism for the anti-inflammatory effect of acupuncture is not yet clear. However, in this study, when the differences between Groups III, VI, VII, and IX were compared, the acupuncture group showed a less anti-inflammatory effect than the other groups. On the other hand, the anti-inflammatory effects of acupuncture were thought to be less effective than oligonol and quantum light. A better median prostatitis score in oligonol + quantum group was obtained, but, due to the limited number of animals in these groups, a statistically significant difference may not be visible.

The mechanisms of anti-inflammatory effects on acupuncture are not yet clear. However, a significant interpersonal variability in the levels of electroacupuncture (EA) analgesia has previously been reported both in animals and in humans [22, 23]. Proposed mechanisms for the effect of EA include the release of endogenous opioid peptides and activation of descendant inhibitory pathways of the CNS [42]. However, EA was not used in this study and manual stimulation of the needles with 10-minute intervals was performed.

5. Conclusions

Although all of the treatment modalities tested in this study showed anti-inflammatory effects in the treatment of estrogen-induced chronic nonbacterial prostatitis in male rats, a better median prostatitis score in oligonol plus quantum light group and oligonol group was obtained. Monotherapy with oligonol showed a superior anti-inflammatory efficacy as compared to quantum light and acupuncture monotherapies. But it might be thought that the combination therapy such as oligonol plus quantum light has a synergism.

We believe that findings of this study may help further stimulate multicenter prospective studies that would better quantify these findings.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors thank Eric Larson for editing the English revision of the paper. This study was funded and supported by the Scientific Research and Project Development Unit of Trakya University.

- [1] D. S. Kim, E. J. Lee, K. S. Cho, S. J. Yoon, Y. H. Lee, and S. J. Hong, "Preventive effects of oligomerized polyphenol on estradiolinduced prostatitis in rats," *Yonsei Medical Journal*, vol. 50, no. 3, pp. 391–398, 2009.
- [2] E. Fowler Jr., "Prostatitis," in Adult and Pediatric Urology, J. A. Gillenwater, J. T. Grayhack, S. S. Howard, and J. W. Duckett, Eds., Mosby-Year Book, St. Louis, Mo, USA, 1991.
- [3] H. Fujii, B. Sun, H. Nishioka, A. Hirose, and O. I. Aruoma, "Evaluation of the safety and toxicity of the oligomerized polyphenol Oligonol," *Food and Chemical Toxicology*, vol. 45, no. 3, pp. 378–387, 2007.
- [4] M. J. Naslund, J. D. Strandberg, and D. S. Coffey, "The role of androgens and estrogens in the pathogenesis of experimental nonbacterial prostatitis," *Journal of Urology*, vol. 140, no. 5, pp. 1049–1053, 1988.
- [5] L. Seethalakshmi, R. S. Bala, R. K. Malhotra et al., "17β-Estradiol induced prostatitis in the rat is an autoimmune disease," *Journal* of *Urology*, vol. 156, no. 5, pp. 1838–1842, 1996.
- [6] R. Lundgren, B. Holmquist, M. Hesselvik, and J. Muntzing, "Treatment of prostatitis in the rat," *Prostate*, vol. 5, no. 3, pp. 277–284, 1984.
- [7] J. Muntzing, G. Sufrin, and G. P. Murphy, "Prostatitis in the rat," *Scandinavian Journal of Urology and Nephrology*, vol. 13, no. 1, pp. 17–22, 1979.
- [8] A. Scalbert, I. T. Johnson, and M. Saltmarsh, "Polyphenols: antioxidants and beyond," *The American journal of clinical nutrition*, vol. 81, no. 1, 2005.
- [9] I. Rahman, S. K. Biswas, and P. A. Kirkham, "Regulation of inflammation and redox signaling by dietary polyphenols," *Biochemical Pharmacology*, vol. 72, no. 11, pp. 1439–1452, 2006.
- [10] I. B. Kim, D. Y. Kim, S. J. Lee et al., "Inhibition of IL-8 production by green tea polyphenols in human nasal fibroblasts and A549 epithelial cells," *Biological and Pharmaceutical Bulletin*, vol. 29, no. 6, pp. 1120–1125, 2006.
- [11] D. A. Shoskes, S. I. Zeitlin, A. Shahed, and J. Rajfer, "Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial," *Urology*, vol. 54, no. 6, pp. 960–963, 1999.
- [12] Y. Fyodorov, *Quantum Therapy and the Prevention of a Wide Range of Diseases*, Quantum Medicine Association, Moscow, Russia, 10th edition, 2007.

- [13] A. N. Alves, K. P. S. Fernandes, C. A. V. Melo et al., "Modulating effect of low level-laser therapy on fibrosis in the repair process of the tibialis anterior muscle in rats," *Lasers in Medical Science*, vol. 29, no. 2, pp. 813–821, 2014.
- [14] J.-Y. Wu, C.-H. Chen, L.-Y. Yeh, M.-L. Yeh, C.-C. Ting, and Y.-H. Wang, "Low-power laser irradiation promotes the proliferation and osteogenic differentiation of human periodontal ligament cells via cyclic adenosine monophosphate," *International Journal of Oral Science*, vol. 5, no. 2, pp. 85–91, 2013.
- [15] T. Ebrahimi, N. Moslemi, A. Rokn, M. Heidari, H. Nokhbatolfoghahaie, and R. Fekrazad, "The influence of low-intensity laser therapy on bone healing," *Journal of Dentistry*, vol. 9, pp. 238–248, 2012.
- [16] L. Assis, A. I. S. Moretti, T. B. Abrahão et al., "Low-level laser therapy (808 nm) reduces inflammatory response and oxidative stress in rat tibialis anterior muscle after cryolesion," *Lasers in Surgery and Medicine*, vol. 44, no. 9, pp. 726–735, 2012.
- [17] H. L. Casalechi, E. C. P. Leal-Junior, M. Xavier et al., "Low-level laser therapy in experimental model of collagenase-induced tendinitis in rats: effects in acute and chronic inflammatory phases," *Lasers in Medical Science*, vol. 28, no. 3, pp. 989–995, 2013.
- [18] S. Dahan, "Laser and intense pulsed light management of couperose and rosacea," *Annales de Dermatologie et de Vénéréologie*, vol. 138, no. 3, pp. S219–S222, 2011.
- [19] T. A. Kupriianova, B. P. Markov, L. A. Vilkova, and A. G. Barabash, "The use of a permanent magnetic field in the combined treatment of lichen ruber planus of the oral mucosa," *Stomatologiia*, vol. 68, pp. 68–33, 1989.
- [20] A. Ellis, N. Wiseman, and K. Boss, Fundamentals of Chinese Acupuncture, Paradigm Publications, Brookline, Mass, USA, 1991
- [21] "1998 NIH Consensus Conference. Acupuncture," *JAMA*, vol. 280, no. 17, pp. 1518–1524, 1998.
- [22] J. Sun, W. Qin, M. Dong et al., "Evaluation of group homogeneity during acupuncture stimulation in fMRI studies," *Journal of Magnetic Resonance Imaging*, vol. 32, no. 2, pp. 298–305, 2010.
- [23] N. M. Tang, H. W. Dong, X. M. Wang, Z. C. Tsui, and J. S. Han, "Cholecystokinin antisense RNA increases the analgesic effect induced by electroacupuncture or low dose morphine: conversion of low responder rats into high responders," *Pain*, vol. 71, no. 1, pp. 71–80, 1997.
- [24] Y. Chae, H.-J. Park, D.-H. Hahm, S.-H. Yi, and H. Lee, "Individual differences of acupuncture analgesia in humans using cDNA microarray," *The Journal of Physiological Sciences*, vol. 56, no. 6, pp. 425–431, 2006.
- [25] National Center for Complementary and Alternative Medicine website, http://nccam.nih.gov/.
- [26] H. Watkin, "Back pain—an integrated approach in primary care," Acupuncture in Medicine, vol. 22, no. 4, pp. 203–206, 2004.
- [27] R. Sekido, K. Ishimaru, and M. Sakita, "Differences of electroacupuncture-induced analgesic effect in normal and inflammatory conditions in rats," *The American Journal of Chinese Medicine*, vol. 31, no. 6, pp. 955–965, 2003.
- [28] C. Yuting, "Clinical observation on combined treatment of 360 cases of prostatitis with acupuncture of Sishenchong point, etc. and selfdrafted prescription I, II, and III," World Journal of Acupuncture-Moxibustion, vol. 10, pp. 1–4, 2000.
- [29] A. S. Al Rashoud, R. J. Abboud, W. Wang, and C. Wigderowitz, "Efficacy of low-level laser therapy applied at acupuncture points in knee osteoarthritis: a randomised double-blind comparative trial," *Physiotherapy*, vol. 100, no. 3, pp. 242–248, 2014.

- [30] J. L. Capodice, Z. Jin, D. L. Bemis et al., "A pilot study on acupuncture for lower urinary tract symptoms related to chronic prostatitis/chronic pelvic pain," *Chinese Medicine*, vol. 2, article 1, 2007.
- [31] C. L. Robinette, "Sex-hormone-induced inflammation and fibromuscular proliferation in the rat lateral prostate," *Prostate*, vol. 12, no. 3, pp. 271–286, 1988.
- [32] R. J. Olds and J. R. Olds, "A Colour Atlas of the Rat. Dissection Guide," ELBS with Wolfe Publishing Educational Low-Priced Books Scheme funded by the British Government, 1991.
- [33] C. Focks, *Atlas of Acupuncture*, Churchill Livingstone, Elsevier, Munich, Germany, 2008.
- [34] M. J. Wilson, M. Woodson, C. Wiehr, A. Reddy, and A. A. Sinha, "Matrix metalloproteinases in the pathogenesis of estradiolinduced nonbacterial prostatitis in the lateral prostate lobe of the Wistar rat," *Experimental and Molecular Pathology*, vol. 77, no. 1, pp. 7–17, 2004.
- [35] J. Bernoulli, E. Yatkin, Y. Konkol, E.-M. Talvitie, R. Santti, and T. Streng, "Prostatic inflammation and obstructive voiding in the adult noble rat: impact of the testosterone to estradiol ratio in serum," *Prostate*, vol. 68, no. 12, pp. 1296–1306, 2008.
- [36] M. H. Li, J. H. Jang, B. Sun, and Y. J. Surh, "Protective effects of oligomers of grape seed polyphenols against β -amyloid-induced oxidative cell death," *Annals of the New York Academy of Sciences*, vol. 1030, pp. 317–329, 2004.
- [37] I. A. Vladimirov, G. I. Klebanov, G. G. Borisenko, and A. N. Osipov, "Molecular and cellular mechanisms of the low intensity laser radiation effect," *Biofizika*, vol. 49, no. 2, pp. 339–350, 2004.
- [38] M. I. Kogan, A. V. Shangichev, and I. I. Belousov, "Efficacy of magnetolaser therapy of patients with an inflammatory form of chronic abacterial prostatitis," *Urologiiia*, no. 2, pp. 42–44, 2010.
- [39] Z.-X. Yang, P.-D. Chen, H.-B. Yu, M. Pi, W.-S. Luo, and Y.-Y. Zhuo, "Study strategies for acupuncture treatment of chronic nonbacterial prostatitis," *Zhong Xi Yi Jie He Xue Bao*, vol. 10, no. 3, pp. 293–297, 2012.
- [40] J. L. Capodice, D. L. Bemis, R. Buttyan, S. A. Kaplan, and A. E. Katz, "Complementary and alternative medicine for chronic prostatitis/chronic pelvic pain syndrome," *Evidence-Based Complementary and Alternative Medicine*, vol. 2, no. 4, pp. 495–501, 2005.
- [41] J. F. Audette and A. H. Ryan, "The role of acupuncture in pain management," *Physical Medicine and Rehabilitation Clinics of North America*, vol. 15, no. 4, pp. 749–772, 2004.
- [42] J. S. Han, "Acupuncture and endorphins," *Neuroscience Letters*, vol. 361, no. 1–3, pp. 258–261, 2004.

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 802846, 8 pages http://dx.doi.org/10.1155/2015/802846

Research Article

Efficacy and Cost Effectiveness of the Acupuncture Treatment Using a New Skin Stimulus Tool Called M-Test Which Is a Measure Based on Symptoms Accompanied with Body Movements: A Pragmatic RCT Targeting Hemodialysis Patients

Shuji Ono¹ and Yoshito Mukaino²

¹Department of Oriental Medicine of Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan ²Faculty of Sports and Health Science, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

Correspondence should be addressed to Shuji Ono; onoshu_8@yahoo.co.jp and Yoshito Mukaino; mukaino.y@gmail.com

Received 10 October 2014; Revised 17 January 2015; Accepted 19 January 2015

Academic Editor: Xinyan Gao

Copyright © 2015 S. Ono and Y. Mukaino. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

M-Test can simultaneously reduce hemodialysis patients' diverse symptoms. Its diagnosis and treatment are based on simple movements that can be performed by anyone and allow determining which meridians have problems by analyzing symptoms accompanied with movement. It also enables to conduct a safe and effective treatment with use of microcorn which is a noninvasive treatment tool. This time we conducted microcorn intervention on hemodialysis patients based on diagnosis of M-Test. As a result, almost all of the dialysis patients' complaints have been relieved while the score of HR-QOL increased. According to our calculation of cost effectiveness, it confirmed that it is very cost-effective.

1. Introduction

Although every hemodialysis patient has multiple symptoms [1], many previous studies on the efficacy of acupuncture treatment for hemodialysis patients were focused on their typical symptoms individually such as itchiness, fatigue, insomnia, and pain [2, 3]. However, a hemodialysis patient has a wide range of nonmotor symptoms such as itchiness, dizziness, and palpitations in addition to orthopedic pain including back pain. Acupuncture treatment can simultaneously reduce a wide range of dialysis patients' symptoms; however, there have been little studies discussing the efficacy of acupuncture treatment focusing on all symptoms that a single patient suffers.

With *M*-Test [4, 5], our new acupuncture therapeutic method introduced in 1995, diverse symptoms of dialysis patients can be simultaneously relieved. *M*-Test is a treatment approach to diagnose and treat patients by using a measure based on symptoms accompanied by body movements such as pain and dizziness. Its basic movements consist of simple movements that anyone can perform. By analyzing symptoms

accompanied by movements, we can easily determine which meridians have problems and how they should be restored and what kind of treatments are required. *M*-Test is simple and safe and treat patients' complaints effectively and quickly [6].

By simulating acupuncture points that are led by this method, many case studies show that a patient's various symptoms get simultaneously relieved when the body movement gets improved. Multiple medicines are required to treat diverse symptoms of dialysis patients based on Western medicine. It is of a low cost and has a significant economic benefit to be able treat patients without medicine.

In addition, needles have been mainly used as a stimulating tool in discussing efficacy of acupuncture treatment for dialysis patients. It is a safe treatment approach if conducted by trained acupuncturist; however, there are risks of increased susceptibility to infection due to their lower immunity as well as hemorrhage from use of an anticoagulant. Therefore it is desirable to use a less-invasive or noninvasive stimulation approach.

In the current clinical study for hemodialysis patients, we used a noninvasive skin stimulating tool which was developed in 2006. Type II is a brush (or microcorn) which has approximately 400 microspikes that are regularly aligned on a disc in diameter of 11 mm. It is not inserted but only lightly stimulates the skin surface with microspikes. For this reason, there is no danger of bleeding and infection and it is pain-free for patients. Based on our experiences, it has equivalent or even more effects to use it as a stimulating tool during acupuncture treatment for various symptoms. In animal experiments, it has been reported by Hotta et al. that the light mechanical stimulation by the microcorn can induce a strong analgesic effect on autonomic reflex [7]. Efficacy of microcorn is becoming clear in the fundamental medicine.

If we can prove effectiveness of the skin stimulating tool for acupuncture points led by the newly developed symptoms, we believe it will open up acupuncture's new possibilities not only for hemodialysis patients' symptoms but also for various diseases in different areas.

Therefore, we conducted a pragmatic randomized controlled trial (P-RCT) for hemodialysis patients using the acupuncture point selecting method based on *M*-test which is measured by symptoms accompanied by body movements and newly developed microcorn symptoms in order to discuss its efficacy and cost-effectiveness of the treatment.

2. Subjects and Methods

- 2.1. Subjects. We targeted 47 patients who understood and agreed to the study's purpose and content out of 100 hemodialysis outpatients at hemodialysis facilities in Kagawa Prefecture. Primary diseases which led to the introduction of hemodialysis included 16 chronic glomerulonephritis, 17 diabetic nephropathy, 4 nephrosclerosis, 1 chronic pyelonephritis, 1 ANCA-related nephritis, 1 IgA nephritis, 1 membranous nephropathy, 1 secondary hyperparathyroidism, and 5 unknown causes.
- 2.2. Condition of Maintenance Hemodialysis. We made a comparison on regular monthly blood test results for patients with maintenance hemodialysis in order to understand effectiveness of hemodialysis, abnormal bone metabolism, anemia, and self-management. Measurement of blood test included erythrocyte, leukocyte, hematocrit value, hemoglobin, urea nitrogen, creatinine, calcium, inorganic phosphorus, total protein, and albumin.
- 2.3. Study Design. Subjects who receive maintenance hemodialysis were randomly allocated to 2 groups: one with acupuncture treatment (acupuncture group) and one without it (traditional treatment group). We allocated subjects by a draw using envelopes. Both groups continued dialyzing before intervention for a hemodialysis.

This research was conducted for 21 weeks and the pretreatment was set as treatment phase 0. For the group with acupuncture, treatment was given once a week and 8 times in total. We defined a week after the first treatment as treatment phase 1, a week after the second treatment as treatment phase 2, and then phases 3, 4, 5, 6, 7, and 8 subsequently on a weekly basis. We also defined 4 weeks after treatment phase 8 as follow-up phase 4 and after 12 weeks as follow-up phase 12. For the traditional treatment group, only hemodialysis was given with the same schedule of observation criteria. Symptoms and EQ-5D were researched by survey sheet 5 times in total at treatment phase 0, treatment phase 4, treatment phase 8, follow-up phase 4, and follow-up phase 12. Observation criteria will be explained more in detail in a later chapter. Each survey sheet is filled directly by a patient and collected before starting hemodialysis. Blood test was performed on monthly basis.

2.4. Treatment Methods. M-Test was employed for acupuncture treatment for the acupuncture group. M-Test is a diagnostic treatment system that has a measure for symptoms accompanied by body movement. This method allows determining problematic meridians by analyzing symptoms associated with movement. By performing movements classified into 30 items and facilitating positive findings induced by a movement such as pain and tension as Numerical Rating Scale (NRS), this method evaluates 11 degrees of conditions between 0 which is a state free of pain and tension to 10 which is a state with the strongest pain and tension. It allows us to easily determine how meridians should be restored and what kind of treatments is required by summarizing the result. M-Test is simple and safe and treats patients' complaints effectively and quickly. As the body movement is improved, not only locomotory symptoms but also various symptoms including aplanetic ones can be simultaneously improved. Treatment procedure in detail conformed to a principle of M-Test. First, therapist measures patient's M-Test finding. 30 items of M-Test finding consist of movement by which the anterior, the posterior and the lateral-medial are extended. Movement is classified by the upper part of body and the lower part of the body and it is classified into 6 blocks (anterior (A block), posterior (B block), and lateral-medial (C block) upper body; anterior (D block), posterior (E block), and lateral-medial (F block) lower body). Therapist estimates patient's movement in NRS and this is *M*-Test finding.

The occasion with the finding is regarded as abnormality of the meridian distributed over the block. In other words, when there is abnormality in an A block, it is a problem of a lung and large intestine meridians; in a B block, it is a problem of a heart and small intestine meridians; in a C block, it is a problem of a pericardium and triple energizer meridians; in a D block, it is a problem of a spleen and stomach meridians; in a E block, it is a problem of a kidney and bladder meridians; and in a F block, it is a problem of a liver and gallbladder meridians. A basic acupuncture point is set in M-Test. It is LU5 LU9, LI2, and LI11 in A block, HT7, HT9, SI3, and SI8 in B block, PC7, PC9, TE3, and TE10 in C block, SP2, SP5, ST41, and ST45 in D block, KI1, KI7, BL65, and BL67 in E block, and LR2, LR8, GB38, and GB43 in F block. Next, therapist treats a patient. Therapist touches patient's basic acupuncture point, and a patient does the movement with positive movement of M-Test finding. Therapist chooses the most effective acupuncture point for a patient and treats it with a treatment tool. Therapist obeys the following rules. (1) A therapist checks all *M*-Test findings. (2) It is treated from a lower body. (3) It is treated from the highest score of *M*-Test finding.

When a basic acupuncture point shows the enough effect, a medical person treats the next point. If the effect by the basic treatment point is insufficient or it is ineffective, therapist treats muscle on the meridian that runs each block. This is repeated until all *M*-Test findings decrease. When a *M*-Test finding was not improved, the next step was prepared, but a skill until this stage was used by this study.

- 2.5. Treatment Tool. Microcorn (Somacept type III and Somareson type III), noninvasive simulating tools manufactured by Tokyo Resin Corp, was used in this study. Somareson type III is a small disc of 4 mm in diameter and attached to a tape. It is made of elastomer and has about 40 microspikes in height of 0.03 mm on the stimulating surface. The microspikes are regularly aligned at interval of 0.4 mm and lightly stimulate skin surface with a fixed pressure by attaching to the skin. Although it is same form and size as Somacept type III, its material is made of hard plastic and its microspike has a different shape. It is 0.15 mm in height while its grid interval is 0.45 mm.
- 2.6. Patient's Symptoms. Multiple-answer questionnaire of 40 criteria was created with use of reference documents to study patients' symptoms [8]. We selected 20 criteria that have the highest symptom prevalence. Symptoms shown from the highest occurrence are as follows: headache, blurred vision, difficulty in hearing, dizziness, ear buzzing, palpitation, depression, constipation, cervical pain, stiff shoulders, back pain, knee pain, leg cramp, lower limb pain, numbness in upper limb, numbness in lower limb, itchiness, difficulty in sleeping, edema, and listlessness. Each symptom was evaluated by its degree with Visual Analogue Scale (VAS) [9].
- 2.7. EQ-5D and Utility. QOL (quality of life) score (utility) was calculated by using EuroQol5-Dimension (EQ-5D) questionnaire [10, 11]. EQ-5D is a questionnaire used to evaluate health related QOL (HR-QOL) as a preference-based measure developed in UK. It consisted of five-dimensional approach and visual evaluation. The currently collected responses from the five-dimensional approach were computed with Tarrif Value set or so-called conversion for utility that converted death as 0 and perfect health as 1 which is one-dimensional QOL specified by an interval scale. Utility collected from the five-dimensional approach was used in this study for cost analysis.
- 2.8. Incremental Cost-Effectiveness Ratio (ICER). As an effective index for cost effectiveness analysis, utility calculated by survey sheets and survived period under the applicable conditions was multiplied while the index called quality-adjusted life years (QALY) was used to consider both the quality and the extension of life [12]. In this research, we

Table 1: Demographic characteristics and laboratory date at time of study recruitment.

	Acupuncture group	Traditional treatment group
Number of patients (n)	24	23
Age (years)	70.0 ± 9.6	67.3 ± 13.0
Height (cm)	155.6 ± 10.8	158.9 ± 9.5
Dry weight (kg)	50.0 ± 9.4	53.2 ± 11.7
Time on hemodialysis (years)	10.3 ± 8.2	6.5 ± 6.8
Primary diseases		
Chronic glomerulonephritis	10	6
Diabetic nephropathy	6	11
Nephrosclerosis	2	2
Chronic pyelonephritis	1	0
ANCA-related nephritis	1	0
IgA nephritis	1	0
Membranous nephropathy	1	0
Secondary hyperparathyroidism	1	0
Unknown cause	1	4

No significant differences between the two groups.

calculated ICER, the amount of money required to increase QALY for a year, and used utility which was collected from the results of EQ-5D. We calculated ICER as the cost of *M*-test per a patient in the acupuncture group and that of medicines actually prescribed as direct costs:

ICER (Yen/QALY)

- = Materials used for acupuncture treatment \cdot (QALY for treatment phase 8 less QALY right before introduction)⁻¹.
- 2.9. Statistical Processing. We conducted two-way repeated measures analysis of variance to evaluate the groups (two standards: acupuncture group and traditional treatment group) with VAS and utility, as well as 2 factors of each group's timeline. Significance level was set below 5% while SPSS15.0 was used for statistical processing.

3. Results

3.1. Characteristics of Patients. We clarified patients in each group for their height, dry weight (DW), age, average years of dialysis, standard deviation, and primary diseases. There was not a significant characteristic difference in those patients (Table 1).

During the study, one patient dropped out of acupuncture group due to hospitalization to another hospital. Six patients dropped out from the traditional treatment group for reasons specified as follows. One patient deceased, 4 patients were

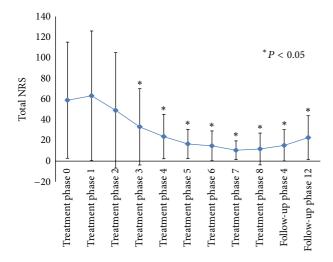


FIGURE 1: Total NRS of *M*-test finding.

hospitalized to other hospitals, and 1 patient refused to respond to the questionnaire.

- 3.2. States of Maintenance Hemodialysis. Blood test results were compared by each criterion (Table 2). There was no significant difference for all criteria between the two groups.
- 3.3. M-Test Finding. To achieve findings for M-Test, we compared the total points of all movements' NRS collected at each pretreatment (Figure 1). Comparing from treatment phase 0, total NRS went down significantly after treatment phase 3.
- 3.4. Patients' Symptoms. The results from the questionnaire are shown in the Table 3. There was no criterion with a significant difference at treatment phase 0 between the two groups. During the measurement period, 12 VAS of symptoms were significantly decreased for acupuncture group compared from treatment phase 0 as follows: headache, blurred vision, dizziness, ear buzzing, cervical pain, stiff shoulders, back pain, lower limb pain, numbness in lower limb, numbness in upper limb, itchiness, and difficulty in sleeping. For the traditional treatment group, 3 symptoms were decreased as follows: difficulty in hearing, stiff shoulders, and difficulty in sleeping. During the measurement period, variances were confirmed between the two groups for the 12 VAS of symptoms as follows: blurred vision, dizziness, palpitation, depression, constipation, cervical pain, stiff shoulders, leg cramp, numbness in lower limb, numbness in upper limb, itchiness, and difficulty in sleeping. In all symptoms, the acupuncture group showed significantly low values. In addition, most of symptoms decreased their value from treatment phase 0 to 8 and increased from treatment phase 8 to follow-up phase 12.
- 3.5. Utility. Utility collected by EQ-5D is shown in Table 4. Utility of those in acupuncture group increased significantly at treatment phase 8 while utility of those in traditional

treatment group confirmed no significant difference. In addition, the acupuncture group showed significantly high points at treatment phase 8.

3.6. Costs and ICER. The amount of microcorns spent per patient was 4,328 Yen (SD = 778 Yen) at average. Quantity of microcorn used in a single M-Test was 4 at least and 20 at most with an average of 10.8 (SD = 1.94). The cost per a single M-Test was 540 Yen. ICER calculated based on the utility collected by EQ-5D questionnaire was 980,998 Yen/QALY.

4. Discussion

4.1. Patients' Symptoms. Every hemodialysis patient in this clinical study has multiple symptoms. For example, they have a wide range of nonmotor symptoms such as itchiness, dizziness, and palpitations in addition to orthopedic pain including back pain. It is a widely known fact that these symptoms limit activities and decrease QOL due to physical and mental loads. Multiple medicines are required to treat them with traditional western medicine and can be expensive.

After 8 weeks of acupuncture treatment in this study for the acupuncture group, 12 symptoms out of 20 were significantly improved. Six out of 12 were locomotory disorders including cervical pain, stiff shoulders, back pain, lower limb pain, numbness in lower limb, and numbness in upper limb. The remaining 6 were other types of disorders included headache, blurred vision, dizziness, ear buzzing, itchiness, and difficulty in sleeping. Since M-Test treats movement, it is obvious that locomotory symptoms get improved. In addition it confirmed that it is also effective to improve symptoms other than locomotory symptoms. This result indicates that multiple symptoms can be simultaneously treated by focusing on treatment on abnormal movements. Symptoms improved by the traditional treatment group such as blurred vision, difficulty hearing, and stiff shoulders were improved due to seasonal variations and the effect of traditional dialysis treatments while the 2 symptoms including blurred vision and stiff shoulders were believed to reduce symptoms by adding M-Test since these showed significantly low points in acupuncture treatment group apart from seasonal variations. We believe addition of M-Test to the traditional dialysis treatments enabled to effectively treat other symptoms such as dizziness, palpitation, depression, constipation, numbness in lower limb, numbness in upper limb, itchiness, and difficulty in sleeping. Judging from these said reasons and the status quo that dialysis patients with multiple disorders are prescribed a medicine per symptom, we believe M-Test treatment can simultaneously treat multiple symptoms and can be an effective treatment by improving body movements. Previous clinical observations also indicate that dialysis patients' symptoms are deeply related to aggravation of body movements. It is assumed that one of causes for a development or aggravation of a symptom is related to worsened body movement.

4.2. Utility and QOL. In order to examine the influence for EQ-5D and QOL, we researched utility that is an index of

Table 2: Blood test results were compared by each criterion.

Blood test	Group	Treatment phase 0	Treatment phase 4	Treatment phase 8	Follow-up phase 4	Follow-up phase 12
T 1.0 (102/)	Acupuncture group $n = 23$	366.7 ± 40.7	357.7 ± 40.5	352.6 ± 37.3	365.6 ± 51.4	365.2 ± 53.8
Leukocyte (10 $/\mu$ L)	Traditional treatment group $n = 17$	371.1 ± 65.2	364.5 ± 78.2	340.6 ± 55.7	362.7 ± 58.2	364.2 ± 48.7
T14- (102 /)	Acupuncture group $n = 23$	51.8 ± 14.9	51.7 ± 18.6	51.8 ± 18.4	54.3 ± 19.4	54.6 ± 19.5
Leukocyte (10 $/\mu$ L)	Traditional treatment group $n = 17$	63.6 ± 22.5	62.8 ± 22.5	60.1 ± 23.4	63.6 ± 23.8	66.4 ± 29.7
Uses at south value ()()	Acupuncture group $n = 23$	35.2 ± 3.0	34.8 ± 3.7	35.0 ± 3.2	35.4 ± 4.2	35.3 ± 4.4
riematocrit value (%)	Traditional treatment group $n = 17$	36.5 ± 4.5	36.7 ± 6.0	34.3 ± 4.3	35.9 ± 4.0	36.3 ± 2.9
Umonlohin (n/dI)	Acupuncture group $n = 23$	11.7 ± 1.1	11.6 ± 1.2	11.7 ± 1.0	11.9 ± 1.4	11.7 ± 1.5
Helifoglobili (g/al.)	Traditional treatment group $n = 17$	12.1 ± 1.4	12.2 ± 1.9	11.6 ± 1.4	12.1 ± 1.3	12.2 ± 1.0
The mit was a sit and a site of the second o	Acupuncture group $n = 23$	22.7 ± 5.9	22.6 ± 7.3	19.1 ± 5.0	18.7 ± 5.4	20.0 ± 5.7
Orea mirogen (mg/ar.)	Traditional treatment group $n = 17$	214.4 ± 8.2	21.7 ± 6.0	20.6 ± 6.5	22.1 ± 8.2	22.4 ± 8.1
(IF/~~) ~~i~:+~~~	Acupuncture group $n = 23$	4.1 ± 1.1	4.2 ± 1.1	4.0 ± 0.9	4.0 ± 1.0	4.8 ± 3.3
Cleaning (mg/ar)	Traditional treatment group $n = 17$	4.5 ± 1.0	4.4 ± 1.1	4.2 ± 1.0	4.7 ± 2.2	4.8 ± 2.2
Coloinm (ma/d1)	Acupuncture group $n = 23$	9.5 ± 0.6	9.7 ± 0.5	9.5 ± 0.4	9.4 ± 0.5	9.4 ± 0.6
Calcium (mg/ur)	Traditional treatment group $n = 17$	9.7 ± 0.6	9.8 ± 0.8	9.8 ± 0.7	9.8 ± 0.5	9.6 ± 0.5
(16/200) como describes ciacomo el	Acupuncture group $n = 23$	2.4 ± 0.5	2.5 ± 0.6	2.3 ± 0.5	2.3 ± 0.4	2.2 ± 0.4
morgamic pmospnorus (mg/ur.)	Traditional treatment group $n = 17$	2.6 ± 0.6	2.4 ± 0.5	2.3 ± 0.6	2.5 ± 0.9	2.4 ± 0.7
Total mantain (201)	Acupuncture group $n = 23$	6.1 ± 0.6	8.5 ± 11.4	6.1 ± 0.5	5.9 ± 0.5	6.0 ± 0.5
iotai pioteiii (g/uL)	Traditional treatment group $n = 17$	6.5 ± 0.4	6.6 ± 0.3	6.5 ± 0.2	6.3 ± 0.3	6.6 ± 0.4
1 1 2 min (1/1)	Acupuncture group $n = 23$	3.6 ± 0.2	3.6 ± 0.2	3.5 ± 0.2	3.6 ± 0.2	3.5 ± 0.3
Audinen (pinol/L)	Traditional treatment group $n = 17$	3.7 ± 0.2	3.7 ± 0.2	3.6 ± 0.1	3.6 ± 0.1	3.7 ± 0.2
No significant difference between the two groups.	two groups.					

TABLE 3: The change in patient's symptoms in each phase.

(•			1		
Symptom	Group	Treatment phase 0	Treatment phase 4	Treatment phase 8	Follow-up phase 4	Follow-up phase 12
Hondocho	Acupuncture group $n = 23$	17.1 ± 26.1	10.7 ± 15.3	$6.2 \pm 13.5^{*}$	$8.5 \pm 20.0^{*}$	8.2 ± 13.8
Headache	Traditional treatment group $n = 17$	8.6 ± 16.3	11.6 ± 20.1	9.9 ± 17.7	8.5 ± 14.3	15.6 ± 26.9
Diversity rations	Acupuncture group $n = 23$	33.4 ± 32.7	$17.0 \pm 22.2^{\#}$	$12.7 \pm 20.9^{**}$	$13.5 \pm 17.9^{**}$	$19.4 \pm 20.9^{**}$
blurred vision	Traditional treatment group $n = 17$	34.5 ± 36.3	33.4 ± 30.4	43.7 ± 37.1	33.9 ± 31.5	41.6 ± 30.7
D:# 14 i 1	Acupuncture group $n = 23$	17.8 ± 24.8	17.7 ± 22.7	13.0 ± 22.8	12.4 ± 18.4	18.6 ± 28.6
Difficulty in nearing	Traditional treatment group $n = 17$	20.6 ± 28.9	26.4 ± 31.5	25.6 ± 34.1	29.3 ± 34.6	$33.2 \pm 36.1^{*}$
	Acupuncture group $n = 23$	13.0 ± 21.4	10.2 ± 17.7	1.4 ± 6.3 **	$2.8 \pm 7.4^{*}$	7.9 ± 13.9
Dizzmess	Traditional treatment group $n = 17$	9.4 ± 16.4	14.7 ± 22.9	15.8 ± 23.3	9.1 ± 14.5	8.1 ± 36.1
	Acupuncture group $n = 23$	17.9 ± 27.2	13.5 ± 23.7	8.0 ± 13.2	$8.0 \pm 14.7^{*}$	10.7 ± 19.5
Ear Duzzing	Traditional treatment group $n = 17$	21.1 ± 30.2	16.0 ± 23.3	21.7 ± 34.3	16.6 ± 28.4	24.3 ± 31.5
D. 1	Acupuncture group $n = 23$	16.6 ± 27.8	14.0 ± 19.5	$6.5 \pm 17.2^*$	11.1 ± 23.5	15.3 ± 20.8
Faipitation	Traditional treatment group $n = 17$	12.2 ± 25.0	18.4 ± 21.1	21.4 ± 27.7	11.4 ± 21.2	16.8 ± 24.4
	Acupuncture group $n = 23$	15.4 ± 29.1	$7.8 \pm 15.7^*$	$6.4 \pm 19.3^*$	$4.4 \pm 8.5^*$	9.7 ± 20.3
Depression	Traditional treatment group $n = 17$	19.3 ± 30.5	24.7 ± 30.7	22.4 ± 30.2	26.8 ± 32.4	21.9 ± 31.6
on the state of th	Acupuncture group $n = 23$	25.0 ± 35.1	18.5 ± 30.3	$13.7 \pm 23.0^*$	$7.4 \pm 11.7^*$	$15.8 \pm 25.7^*$
Consupation	Traditional treatment group $n = 17$	45.4 ± 41.0	35.6 ± 34.1	31.4 ± 32.9	43.8 ± 39.0	41.4 ± 40.0
200	Acupuncture group $n = 23$	37.7 ± 39.1	$25.3 \pm 29.7^{*}$	$14.2 \pm 21.9^{**}$	$23.1 \pm 24.3^{*}$	25.1 ± 27.7
Cei vicai paiii	Traditional treatment group $n = 17$	16.0 ± 24.5	25.2 ± 24.9	34.5 ± 33.6	29.5 ± 35.4	30.2 ± 33.5
Stiff of our down	Acupuncture group $n = 23$	29.9 ± 28.6	34.5 ± 25.6	$12.5 \pm 21.6^{**}$	$21.3 \pm 25.2^{*}$	$29.9 \pm 28.6^{*}$
Sun snomaers	Traditional treatment group $n = 17$	25.1 ± 27.1	25.9 ± 26.2	37.2 ± 34.2	$39.1 \pm 39.3^{*}$	35.5 ± 33.9
Dadragia	Acupuncture group $n = 23$	38.5 ± 33.7	27.3 ± 29.6	$9.3 \pm 18.1^{\#}$	$20.7 \pm 31.2^{*}$	33.8 ± 31.8
Баск ралп	Traditional treatment group $n = 17$	25.5 ± 22.8	22.1 ± 27.4	23.0 ± 27.1	28.1 ± 29.9	27.9 ± 26.4
Vicencia	Acupuncture group $n = 23$	26.0 ± 32.1	24.8 ± 28.2	15.7 ± 25.8	20.8 ± 31.5	29.8 ± 31.4
Miee Pain	Traditional treatment group $n = 17$	23.1 ± 31.9	23.8 ± 33.4	15.8 ± 27.5	21.6 ± 33.1	24.3 ± 32.1
**************************************	Acupuncture group $n = 23$	20.5 ± 29.1	21.4 ± 29.5	$12.1 \pm 17.8^*$	15.1 ± 30.0	$13.7 \pm 24.5^*$
reg cramp	Traditional treatment group $n = 17$	40.8 ± 37.8	38.2 ± 25.9	33.6 ± 33.1	33.2 ± 32.1	34.7 ± 35.8
I consolimit action	Acupuncture group $n = 23$	29.4 ± 36.4	29.4 ± 30.1	$17.1 \pm 23.3^{*}$	16.7 ± 27.2	23.2 ± 32.7
гомет шпо раш	Traditional treatment group $n = 17$	21.5 ± 33.9	28.5 ± 35.8	25.5 ± 36.3	27.2 ± 35.5	26.6 ± 34.3
Amil readu ai seedamil	Acupuncture group $n = 23$	18.9 ± 30.4	$12.5 \pm 34.9^*$	$4.0 \pm 29.5^{**}$	$9.0 \pm 29.0^{\#}$	9.5 ± 26.1
isumoness in apper mino	Traditional treatment group $n = 17$	29.6 ± 40.3	21.0 ± 37.9	11.6 ± 38.6	23.2 ± 40.5	20.1 ± 38.0
Mimbass in lower limb	Acupuncture group $n = 23$	21.9 ± 34.9	$16.0 \pm 25.3^*$	$9.8 \pm 23.1^*$	$11.0 \pm 26.2^{**}$	12.6 ± 24.2
transciss in tower mine	Traditional treatment group $n = 17$	32.5 ± 40.6	39.1 ± 40.7	34.9 ± 33.9	33.0 ± 38.5	29.8 ± 37.5
14-11-11-11-11-11-11-11-11-11-11-11-11-1	Acupuncture group $n = 23$	38.7 ± 40.7	$29.3 \pm 31.5^{*}$	18.6 ± 29.7 ^{**}	18.6 ± 27.7 [#]	$22.7 \pm 28.1^{*}$
TCITITOS S	Traditional treatment group $n = 17$	33.2 ± 35.5	33.3 ± 31.2	43.9 ± 37.2	35.7 ± 39.7	40.4 ± 42.3
Difficultarin clooning	Acupuncture group $n = 23$	34.8 ± 36.9	$28.2 \pm 31.2^*$	12.8 ± 22.5 **	$12.2 \pm 21.4^{**}$	19.6 ± 26.9 [#]
Cincurty in siccping	Traditional treatment group $n = 17$	39.3 ± 40.4	$54.5 \pm 38.0^{*}$	43.9 ± 37.2	35.7 ± 39.7	40.4 ± 42.3
Holoma	Acupuncture group $n = 23$	13.9 ± 27.0	10.3 ± 24.8	8.8 ± 19.8	9.4 ± 22.4	14.0 ± 29.5
Duenna	Traditional treatment group $n = 17$	16.1 ± 27.6	17.5 ± 26.1	14.2 ± 26.2	14.6 ± 21.2	18.2 ± 32.9
l istlessness	Acupuncture group $n = 23$	31.7 ± 33.8	26.8 ± 25.6	20.6 ± 29.8	19.9 ± 23.7	29.0 ± 31.3
	Traditional treatment group $n = 17$	41.3 ± 36.4	42.9 ± 32.6	36.4 ± 29.3	38.6 ± 35.5	38.4 ± 33.1
LO 0						

 $^*P < 0.05$, compared to traditional treatment group. $^*P < 0.05$ compared to the phase 0 in the group.

TABLE 4: The change in utility in each phase.

	Treatment phase 0	Treatment phase 4	Treatment phase 8	Follow-up phase 4	Follow-up phase 12
Acupuncture group $n = 23$	0.66 ± 0.15	0.65 ± 0.18	$0.76 \pm 0.17^{**}$	0.71 ± 0.16	0.66 ± 0.20
Traditional treatment group $n = 17$	0.64 ± 0.18	0.63 ± 0.20	0.64 ± 0.18	0.63 ± 0.19	0.64 ± 0.21

^{*}P < 0.05, compared to traditional treatment group.

HR-QOL for 5 times in total including treatment phase 0, treatment phase 4, treatment phase 8, follow-up phase 4, and follow-up phase 12. Collected QOL was significantly high for acupuncture group at treatment phase 8 (P < 0.05). QOL is the index of HR-QOL and if it has increased, it translates as improvement of the dialysis patient's QOL. M-Test treatment for 8 weeks has reduced dialysis patients' symptoms and it is believed that the QOL has improved as a result. We did not confirm a change in utility at EQ-5D upon treatment phase 4 when the 4th treatment out of 8 was completed which indicated that it might require a certain period of treatment to expect effectiveness of the adequate degree to increase QOL.

4.3. ICER. ICER calculable from utility is the differences of medical fees less than QALY before and after the interventions and indicates the cost required to prolong 1QALY. In this case, it is equivalent of the medical fees including the cost of microcorns required to extend a year of dialysis patient's QALY. The cost of microcorns required for this study as well as dialysis patient's ICER calculated from the varied traditional dialysis treatment costs was 980,998 Yen per QALY. Okusa has reported the affordable cost per QALY for the Japanese society as 6 million Yen [13]. These 6 million Yen are reviewed as a maximum amount for cost-effectiveness upon discussing a new medical practice and it is concluded to be cost-effective if it is below this amount.

4.4. M-Test. M-Test treatment differs from traditional acupuncture treatment. It is very simple and safe, which allows quick judging and getting results effectively. There are a lot of choices in a check, a remedy, a skill, and a tool for conventional acupuncture and a variable of the factor by which public welfare does that is too big for the check and treatment, and it is difficult to indicate reproducibility and objectivity.

But the *M*-Test is also similar to the manual muscle testing a doctor and a physical therapist use, so it is easy for a therapist to understand. The therapeutic effect does not influence skill of a therapist, like a sphygmoscopy or tongue diagnosis. Reproducibility is high because a procedure from a check to treatment is decided even if an unskillful therapist treats a patient in *M*-Test. We can tell the self-care for which *M*-Test was utilized to a patient when a patient understood that various symptoms decreased by improving *M*-test finding. Since patient's reaction can be confirmed on sites, it allows medical practitioners to learn effective points for treatment and improve their clinical techniques. *M*-Test requires a short treatment which will hardly be a burden for patients and is very simple and easy to introduce to the traditional dialysis treatments. In addition, patients become

more conscious of their own health management as they can confirm effectiveness with their body movement. Once they understand their own characteristics, they can conduct selfcare by stretching since the movements of *M*-Test are in form of stretching at the same time. In considering characteristics of dialysis treatment, it is very important for patients to be able to perform self-care. It is also promising to reduce medical costs.

It is believed that *M*-Test treatment is cost-effective and effective to reduce patients' symptoms and maintain and improve QOL.

4.5. Microcorns. Emergence of microcorn has opened up possibilities for acupuncture treatment to be an applicable approach for other medical license holders in the future such as nurses and physiotherapists while acupuncture treatment is traditionally performed by limited practitioners such as doctors and acupuncturists. In addition, there are possibilities to develop it as a methodology that can be performed by patients as self-care. We have been advising patients to use microcorns as self-care and are confident it will be a very effective self-care method.

5. Summary

In this study, we researched dialysis patients' symptoms and effects on QOL to evaluate its economic performance. The result indicated that an introduction of acupuncture treatment to dialysis treatment is cost-effective and beneficial to reduce dialysis patients' symptoms and improve QOL. In particular, use of *M*-Test allows safe and prompt evaluation, as well as delivery of quantified effects. Use of microcorn also expands places and situations where nonacupuncturists can practice acupuncture treatment which can be a very useful self-care method.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] S. Nakai, K. Sukuki, I. Masakane et al., "Overview of regular dialysis treatment in Japan (as of 31 December 2008)," *Therapeutic Apheresis and Dialysis*, vol. 14, no. 6, pp. 505–540, 2010.
- [2] T. Okuno, M. Akamatu, and T. Agishi, "Actual acupuncture treatment for hemodialysis patients," *Therapeutic Apheresis and Dialysis*, vol. 23, no. 3, pp. 471–476, 2008.

 $^{^{\#}}P < 0.05$ compared to the phase 0 in the group.

- [3] S. Shunnji, T. Yamasaki, H. Ikefuji et al., "I case of acupuncture treatment for intermittent claudication in diabetic dialysis patients," *Therapeutic Apheresis and Dialysis*, vol. 39, no. 7, pp. 1257–1263, 2006.
- [4] Y. Mukaino, Meridian Test, Ishiyaku, 1999.
- [5] Y. Mukaino, *Diagnosis and Treatment by the Meridian Test*, Ishiyaku Publishers, 2002.
- [6] H. Sakuraba, K. Sawasaki, H. Takeuchi et al., "A study on the effect with the introduction of acupuncture that aims to improve and maintain QOL of dialysis patients—practice of acupuncture therapy for itching," *Kidney*, vol. 30, no. 2, pp. 167– 174, 2007.
- [7] H. Hotta, R. F. Schmidt, S. Uchida, and N. Watanabe, "Gentle mechanical skin stimulation inhibits the somatocardiac sympathetic: C-reflex elicited by excitation of unmyelinated C-afferent fibers," *European Journal of Pain*, vol. 14, no. 8, pp. 806–813, 2010.
- [8] H. Sakuraba, H. Takeuchi, M. Takeuchi, and M. Shouji, "The questionnaire survey on acupuncture and symptoms of maintenance hemodialysis patients," *Therapeutic Apheresis and Dialysis*, vol. 40, no. 6, pp. 513–516, 2007.
- [9] S. Nakamura, "Clinical assessment of pain: VAS, NRS, McGill pain questionnaire, face scale," *Journal of Physical Therapy*, vol. 23, pp. 67–73, 2006.
- [10] N. Ikegami, K. Simoduma, S. Fuuhara, and S. Ikegami, QOL Assessment Handbook for Clinical, Igaku-Shoin, 2001.
- [11] Japanese Version of EQ-5D Development Committee, "Development of the Japanese version of EQ-5D," *Social and Medical*, vol. 8, no. 1, pp. 109–123, 1998.
- [12] S. Ikegami, "Basic knowledge of health economics, economic evaluation of medical technology. Focusing on quality-adjusted life year," *The Bone*, vol. 23, no. 2, pp. 145–150, 2009.
- [13] Y. Okusa, "Studies on the upper limit of the social burden of per QALY," *Iryoutoshakai (Social and Medical)*, vol. 13, pp. 121–130, 2003

Hindawi Publishing Corporation Evidence-Based Complementary and Alternative Medicine Volume 2014, Article ID 950326, 5 pages http://dx.doi.org/10.1155/2014/950326

Research Article

Inhibiting Effect of Electroacupuncture at Zusanli on Early Inflammatory Factor Levels Formed by Postoperative Abdominal Adhesions

Lijian Zhang,¹ Huizhen Wang,¹ Zhenjun Huang,¹ Xian Shi,² Sen Hu,³ Ingrid Gaischek,⁴ Daniela Litscher,⁴ Lu Wang,⁴ and Gerhard Litscher⁴

Correspondence should be addressed to Xian Shi; 301sx@live.cn and Gerhard Litscher; gerhard.litscher@medunigraz.at

Received 7 July 2014; Accepted 27 July 2014; Published 12 August 2014

Academic Editor: Xinyan Gao

Copyright © 2014 Lijian Zhang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We observed the inhibitive effect of electroacupuncture (EA) at Zusanli on inflammatory mediators of postoperative intraabdominal adhesions to find out the relationship between EA and the cholinergic anti-inflammatory pathway. Sixty-four rats were divided into 8 groups (A–H, each = 8): A = sham control; B = abdominal adhesions model; C = abdominal adhesions plus EA; D = sham acupoint control; E = abdominal adhesions plus vagotomy; F = abdominal adhesions plus EA after vagotomy; G = abdominal adhesions plus α -bungarotoxin (BGT); and H = abdominal adhesions plus EA after α -BGT. α -BGT (1 μ g/kg) was injected into the abdominal cavity after surgery, and the bilateral celiac vagotomy was done during the surgery. On the third day the levels of inflammatory mediators (TNF- α , nitric oxide (NO), and nitric oxide synthase (NOS)) in tissues were evaluated. The abdominal adhesion groups developed obvious edema. Compared with sham control, the abdominal adhesion resulted in a significant elevation of inflammatory mediators. EA lowered the elevated levels of inflammatory mediators significantly; EA plus α -BGT and vagotomy showed less anti-inflammatory effects. The activation of the cholinergic anti-inflammatory pathway might be one of the mechanisms of EA at Zusanli acupoints to exert the anti-inflammatory effects.

1. Introduction

Abdominal adhesion is a common complication in pelvic surgery, with an incidence of up to 90%. Severe cases can lead to intestinal obstruction and female infertility, thus bringing great suffering and a heavy burden to the patient [1]. For ischemia, injury, and foreign body irritation during surgery, large amounts of proinflammatory cytokines in tissues are produced, which can lead to an increase of vascular permeability and angiogenesis in the adhesion sites, resulting in abdominal adhesions [2]. Therefore, an early lowering of abnormally elevated proinflammatory cytokine levels is one of the main ways to prevent and treat abdominal adhesions.

Acupuncture treatment has a wide range of clinical applications. References show that electroacupuncture at

the Zusanli (ST36) acupoint has significant inhibiting effects on sepsis and endotoxemia with proinflammatory cytokine levels, which can effectively protect organ function [3, 4].

The aim of this study was to observe the effects of electroacupuncture (EA) at the Zusanli acupoint on early inflammatory cytokines formed by postoperative abdominal adhesion and to explore the anti-inflammatory mechanism of Zusanli.

2. Materials and Methods

2.1. Experimental Animals and Grouping. Sixty-four male Wistar rats, weighing 220 \pm 20 g, were obtained from the Animal Center of Military Medical Sciences (Certificate

¹ Department of Rehabilitation of the 309th Hospital of People's Liberation Army, Beijing 100091, China

² Department of Acupuncture and Moxibustion, Military Acupuncture Training Centre, People's Liberation Army General Hospital, No. 28, Fuxing Road, Beijing 100853, China

³ Laboratory of Shock and Organ Dysfunction, Burns Institute, First Affiliated Hospital of PLA General Hospital, Beijing 100037, China

⁴ Research Unit for Complementary and Integrative Laser Medicine, Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, TCM Research Center Graz, Medical University of Graz, Auenbruggerplatz 29, 8036 Graz, Austria

number SXCL-(Army-2007-004)). The rats were housed at a constant temperature of $24 \pm 2^{\circ}$ C and constant humidity (50 ± 5%) conditions for one week. They received no food in the 12 hours before the experiment but had free access to water.

The rats were randomly divided into 8 groups (each = 8): group A (sham control), group B (abdominal adhesions model), group C (abdominal adhesions plus EA), group D (sham acupoint control), group E (abdominal adhesions plus vagotomy), group F (abdominal adhesions plus EA after vagotomy), group G (abdominal adhesions plus α -bungarotoxin (BGT)), and group H (abdominal adhesions plus EA after α -BGT).

2.2. Experimental Methods

- (1) Model Making. The method described by Chiang et al. [5] was used to achieve the rats abdominal adhesions model. After successful intramuscular anesthesia using ketamine plus Sumianxin (2:1 preparation, 0.5 mL/kg), the rats were fixed in supine position. The skin was prepared routinely and disinfected, and sterile towels were prepared. After cutting 2 cm along the abdominal midline, the cecum was carefully pulled out and fricted to bleed by sterile dry gauze, with an area of approximately $2 \text{ cm} \times 1 \text{ cm}$. Number 0 silk was used to fix a $1 \text{ cm} \times 1 \text{ cm}$ medical silicone membrane, trying not to damage other tissues. The cecum was inserted back into the abdominal cavity, and the abdomen was closed with number 0 silk. Rats had free access to water and food after surgery.
- (2) Processing Methods. For group A, the cecum was flipped and the abdomen closed without any special treatment. In groups B-F, abdominal adhesions surgery was conducted. For groups C, F, and H, about 40 minutes was spent before the rats were awake after abdominal adhesions surgery. Then they were fixed with a bag (limbs exposed through four holes), and the bilateral Zusanli acupoint (outside of the knee, about 5 mm below the fibular head) [6] was selected and acupunctured. The two needles were connected with two electrode coils, and the acupoint was stimulated continuously (2 mA, 2-100 Hz) for 1 hour with an EA device (domestic HANS, LH202H). For group D, a nonacupoint (about 5 mm below the outer of Zusanli acupoint) was stimulated using the same electrode, parameters of intensity, frequency, and time (2 mA, 2-100 Hz, 1 h). For groups E and F, the bilateral abdominal vagus nerve was precut before modeling. The α 7 receptorspecific antagonist α -BGT (1 μ g/kg) was immediately injected into abdominal cavity after surgery. After surgery, the rats had free access to water and food and were sacrificed on the third day.
- 2.3. Observations and Detection Methods. On the third day, all rats were fixed after intramuscular anesthesia by ketamine plus Sumianxin (2:1 preparation, 0.5 mL/kg), and the abdominal cavity of those was cut again. The rats were sacrificed by draining abdominal aortic blood. A part of appendix was clipped and was packed in liquid nitrogen cryopreservation. 100 mg appendix and 9 mL saline were

added to prepare a 10% homogenate. Then it was centrifuged for 10-30 min with a speed of 1000 and 3000 rev/min, respectively (the speed depends on the measurement targets). The supernatant after centrifuging was cryopreserved (-80° C) and prepared to be detected.

- (1) $TNF-\alpha$ Levels. A rat $TNF-\alpha$ ELISA test kit (Diaclone Company) was used (sensitivity 20 pg/mL, detection range 20-1000 pg/mL). In strict accordance with the manual steps, the instrument automatically calculated a standard curve regression equation: y = 0.0173 + 0.0003x, r = 0.9942. The optical density of the sample was put into a standard curve and multiplied by the appropriate dilution factor to calculate the sample's $TNF-\alpha$ content, with a unit of pg/mL.
- (2) Detection of Nitric Oxide (NO) Content. An NO kit (Nanjing Jiancheng Bioengineering Institute) was used in strict accordance with the instructions; the results are given in μ mol/gprot unit.

The formula is NO content (μ mol/gprot) = (absorbance measurement tube – tube blank absorbance)/(standard Quasi absorbance tube – absorbance of blank tube) × standard concentration (20 μ mol/L) × sample protein content (gprot/L).

(3) Detection of Nitric Oxide Synthase (NOS) Content. We used an NOS kit (Nanjing Jiancheng Bioengineering Institute) in strict accordance with the instructions; results are given in U/gprot unit.

The formula is Total NOS activity = (total NOS tube optical density value measured – blank tube optical density)/coloring matter nanomolar extinction coefficient \times reaction liquid total volume/sample volume \times 1/(optical path \times reaction time) \div 1000.

2.4. Statistical Analysis. ANOVA statistical analysis software was used to process the data. Differences between each group were compared, indicated with $(\overline{x} \pm s)$. A P value of <0.05 was considered statistically significant.

3. Results

- 3.1. $TNF-\alpha$ Levels. On the third postoperative day, group A showed a very low content of tissue TNF- α , significantly lower than the other groups (P < 0.01). Compared with group C, groups B, D, E, F, G, and H had a significantly increased TNF- α content (P < 0.01 or P < 0.05), which shows that EA was able to significantly reduce early tissue TNF- α levels of abdominal adhesion but not to reach to the level of Group A. The TNF- α levels of groups B, D, E, F, G, and H showed no significant difference (P > 0.05) between them (see Table 1).
- 3.2. NO Content. On the third postoperative day, all groups showed a significantly increased NO content (P < 0.01) compared with group A. Group C had a significantly lower NO content than groups B, D, E, F, G, and H (P < 0.01 or P < 0.05). Groups B and D, groups E and F, and groups G and H had no significant differences (P > 0.05) (see Table 2).

Groups	Number of animals	TNF-α	P value compared with group A	P value compared with group C
Group A	8	79.73 ± 20.44	_	0.0000
Group B	8	648.30 ± 114.06	0.0000	0.0366
Group C	8	509.29 ± 126.27	0.0000	_
Group D	8	662.12 ± 100.88	0.0000	0.0181
Group E	8	713.92 ± 114.83	0.0000	0.0044
Group F	8	652.43 ± 136.54	0.0000	0.0471
Group G	8	698.15 ± 122.76	0.0000	0.0089
Group H	8	664.26 ± 125.52	0.0000	0.0274

Table 1: Comparison of cecum TNF- α levels [($\overline{x} \pm s$), Pg/gprot].

Table 2: Comparison of cecum NO levels $[(\bar{x} \pm s), \text{Mmol/gprot}].$

Groups	Number of animals	NO	P value compared with group A	P value compared with group C
Group A	8	1.06 ± 0.28	_	0.0000
Group B	8	2.69 ± 0.44	0.0000	0.0286
Group C	8	2.28 ± 0.18	0.0000	_
Group D	8	2.67 ± 0.37	0.0000	0.0179
Group E	8	2.81 ± 0.36	0.0000	0.0023
Group F	8	2.74 ± 0.29	0.0000	0.0019
Group G	8	2.66 ± 0.25	0.0000	0.0036
Group H	8	2.62 ± 0.17	0.0000	0.0017

3.3. NOS Content. The rats that had undergone intraperitoneal adhesions surgery had a higher NOS content (P < 0.01). Group C showed a lower NOS content than groups B, D, E, F, G, and H (P < 0.05). Compared with group B, groups D, E, F, G, and H had no significant NOS content difference (P > 0.05) (see Table 3).

4. Discussion

Abdominal and/or pelvic surgery can lead to peritoneal injury and tissue inflammation, which can produce large amounts of proinflammatory cytokines. These proinflammatory cytokines can increase vascular permeability to deposit fibrin and promote angiogenesis and remodeling, thus triggering the formation of abdominal adhesions [7]. Tumor necrosis factor- α (TNF- α), nitric oxide (NO), nitric oxide synthase (NOS), and other cytokines are involved in inflammation and play an important role in the formation of abdominal adhesions [8]. Thus, early suppression of abnormally elevated proinflammatory cytokine levels is one of the effective means for preventing and treating postoperative abdominal adhesions.

TNF- α is the cytokine-mediated inflammation. In cases of endotoxemia, early sepsis, and burns, plasma or tissue TNF- α levels were found to be significantly increased, adding to the pathological organ tissue damage [9–12]. Saba et al. found that TNF- α levels were significantly associated with the adhesion degree after abdomen surgery, which can be used as a reliable indicator of human biology postoperative peritoneal adhesion formation [13].

In the formation process of tissue adhesions, proinflammatory cytokines can cause a variety of tissues and cells of inducible nitric oxide synthase (iNOS) expression, catalyzing a large amount of catalytic NO, causing a series of pathological responses. iNOS plays an important role in systemic infection and excessive pathophysiology of inflammatory response. Hu et al. [3, 10–12] conducted a series of experiments and found that in rats with severe burns, endotoxemia, and early-stage sepsis, plasma and tissue NOS activity increased, causing a higher NO production leading to multiple organ disorders.

According to traditional Chinese medicine, the pathological bases of postoperative abdominal adhesions are meridian injuries, blood stasis, damp stagnation, and gastrointestinal inhibition, resulting in healthy-qi deficiency and pathogens sufficiency.

Acupuncture points of Yang Ming meridians and abdomen are mainly used in clinical care. Zusanli is the confluent acupoint of Yang Ming meridians, which can promote gastrointestinal motility, improve the blood flow and immune system and can have other effects; in addition, modern research results show that Zusanli has anti-inflammatory effects, which can reduce inflammatory factor levels abnormally elevated in blood plasma or tissue of the sepsis, endotoxin, and scald rats, inhibiting organ dysfunction [9–12].

In our experiment we found that in the early postoperative abdominal adhesion formation, cecums got to be edema. TNF- α , NO, and NOS were significantly increased and thus priming the immune and inflammatory cascade. Group C showed lower levels of inflammatory cytokines, indicating that acupuncture at the Zusanli acupoint can reduce abnormally elevated levels of inflammatory factors, reducing the pathological organ tissue damage. In a series of experiments on peritoneal adhesions, we observed that EA at Zusanli can significantly inhibit the formation of adhesions

Groups	Number of animals	NOS	P value compared with group A	P value compared with group C
Group A	8	1.11 ± 0.26	_	0.0000
Group B	8	2.35 ± 0.21	0.0000	0.0215
Group C	8	2.00 ± 0.32	0.0000	_
Group D	8	2.46 ± 0.42	0.0000	0.0273
Group E	8	2.52 ± 0.41	0.0000	0.0134
Group F	8	2.40 ± 0.18	0.0000	0.0081
Group G	8	2.42 ± 0.28	0.0000	0.0144
Group H	8	2.38 ± 0.26	0.0000	0.0207

TABLE 3: Comparison of cecum NOS activity $[(\bar{x} \pm s), U/gprot]$.

in abdominal tissue angiogenesis, reducing inflammatory infiltration, and thus effectively prevent abdominal adhesion formation [14, 15].

The cholinergic anti-inflammatory pathway goes by the central nervous system and the cholinergic neurotransmitter (acetylcholine, Ach). The Ach can significantly inhibit the release of endotoxin-stimulated human blood TNF- α and IL-6 and other proinflammatory cytokines. In addition, direct electrical stimulation of cholinergic nerves (efferent vagus nerve) can inhibit the synthesis of TNF [16]. The cholinergic nerves mainly undergo functions through both M and N receptors (M and N in the presence of multiple receptor subtypes). The excitatory cholinergic anti-inflammatory effects of the molecular basis of choline are present in the N-type surface of the macrophage receptor α_7 subunit (α 7nAChR) [17]. Torres-Rosas et al. found that sciatic nerve activation with electroacupuncture controlled systemic inflammation and rescued mice from polymicrobial peritonitis, which induces vagal activation of aromatic L-amino acid decarboxylase, leading to the production of dopamine in the adrenal medulla [18]. For rats with endotoxemia and sepsis, a precut bilateral abdominal vagus nerve or injection of α 7nAChR blocks α -BGT; the anti-inflammatory and organ protective effects of EA at Zusanli diminished or disappeared, which resulted in the inflammatory factor levels of plasma or tissue inflammatory elevated [4, 9, 11]. In this experiment, we found the cecum treated was getting inflammation and edema. A part of cecum was clipping in order to observe and detect the inflammatory response. By researching the levels of inflammatory cytokines in tissues, we plan to detect inflammatory factors in plasma and study the systemic inflammatory response.

In our experiment, we found that in the early phase of postoperative abdominal adhesion formation, the proinflammatory cytokine levels produced by precut bilateral abdominal vagus nerves or tissue treated with α -BGT showed no significant differences (P > 0.05) compared with the model group. The implementation of EA at Zusanli had no significant anti-inflammatory effects.

Zusanli acupuncture can significantly reduce inflammatory cytokines levels of postoperative abdominal adhesions, inhibit the activated immune and inflammatory cascade, and prevent abdominal adhesion formation. Precutting abdominal vagus or giving N receptor blocking agent α -BGT treatment can lead to the disappearance of the anti-inflammatory

effects of EA at Zusanli. We believe that EA at Zusanli can effectively inhibit the interaction of early postoperative abdominal adhesion formation mechanism and excite the cholinergic anti-inflammatory pathway.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The scientific investigations were supported by the Austrian Federal Ministries of Science, Research, and Economy and of Health and the Eurasia-Pacific Uninet (Project "Evidence-based high-tech acupuncture and integrative laser medicine for prevention and early intervention of chronic diseases").

References

- [1] Z. Alpay, G. M. Saed, and M. P. Diamond, "Postoperative adhesions: from formation to prevention," *Seminars in Reproductive Medicine*, vol. 26, no. 4, pp. 313–321, 2008.
- [2] T. Liakakos, N. Thomakos, P. M. Fine, C. Dervenis, and R. L. Young, "Peritoneal adhesions: etiology, pathophysiology, and clinical significance. Recent advances in prevention and management," *Digestive Surgery*, vol. 18, no. 4, pp. 260–273, 2001
- [3] L. J. Zhang, X. Shi, H. Y. Bai, C. M. Bao, and S. Hu, "The protective effects of electro-acunpunture at Zusanli point on proinflammatory factors induced- myocardial injury in septic rats," *Journal of Chinese PLA Postgraduate Medical School*, vol. 31, no. 4, pp. 377–381, 2010.
- [4] S. Hu, S. Qi, H. B. Wang et al., "Study on the protective effect and mechanism of electroacupuncturing at Zusanli point on endotoxin induced hepatic injury in rats," *Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care*, vol. 14, no. 5, pp. 296–298, 2007.
- [5] S. C. Chiang, C. H. Cheng, K. S. Moulton, J. M. Kasznica, and S. L. Moulton, "TNP-470 inhibits intraabdominal adhesion formation," *Journal of Pediatric Surgery*, vol. 35, no. 2, pp. 189– 196, 2000.
- [6] Z. R. Li, "Experimental acupuncture," *China Press of Traditional Chinese Medicine*, pp. 327–328, 2003.
- [7] L. Krähenbühl, M. Schäfer, V. Kuzinkovas, P. Renzulli, H. U. Baer, and M. W. Büchler, "Experimental study of adhesion

- formation in open and laparoscopic fundoplication," *The British Journal of Surgery*, vol. 85, no. 6, pp. 826–830, 1998.
- [8] I. Crha, P. Ventruba, M. Petrenko, and H. Visnová, "Present possibilities of prevention of adhesions and their immunologic aspects," *Ceská Gynekologie*, vol. 64, no. 4, pp. 230–234, 1999.
- [9] S. Hu, L. Zhang, H. Bai, and C. Bao, "The effects of electroacupuncturing at Zusanli point on intestinal proinflammatory factors, diamine oxidase and tissue water content in rats with sepsis," *Chinese Critical Care Medicine*, vol. 21, no. 8, pp. 485– 487, 2009.
- [10] S. Hu, L. J. Zhang, H. Y. Bai, and C. M. Bao, "Effects of electro-acupuncture at Zusanli point on the expression of proinflammatory cytokines, the activity of diamine oxidase and the rate of water content in the small intestine in rats with sepsis," World Chinese Journal of Digestology, vol. 26, no. 2, pp. 353–356, 2010.
- [11] S. Hu, Q. Song, L. Wang, Y. Lv, GY. Zhou, and ZY. Sheng, "Effect of activating cholinergic anti-inflammatory pathway by electroacupuncture on proinflammatory cytokines release and organ dysfunction in rat with endotoxin challenge," *Chinese Journal* of Integrated Traditional and Western Medicine in intensive and Critical Care, vol. 15, no. 4, pp. 205–208, 2008.
- [12] S. Hu, L. Wang, Q. Song et al., "Effect and mechanism of electroacupuncture at Zusanli on gastrointestinal mucosal blood flow and motility in rats with scald injury," *Chinese Journal of Integrated Traditional and Western Medicine in intensive and Critical Care*, vol. 16, no. 2, pp. 79–81, 2009.
- [13] A. A. Saba, V. Godziachvili, A. K. Mavani, and Y. J. Silva, "Serum levels of interleukin 1 and tumor necrosis factor α correlate with peritoneal adhesion grades in humans after major abdominal surgery," *The American Surgeon*, vol. 64, no. 8, pp. 734–736, 1998
- [14] L. J. Zhang, Z. J. Huang, H. Y. Bai, S. Hu, and X. Shi, "The empirical study of electro-acupuncture at Zusanli points on abdominal adhesions," *Journal of Chinese Medicine*, vol. 26, no. 163, pp. 1466–1468, 2011.
- [15] L. J. Zhang, Z. J. Huang, S. Hu, and X. Shi, "The empirical study of electro-acupuncture at Zusanli points on angiogenesis of intra-abdominal adhesion tissues," *Journal of Chinese Medicine*, vol. 27, no. 175, pp. 1609–1610, 2012.
- [16] L. V. Borovikova, S. Ivanova, M. Zhang et al., "Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin," *Nature*, vol. 405, no. 6785, pp. 458–462, 2000.
- [17] H. Wang, M. Yu, M. Ochani et al., "Nicotinic acetylcholine receptor α 7 subunit is an essential regulator of inflammation," *Nature*, vol. 421, no. 6921, pp. 384–388, 2003.
- [18] R. Torres-Rosas, G. Yehia, G. Pena et al., "Dopamine mediates vagal modulation of the immune system by electroacupuncture," *Nature Medicine*, vol. 20, no. 3, pp. 291–295, 2014.