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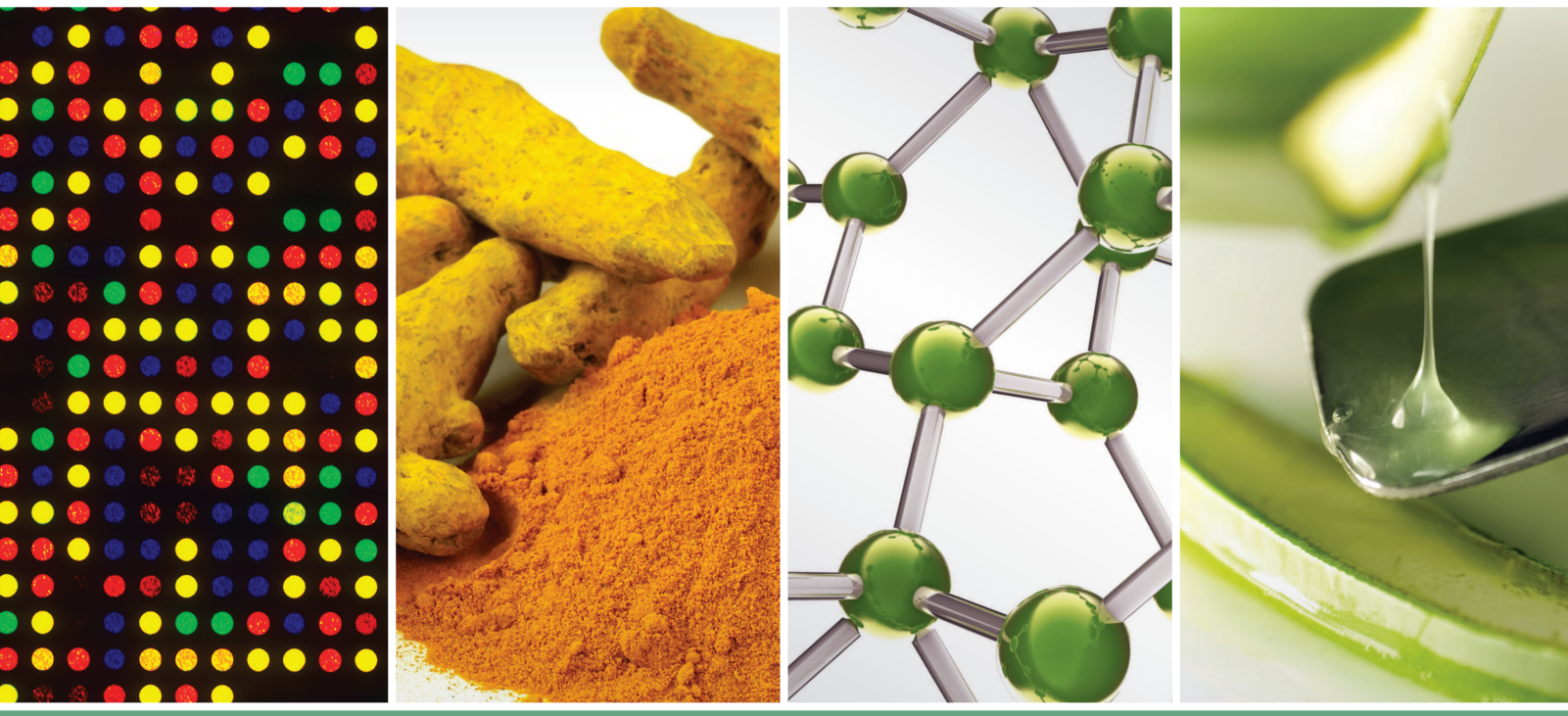
Complementary and Alternative Therapies for Functional Gastrointestinal Diseases

Guest Editors: Jiande D. Z. Chen, Jieyun Yin, Toku Takahashi, and Xiaohua Hou



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Editorial Board

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Editorial

Complementary and Alternative Therapies for Functional Gastrointestinal Diseases

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Functional gastrointestinal diseases (FGID) are common in the world and account for more than 40% of clinical visits to gastroenterology clinics. Common FGID include gastroesophageal reflux disease (GERD), functional dysphagia, functional dyspepsia, gastroparesis, irritable bowel syndrome (IBS), functional constipation, diarrhea, and fecal incontinence. While pathogeneses of FGID are not completely understood, major pathophysiological factors include impaired gastrointestinal motility, visceral hypersensitivity, and psychological issues as well as disruption of the gut microbiota [1]. Gastrointestinal dysmotility is most common in FGID. For example, impaired lower esophageal sphincter function may lead to dysphagia in case of impaired relaxation during swallowing or GERD in case of reduced pressure or increased transient relaxation. In the stomach, reduced gastric relaxation during food intake may lead to impaired gastric accommodation, causing symptoms of early satiety and bloating; impaired antral peristalsis may lead to delayed gastric emptying, causing symptoms of nausea and vomiting. In the lower gut, impaired colon motility slows down transit, resulting in constipation, whereas a weak anal sphincter may lead to fecal incontinence. Visceral hypersensitivity is one of the major causes of pain and discomfort. It is commonly reported in patients with noncardiac chest pain, functional dyspepsia, and IBS. Depression and anxiety are commonly present in patients with FGID. Recently disruption of the gut microbiota has also been reported in patients with FGID.

Although FGID affect a large number of general populations, treatment options for FGID have been limited. Only a few medications have been developed for the treatment of FGID and few or none are available in the market currently depending on where one lives. Meanwhile, alternative and complementary medicine (CAM) has received more and more attention among patients with gastrointestinal diseases and gastroenterologists. In general population, the use of CAM was reported to range from 5% to 72% [2]. In patients with gastrointestinal diseases, the use of CAM was reported to be 40% in pediatric patients [3], 49.5% in patients with inflammatory dowel disease [4], and 50.9% in patients with IBS [5].

Major CAM methods that have been applied for the treatment of FGID include acupuncture/electroacupuncture, herbal medicine, and behavioral therapies. Electroacupuncture was initially designed to mimic manual acupuncture; electrical current was used to produce muscle contractions at the acupoint, mimicking the effect of manual manipulation of the needle inserted into the acupoint. Gradually, electroacupuncture has been evolved to function as neuromodulation or electrical nerve stimulation. That is, the parameters of electrical stimulation are chosen to alter certain functions of the body, such as release of certain hormones and/or neurotransmitter and alterations of certain physiological functions. Recently, a novel method of transcutaneous electroacupuncture (TEA) has been proposed: surface electrodes are used to replace acupuncture needles. This makes the therapy completely noninvasive and self-administrable. By replacing the acupuncture needles with cutaneous electrodes, the therapy can be administrated at home by patients and as frequently

as needed. Acupuncture, electroacupuncture, and TEA have been shown to improve gastrointestinal intestinal motility and reduce visceral hypersensitivity in both humans and animal models of FGID [6]. A number of original research papers are included in this special issue. The study by X. Zhang et al. reported antiemetic effect of TEA in patients with chemotherapy and mechanisms involving serotonin and dopamine. The ameliorating effects of the noninvasive TEA on nausea and vomiting in the delayed phase are appealing as the common medical therapy has limited effects on nausea and vomiting in the delayed phase. The same TEA method was used in a study by F. Xu et al. The authors applied TEA in patients with functional dyspepsia and reported improvement in impaired gastric accommodation and gastric slow waves (electrical rhythms controlling peristalsis of the stomach). It was also reported that these effects were mediated via the vagal mechanisms. In another study by N. Da et al., electroacupuncture was used to treat patients with functional constipation and a comparison was made between shallow puncture and deep puncture. Both methods resulted in a significant increase in spontaneous bowel movement, and electroacupuncture with deep puncture was reported to be more potent than shallow puncture.

Herbal medicine has also been used for the treatment of FGID, such as STW 5 (Iberogast), Rikkunshito (also known as Liu-Jun-Zi-Tang), Daikenchuto, Simotang, *Taraxacum officinale*, modified Xiaoyao San, and Banxiaxiexin decoction [7]. In this special issue, Y. Saegusa et al. reviewed the treatment strategy of Rikkunshito for anorexia and gastrointestinal dysfunction. Rikkunshito was reported to improve gastric motility in both humans and animals and upper gastrointestinal symptoms such as dyspepsia, epigastric pain, and postprandial fullness in a number of clinical studies. Numata et al. in this issue reported improvement in functional constipation in poststroke patients with the use of Daikenchuto. A 4-week treatment with Daikenchuto significantly improved major symptoms or symptom scores associated with constipation in patients after stroke. In a placebo-controlled clinical study by Kamiya et al. in this special issue, Biobran, modified arabinoxylan rice bran, was reported to improve symptoms of diarrhea in IBS patients with diarrhea or mixed diarrhea and constipation, whereas no improvement was noted in the control group. It was speculated that the symptom improvement might be attributed to anti-inflammatory and/or immune modulatory effects of Biobran.

Behavioral therapies include cognitive behavioral therapy, hypnotherapy, relaxation exercise, mindfulness-based therapies, and biofeedback training. Most of these therapies have been applied for the treatment of FGID. One original study and one review paper are included in this special issue. In a study by Tang et al. an adaptive biofeedback training method was proposed and applied for the treatment of functional constipation due to paradoxical contractions of the rectum and the anal sphincter. In this method, the patients were trained to adequately control the contraction of the lower abdomen and relax the anal sphincter during straining; the actual manometric tracings showing the contractile activity of the rectum and anal sphincter were shown to the patients as visual feedbacks. A significant improvement in constipation-related symptoms was noted with both conventional and intensive biofeedback trainings.

In addition to original studies, this special issue also includes three reviews covering three major diseases of FGID, functional dyspepsia, IBS, and constipation. The paper by X. Wang and J. Yin provides a comprehensive and critical review on the applications of various CAM methods for the treatment of functional constipation. The review by M. Aucoin et al. provides a meta-analysis on the treatment of IBS using mindfulness-based therapies. The review by Y. Saegusa et al. presents a summary on the treatment of functional dyspepsia using a special herbal medicine, Rikkunshito.

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Review Article

A New Strategy Using Rikkunshito to Treat Anorexia and Gastrointestinal Dysfunction

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Because the clinical condition of gastrointestinal dysfunction, including functional dyspepsia, involves tangled combinations of pathologies, there are some cases of insufficient curative efficacy. Thus, traditional herbal medicines (Kampo medicines) uniquely developed in Japan are thought to contribute to medical treatment for upper gastrointestinal symptoms. Rikkunshito is a Kampo medicine often used to treat dyspeptic symptoms. Over the past few years, several studies have investigated the efficacy of rikkunshito for dysmotility, for example, upper abdominal complaints, in animals and humans. Rikkunshito ameliorated the decrease in gastric motility and anorexia in cisplatin-treated rats, stress-loaded mice, and selective serotonin reuptake inhibitor-treated rats by enhancing plasma ghrelin levels via serotonin$_{2B/2C}$ receptor antagonism. In addition, rikkunshito ameliorated the decrease in food intake in aged mice and stress-loaded decreased gastric motility via enhanced ghrelin receptor signaling. Several clinical studies revealed that rikkunshito was effective in ameliorating upper gastrointestinal symptoms, including dyspepsia, epigastric pain, and postprandial fullness. In this review, we discuss these studies and propose additional evidence-based research that may promote the clinical use of Kampo medicines, particularly rikkunshito, for treating anorexia and gastrointestinal dysfunction.

1. Introduction

A representative gastrointestinal dysfunction, functional dyspepsia (FD), is associated with symptoms such as gastric pain, anorexia, and postprandial sense of distension. The clinical condition of FD involves numerous factors such as delayed gastric emptying [1], gastric accommodation [2], and psychological factors [3]. The quality of life (QOL) of FD patients is markedly reduced physically, mentally, and socially [4, 5]. In addition, some reports have indicated beneficial therapeutic effects on QOL following improvements in FD symptoms after treatment [6]; thus, the clinical treatment of FD is very important. Although many medications and therapies such as administration of proton-pump inhibitors (PPI), prokinetics, or antidepressants have been attempted, there are some cases of limited curative efficacy. Thus, Kampo medicines have been anticipated to be effective.

Kampo medicines have been uniquely developed in Japan and have been approved by the Ministry of Health, Labour and Welfare of Japan. Clinically, Kampo medicines are used in combination with Western medications or alone. One of these Kampo medicines is rikkunshito, prepared from eight crude drugs: Atractylodis Lanceae Rhizoma, Ginseng Radix, Pinelliae Tuber, Poria, Zizyphi Fructus, Aurantii Nobilis Pericarpium, Glycyrrhizae Radix, and Zingiberis Rhizoma. Figure 1 shows the UV absorbance characteristics of its herbal ingredients after separation using 3-dimensional high-performance liquid chromatography (3D-HPLC).

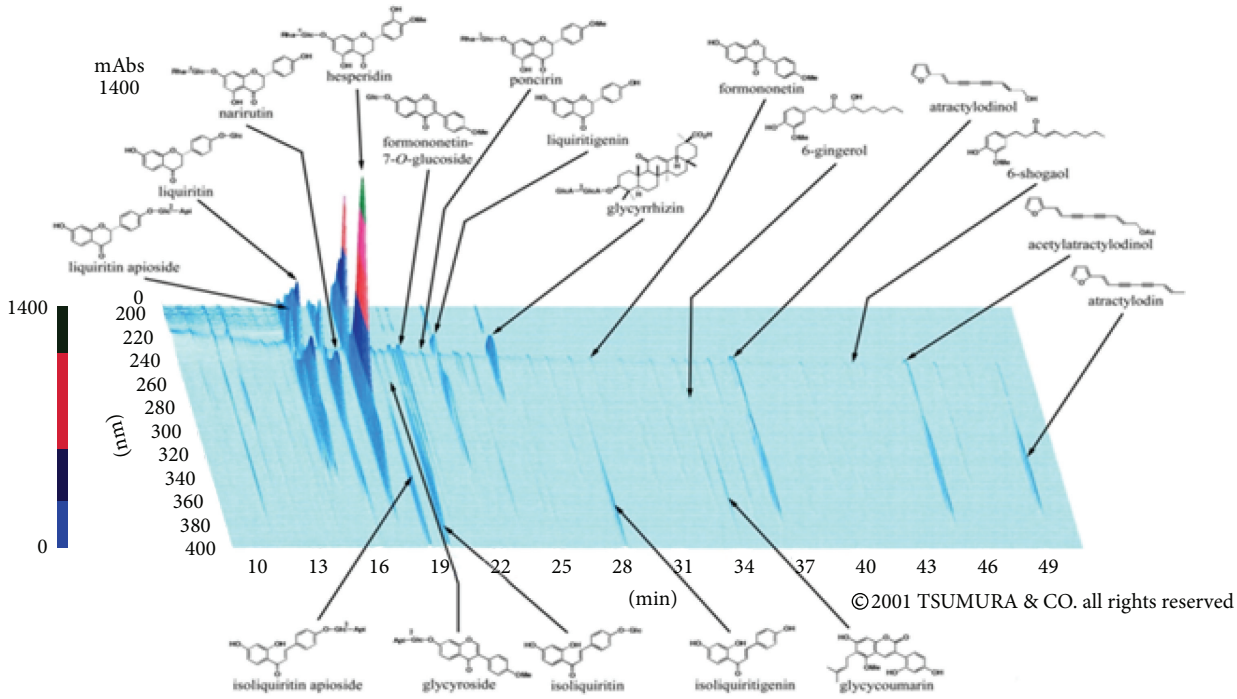

Figure 1: 3D-HPLC profiles of rikkunshito components. Data were provided by Tsumura & Co.

In Japan, rikkunshito is commonly used for dyspeptic symptoms [7–9]. It was shown to improve gastrointestinal symptoms in chronic idiopathic dyspepsia patients in a double-blinded, randomized, placebo-controlled trial [10]. In 1998, a large-scale comparative clinical study of 235 patients conducted by Harasawa et al. showed improvement of dyspepsia in dysmotility-like dyspepsia patients after the administration of rikkunshito (the original report was in Japanese and was summarized in English by Hattori [11, 12]). A recent randomized, placebo-controlled trial of rikkunshito for FD patients was conducted by Suzuki et al., and it demonstrated that the administration of rikkunshito reduced dyspepsia and partially improved symptoms of epigastric pain and postprandial fullness in FD patients [13].

Here, we summarize the results of animal studies that investigated the effects of rikkunshito for treating anorexia caused by various factors by focusing on ghrelin, an appetite-promoting hormone. In addition, we discuss the usefulness of treating gastrointestinal disorders such as FD using Kampo medicines, particularly rikkunshito, on the basis of recent clinical studies.

2. Gastrointestinal Function-Related Factors: Ghrelin and Serotonin

Ghrelin, a 28-amino-acid peptide, is an orexigenic hormone primarily secreted from X/A-like cells, which are ghrelin-producing cells localized in the stomach mucosa [14]. Ghrelin is found in the blood in two main forms, namely, "acylated ghrelin" and "des-acyl ghrelin," at a ratio of 1:10. Acylated ghrelin is rapidly metabolized to des-acyl ghrelin by removal of the octanoyl group in blood, which is catalyzed by esterases such as carboxylesterase (CES) in rodents or butyrylcholinesterase (BuChE) in humans [15].

Acylated ghrelin binds to specific receptor, growth hormone secretagogue receptor type 1a (GHS-R1a), localized at the end of the vagus nerve around the stomach [16, 17]. Ghrelin signals are transmitted to the nuclei of the solitary tract and activate neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the hypothalamic arcuate nucleus (ARC) via noradrenergic neurons, resulting in appetite stimulation [16, 17].

Administration of exogenous acylated ghrelin increases food intake in rodents [16]. In addition, acylated ghrelin plays an important role in stomach and duodenal motility [14, 18]. The peak of plasma acylated ghrelin levels is strongly linked with phase III-like contractions in rodents [19]. Exogenous ghrelin administration results in enhanced stomach and duodenal motility [18], leading to accelerated gastric emptying.

Serotonin (5-hydroxytryptamine, 5-HT) plays an important role in various physiological processes, including gastrointestinal function. Central 5-HT plays a role in fear and anxiety manifestations and is involved in appetite regulation. The 5-HT_2 receptor family is involved in appetite control [20]. 5-HT_{2C} receptors are primarily localized in the brain [21], and 5-HT_{2C} receptor activation induces feeding suppression and anxiety-like behavior in young mice [22–26]. 5-HT_{2C} receptors expressed on proopiomelanocortin (POMC) neurons promote α-melanocyte-stimulating hormone production [27], leading to suppression of feeding. Several reports have established that stimulating 5-$HT_{2C/1B}$ receptors by administering *m*-chlorophenylpiperazine (mCPP) induces anorexia in rodents [20, 24, 28–30].

In contrast, 5-HT_{2B} receptors are primarily found in peripheral tissues, including the gastrointestinal tract and stomach fundus [31], and are localized in the brain, as demonstrated recently [32]. Intraperitoneal (IP) administration of BW723C86 (16 mg/kg), a selective 5-HT_{2B} receptor agonist, decreased food intake in rats [33].

IP administration of BW723C86 and mCPP, a 5-$HT_{2C/1B}$ receptor agonist, decreased plasma acylated ghrelin levels in rodents [28]. This suggested that activation of central and/or peripheral 5-$HT_{2B/2C}$ receptors results in decreased ghrelin secretion from X/A-like cells.

3. Cisplatin-Induced Anorexia

3.1. Cisplatin-Induced Gastrointestinal Disorders. In clinical practice, anticancer drugs such as cisplatin are known to induce gastrointestinal disorders, including acute/delayed nausea, vomiting, anorexia, diarrhea, and weight loss [34]. These markedly affect QOL and may make it difficult to continue chemotherapy. This emetic effect is induced by the activation of 5-HT_3 receptors [35] in the medulla oblongata owing to the release of large amounts of 5-HT from intestinal enterochromaffin cells [36]. However, the detailed mechanism underlying the loss of appetite because of cisplatin remains unclear.

With regard to anorexia caused by cisplatin, we and others found that in rats treated with cisplatin, there was a decreased 24 h food intake after treatment [28, 37, 38]. Yakabi et al. showed that the decreased food intake caused by IP administration of cisplatin at 4 mg/kg to rats persists up to 48 h after treatment [38].

In both clinical and basic research, recent reports have demonstrated a relationship between anorexia and ghrelin dynamics induced by cisplatin. Some reports have shown that, in humans, plasma ghrelin concentrations decreased during cisplatin-based chemotherapy [39, 40]. In animal studies, we and others showed that cisplatin treatment decreased plasma acylated ghrelin levels in rats [28, 38]. IP administration of 5-HT or cisplatin decreased plasma acylated ghrelin levels in a dose-dependent manner in addition to decreasing the 24 h food intake [28]. Moreover, the reduced plasma acylated ghrelin levels and 24 h food intake following cisplatin treatment could be completely recovered by treatment with 5-$HT_{2B/2C}$ receptor antagonists. In addition, decreased food intake in cisplatin-treated rats could be recovered by exogenous ghrelin treatment. This showed that the reduced plasma acylated ghrelin levels reduced via 5-$HT_{2B/2C}$ receptor activities play a major role in cisplatin-induced anorexia [28]. Interestingly, although plasma acylated ghrelin levels recovered to their baseline levels at 24 h after cisplatin treatment in rats, decreased ghrelin secretion in the hypothalamus persisted even 24 h after treatment, which resulted in a late phase of decreased food intake caused by cisplatin [38]. This suggested that central ghrelin dynamics play an important role in regulating feeding behaviors.

3.2. The Effects of Rikkunshito and Its Components on Cisplatin-Induced Anorexia. Rikkunshito administration has been shown to recover decreased food intake and plasma ghrelin levels caused by cisplatin treatment [28, 41]. These effects were also shown to be abolished by administration of [D-Lys^3]-GHRP-6, a GHS-R antagonist [28, 41]. Thus, the effects of rikkunshito in terms of improving decreased food intake and acylated ghrelin levels in cisplatin-treated rats are likely caused by enhanced ghrelin secretion via 5-HT receptor antagonism, particularly that involving 5-$HT_{2B/2C}$ receptors.

We screened 33 compounds among the many components of rikkunshito for their binding activities with 5-HT receptor subtypes [28]. We found that 3,3′,4′,5,6,7,8-heptamethoxyflavone (HMF), nobiletin, tangeretin (contained in Aurantii Nobilis Pericarpium), and 8-shogaol (contained in Zingiberis Rhizoma) exhibited the strongest inhibitory activity against 5-HT_{2B} receptors; these compounds had inhibition constant (K_i) values of 0.21, 0.31, 0.59, and 1.8 μmol/L, respectively. Hesperetin contained in Aurantii Nobilis Pericarpium, the aglycon form of hesperidin, had K_i values of 5.3 μmol/L against 5-HT_{2B} receptors and 20.9 μmol/L against 5-HT_{2C} receptors. Although this inhibitory activity of hesperetin was comparatively weak, the amounts of hesperidin were higher than those of the other compounds tested in our binding assays [42]. Thus, overall, it may exhibit potent 5-$HT_{2B/2C}$ receptor antagonistic activity. Furthermore, hesperetin flavonoids have been reported to enter the brain by passing through the blood-brain barrier [43].

In addition, isoliquiritigenin contained in Glycyrrhizae Radix exhibited the most potent inhibitory activity against 5-HT_{2C} receptor binding (K_i value, 3.5 μmol/L) among all the components tested. In addition, it inhibited 5-HT_{2B} receptor binding inhibitory activity (K_i value, 3.3 μmol/L). Isoliquiritigenin inhibited 5-HT_{2C} receptor activation in a cell functional assay [30]. Furthermore, oral administration of HMF, hesperidin, or isoliquiritigenin in a cisplatin-induced anorexia model resulted in amelioration of the reduced plasma acylated ghrelin levels in a dose-dependent manner [28].

We believe that changes in plasma acylated ghrelin to des-acyl ghrelin (A/D) ratios are also important for regulating feeding behavior. An increase in the A/D ratio after oral administration of rikkunshito in normal control rats and cisplatin-treated rats suggested that rikkunshito inhibits the degradation of acylated ghrelin [44]. We tested 48 rikkunshito components for their inhibitory activities against CES and BuChE and found that 10-gingerol, contained in Zingiberis Rhizoma, had the most potent CES inhibitory activity [44]. We also showed that oral administration of rikkunshito or 10-gingerol increased plasma acylated ghrelin levels and the A/D ratios in acylated ghrelin-treated rats. In addition, administering the CES inhibitor bis(4-nitrophenyl) phosphate resulted in the amelioration of a cisplatin-induced decrease in food intake [44]. These results suggested that the amelioration of cisplatin-induced decreases in food intake and plasma acylated ghrelin levels by rikkunshito is partly attributable to its CES inhibitory effect.

4. Stress-Induced Anorexia

4.1. Stress and Ghrelin. Stress is a significant social problem [45, 46] known to be associated with anorexia and gastrointestinal function [47, 48]. It has been strongly suggested that stress causes several abnormalities of feeding behavior, such as bulimia and anorexia. In animal studies, food intake reportedly decreases after stress loading, including restraint stress and immobilization stress [49–51] and emotional stress using a communication box [52]. In contrast, increased food intake has been observed after long-term isolation for 3 weeks [53].

Ghrelin levels may also be affected by feeding behaviors of animals under stress. However, there are conflicting data regarding the effects of several stressors on plasma ghrelin levels. Increased plasma ghrelin concentrations were found in a water avoidance stress [54], chronic social defeat stress [55] and repeated restraint stress [56] in rodents, Trier Social Stress Test in humans [57], and cold stress in rodents [58] and humans [59]. In comparison, decreased plasma ghrelin levels have been found to result from immune stress induced by lipopolysaccharide in rodents [60–62], administration of urocortin 1 to rodents [63, 64] and humans [65], and physical exercise at 50% of $VO_{2\,max}$ in humans [66]. We recently reported that restraint stress causes a significant elevation of plasma des-acyl ghrelin levels only, whereas plasma acylated ghrelin levels remain unaffected [67].

4.2. Plasma Ghrelin Levels in Novelty Stressed Mice. One of the stressors that we may experience during daily life is exposure to a new environment. Psychological factors, loneliness, social networks, and environmental changes contribute to decreased food intake, particularly in the elderly [68, 69]. In a novelty stress model, animals are removed from their home cage and placed somewhere they have never been before. This model has been used to estimate anxiety and depression levels [70–72]. We tested the effects of a novel environmental stress on food intake and plasma acylated ghrelin dynamics in young mice [29, 73] and aged mice [30].

We found that novelty stress causes a decrease in food intake, which is associated with decreased plasma ghrelin levels after stress [29]. However, increased plasma ghrelin levels with fasting were not observed in a young mouse novel stress model [73]. Exogenous acylated ghrelin ameliorated the decreased food intake by temporarily increasing plasma acylated ghrelin levels above the physiological concentration [29]. Thus, the transmission of ghrelin signals to the hypothalamic feeding center may be abnormal under novelty stress.

A few studies have investigated a possible relationship between corticotropin-releasing factor (CRF) receptors and plasma ghrelin dynamics. Administration of urocortin 1, a CRF family peptide that binds to both CRF_1 and CRF_2 receptors, reduced plasma acylated ghrelin levels in rodents [63, 64]. Yakabi et al. demonstrated that urocortin 1-induced reductions in plasma acylated ghrelin levels and food intake were mediated via CRF_2 receptors but not CRF_1 receptors [64]. We reported that novelty stress and CRF administration reduced plasma ghrelin levels and food intake and that a CRF_1 receptor antagonist but not a CRF_2 receptor antagonist prevented these decreases [29]. Interestingly, we also found that a selective 5-HT_{2C} or 5-HT_{1B} receptor antagonist and a melanocortin-4 (MC4) receptor antagonist prevented the decreased plasma acylated ghrelin levels in novelty stressed mice [29]. We hypothesized that the acute appetite loss and the decrease in plasma ghrelin levels occurred via CRF_1 receptors, the effects of which were mediated through 5-$HT_{2C/1B}$ and MC4 receptor systems.

In a novelty stress model, higher levels of central 5-HT and 5-HT receptor expression resulted in the activation of serotonergic signals [72]. 5-$HT_{2C/1B}$ receptor stimulation may downregulate appetite control [25, 74, 75]. We showed that, compared with normal mice, intracerebroventricular administration of mCPP induced a significant decrease in food intake in novelty stressed mice [29]. Administration of 5-$HT_{2C/1B}$ receptor antagonists ameliorated the decrease in food intake and plasma acylated ghrelin levels [29]. Thus, an increase in 5-$HT_{2C/1B}$ receptor activity may occur after novelty stress, resulting in anorexia or reduced plasma ghrelin levels.

In addition, we showed that peripheral administration of SB215505 and SB204741, selective 5-HT_{2B} receptor antagonists, prevented the decrease in food intake in novelty stressed mice [73]. 5-HT_{2B} receptor activation also resulted in decreased food intake [33]. It is therefore possible that 5-HT_{2B} receptors participate in part of the mechanism of action involved in this novelty stress model.

4.3. Differential Effects in Aged Mice. It is well known that 5-HT_{2C} receptors are expressed on CRF neurons in the paraventricular nucleus (PVN) and that its activation by 5-HT_{2C} receptor agonists results in adrenocorticotropic hormone (ACTH) secretion [74]. Other studies have shown that CRF mRNA expression and ACTH secretion were enhanced by 5-HT administration to PVN [74, 76] and that mCPP-induced serum corticosterone increases were inhibited by 5-HT_{2C} receptor antagonism [77]. We showed that exposure to a novel environment caused long-term secretion of stress hormones and a continuously decreased food intake in aged mice but not in young mice [30]. In addition, mCPP administration resulted in more severe anorexia in aged control mice than that in young control mice [30]. Thus, the basal level of signal transduction via 5-HT_{2C} receptors may have been enhanced in aged mice.

In our previous report we also found that administering a selective 5-HT_{2C} receptor antagonist, SB242084, to aged mice at a dose that had no effect on food intake in young mice significantly ameliorated both the decrease in food intake and the increase in stress hormone levels after novelty stress [30]. We and others found that novelty stress and social isolation stress enhanced mCPP-responsiveness [29, 71], which may have been linked to upregulated 5-$HT_{2C/1B}$ receptor activity. In addition, we observed increased 5-HT_{2C} receptor gene expression in the hypothalamus at 24 h after novelty stress in aged mice but not in young mice [30]. In summary, we hypothesized that the stimulation or activation of 5-HT_{2C} receptors on CRF neurons in PVN results in activation of the hypothalamic-pituitary-adrenal (HPA) axis in aged mice after novelty stress.

4.4. The Effects of Rikkunshito and Its Components on Novelty Stressed Mice. Rikkunshito ameliorated the novelty stress-induced decreases in food intake and plasma ghrelin levels in young mice [29, 73] and in aged mice [30], and coadministering [D-Lys^3]-GHRP-6 abolished the effects of rikkunshito [29]. Rikkunshito completely ameliorated the decreased food intake in young and aged mice after mCPP injection [30]. Rikkunshito administration attenuated the hyperactivation of the HPA axis and the decreased food intake induced by novelty stress, which was similar to the effects of SB242084 [30]. We and others reported that rikkunshito had an antagonistic effect on 5-HT$_{2C}$ receptors *in vivo* [18, 28]. In addition, the results of *in vitro* radiobinding assays revealed that components in rikkunshito, such as isoliquiritigenin, exhibited 5-HT$_{2B/2C}$ receptor binding inhibitory activity [28]. We also found that glycycoumarin and isoliquiritigenin, which are contained in Glycyrrhizae Radix, ameliorated the reduced food intake in novelty stressed mice [29, 73]. These findings suggest that rikkunshito ameliorates novelty stress-induced anorexia and reduced plasma ghrelin levels via antagonism-like effects on 5-HT$_{2C}$ and 5-HT$_{2B}$ receptors.

4.5. The Effects of Rikkunshito on Postprandial Gastric Motility in a Restraint Stress Model. We found that restraint stress decreased the frequency of phase III-like contractions in the fasted state and postprandial gastric contractions in mice [67], leading to delayed gastric emptying. Furthermore, exogenously administered acylated ghrelin and rikkunshito improved the delayed gastric emptying and decreased gastric motility caused by restraint stress, and the rikkunshito effects were completely abolished by a GHS-R antagonist [67]. However, there were no changes in plasma acylated ghrelin levels. Thus, we hypothesized that rikkunshito may have improved the delayed gastric emptying and decreased motility via mechanisms of action other than the enhancing effects on ghrelin release.

Fujitsuka et al. demonstrated that rikkunshito potentiated ghrelin receptor signaling via increased binding between ghrelin and ghrelin receptors [78]. Thus, exogenous ghrelin supplementation or ghrelin signal enhancement by rikkunshito may be effective for improving symptoms in FD patients.

5. Aging-Induced Anorexia

5.1. Anorexia-Associated Malnutrition in the Elderly. In the elderly, malnutrition can cause various problems such as problems related to daily life activities, reduced immune function, and loss of muscle strength [79–81]. Therefore, dealing with malnutrition is quite important. Anorexia is the main cause of malnutrition in the elderly [82]. Food intake has been shown to decrease gradually with age [82]. Various factors are responsible for anorexia in the elderly, including social isolation, diseases such as depression and physical disorders, reduced gustatory and olfactory senses, and medicines [83].

Appetite is controlled by central and peripheral orexigenic/anorexigenic factors [84]. As a central control mechanism, NPY and AgRP levels are altered with aging [85–88] and NPY signaling is dysfunctional in old rats [89]. However, few reports regarding the changes in neurotransmitters of the central nervous system that accompany aging in humans are available.

The elderly have lower levels of plasma ghrelin than the young people, and ghrelin secretion from the stomach decreases with aging [90, 91]. However, some reports have shown that there were no differences in the ghrelin levels between young and aged humans [92] and mice [93], which reflects controversy with regard to age-associated changes in ghrelin dynamics.

5.2. Ghrelin Resistance and Hyperleptinemia in Aged Mice. In animal models, 24 h food intake and 2-week body weight gain decreased in aged mice compared with young mice [94]. Our results showed that the plasma ghrelin levels in aged mice did not increase while fasting and that the levels were higher while feeding than those in young mice [94]. These results prompted us to conclude that the regulation of ghrelin secretion may be disturbed in aged mice. Moreover, exogenous ghrelin administration markedly enhanced food intake in young mice but not in aged mice [94]. Thus, ghrelin signaling may be impaired in aged mice.

Leptin, an adipocyte-derived hormone, suppresses food intake and decreases body adiposity [95]. We found that plasma leptin levels in aged mice were very high and this increased plasma leptin level was maintained regardless of ingestion [94]. In ARC, leptin receptors are expressed on NPY neurons and POMC neurons [96, 97], and GHS-R is expressed on NPY neurons [98]. Ghrelin and leptin may have opposing actions on NPY neurons; thus, abnormally high concentrations of leptin are considered to reduce the effects of ghrelin [99]. Another report showed that hyperleptinemia prevented an increase in ghrelin levels [100].

It was also suggested that leptin suppressed ghrelin signaling by NPY neurons via the activation of the phosphoinositide 3-kinase- (PI3K-) phosphodiesterase 3 (PDE3) pathway, which may have abolished the adenylate cyclase-cAMP-protein kinase A system implicated in the effects of ghrelin [101]. We found that the administration of a PI3K inhibitor and a PDE3 inhibitor ameliorated the anorexia in aged mice [94]. Thus, we propose that the hyperleptinemia accompanying aging may induce resistance to ghrelin reactivity in aged mice by downregulating cAMP levels [94].

5.3. The Effects of Rikkunshito and Its Components on Anorexia in Aged Mice. We showed that the administration of rikkunshito could ameliorate some effects of aging-associated anorexia [94]. Exogenous ghrelin ameliorated decreased food intake in a cisplatin-induced anorexia model [28] and a novelty stress-induced anorexia model [29, 73] but not in our aging-anorexia model [94]. After administering rikkunshito, increased plasma ghrelin levels were not observed in aged mice; thus, increased ghrelin secretion was not the main mechanism underlying the amelioration caused by rikkunshito.

We tested 33 components of rikkunshito and found that HMF, nobiletin, isoliquiritigenin, and glycycoumarin exhibited inhibitory effects on PDE3 activity. It was previously reported that nobiletin flavonoids could enter the brain by passing through the blood-brain barrier [102]. Thus, these results suggested that rikkunshito ameliorates aging-induced anorexia via enhanced ghrelin receptor signaling by PDE3 inhibition.

6. Clinical Applications of Rikkunshito

FD is likely to occur through the combined effects of different pathologies. As described in this paper, the results of animal studies suggest that rikkunshito enhances appetite and gastric motility [18, 67] by increasing endogenous ghrelin levels [18, 28, 29, 73, 103] or ghrelin signals [78, 94] and thereby ameliorates upper gastrointestinal dysfunctions, including FD. Studies of healthy human volunteers [103, 104] and FD patients [105] have shown that endogenous acylated ghrelin levels increase after rikkunshito administration.

In a clinical study conducted by Arai et al. using a parallel, randomized, controlled trial of gastroprokinetic agents for 27 patients, it was shown that rikkunshito was effective in ameliorating upper gastrointestinal symptoms, as evaluated by their scores on the Gastrointestinal Symptom Rating Scale questionnaire [105]. Tominaga et al. conducted a randomized, placebo-controlled, double-blind clinical trial of rikkunshito for 242 patients with nonerosive reflux disease refractory to PPI [106]. Treatment for 4 weeks with rikkunshito significantly improved their mental component summary (MCS) scores in the Short-Form Health Survey-8 (SF-8). After 8 weeks of treatment with rikkunshito, MCS scores in SF-8 improved in patients with low body mass index values (<22), and acid-related dysmotility symptoms assessed by the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease also improved in females and the elderly. Another clinical trial was conducted by Suzuki et al.; it was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial on the effect of rikkunshito on 247 patients [13]. Administration of rikkunshito for 8 weeks reduced dyspepsia, epigastric pain was significantly improved, and postprandial fullness tended to improve.

Anorexia is a cause of concern for cancer patients since a persistent loss of appetite develops into cancer cachexia. A clinical trial of ghrelin receptor agonists has revealed that there is a remarkable effect on weight gain in patients with non-small-cell lung cancer [107]. It has been confirmed that rikkunshito also improves QOL in advanced esophageal cancer patients [108] and prolongs survival in stage III/IV pancreatic cancer patients and tumor-bearing rats [78]. Unlike other ghrelin receptor agonists, rikkunshito displays multiple actions related to ghrelin signal activation, that is, stimulation of ghrelin secretion and sustained activity of GHS-R, and prevention of the degradation of endogenous acylated ghrelin. Therefore, it is expected that rikkunshito may be effective to the ghrelin resistance seen in cancer anorexia-cachexia [78]. Further, rikkunshito is potentially effective in improving gastrointestinal symptoms in patients after gastrectomy [109, 110]. However, since there are few reports in patients with cancer cachexia or with upper gastrointestinal surgery, further large-scale clinical trials are required.

Evidence of the relevance of using rikkunshito to treat anorexia and gastrointestinal dysfunction continues to accumulate, as summarized here. In addition, the use of Kampo medicines as therapeutic agents for FD has recently been proposed in Japan (guidelines for functional gastrointestinal diseases: 2014). With continuing evidence-based high-quality research, the mechanisms of action of Kampo medicines, particularly those of rikkunshito, may be elucidated to a greater extent, and the use of Kampo medicines may expand as a front line treatment for anorexia and gastrointestinal dysfunction.

Conflict of Interests

Yayoi Saegusa, Tomohisa Hattori, Miwa Nahata, and Chihiro Yamada are employed by Tsumura & Co.

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Research Article

The Effectiveness of Electroacupuncture for Functional Constipation: A Randomized, Controlled, Clinical Trial

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Background. Electroacupuncture (EA) has been reported to treat functional constipation (FC). The aim of this study was to investigate the efficacy and safety of EA with different needle insertion method for FC. *Methods*. Sixty-seven participants were randomly assigned to control (EA with shallow puncture) and EA (with deep puncture) groups. Every patient received 5 treatments per week in the first two weeks, then 3 treatments per week during the following six weeks. Complete spontaneous bowel movements (CSBM), spontaneous bowel movements (SBM), Bristol stool scores (BSS), and Patient Assessment of Constipation Quality of Life (PAC-QOL) were assessed. *Results*. Both shallow and deep EA significantly increased CSBM frequency compared to the baseline. CSBM was increased from 0.50 ± 0.59/wk to 2.00 ± 1.67/wk with deep EA and from 0.48 ± 0.59/wk to 1.33 ± 1.09/wk with shallow EA ($P < 0.05$, resp.). Similar finding was noted in SBM. Deep EA was more potent than shallow EA ($P < 0.05$) during the treatment period. No difference was found on BSS and PAC-QOL between two groups. *Conclusion*. It is effective and safe with EA to treat FC. Studies with large sample size and long-term observation are needed for further investigation.

1. Introduction

According to Rome III diagnostic criteria [1], functional constipation (FC) is characterized by hard, infrequent, or incomplete defecation. The prevalence of FC in North America is from 1.9% to 27.2% [2], 7.4% in Mexico [3], and 2.4–11.2% in Iran [4]. In recent years, functional constipation occurs more frequently in China, with total prevalence of 9.18% [5], and in the elderly was 67.87% [6].

Constipation may cause disorders in perianal, such as perianal abscess and anal fistula; anorectal lesions, such as hemorrhoids and colorectal cancer; digestive system diseases, such as bloating, indigestion, and diverticulosis; psychiatric symptoms, such as headache, insomnia, and irritability, aggravating the symptoms, even threatening the life, such as increasing blood pressure, inducing acute cerebral vascular disease, and even sudden death [7, 8]. Constipation also seriously affects the quality of life [9]. It was reported that in 2010 the costs related to hospitalizations of constipation as the primary diagnosis were over 850 million dollars in the US [10]. In addition, patients with constipation were known to have reduced quality of life.

More and more constipation patients prefer alternative and complementary treatment because of worry from drug side effect and deficiency of long-term effect [11], despite laxatives having been widely used. A few studies have reported the effectiveness of acupuncture for treating FC [12, 13]; however, these studies lacked comprehensive study design. Therefore, it is necessary to complete a randomized, controlled, patient blinded, and clinical trial to investigate the efficacy and safety of electroacupuncture treatment of functional constipation.

2. Methods

2.1. Study Design and Ethics Approval. The recruitment of subjects took place from October 2012 to September 2013. The study was approved by Medical Ethics Committee and

completed in the Outpatient Department of Guo Yi Tang in Nanjing, China.

As shown in Figure 1, total 67 patients (13 male and 54 female) with FC were finally enrolled to the experiment. Participants were included if they met all of the following conditions: (1) diagnosed with FC according to the Roman III criteria [1]; (2) aged between 18 and 65 years; (3) CSBM ≤ twice per week at least three months; (4) without any treatments (except rescue methods being used when participants had intolerable discomfort) at least two weeks before joining this study.

Participants were excluded from the study if they had a diagnosis of irritable bowel syndrome (IBS), or constipation caused by other diseases or medicine, or other significant diseases and medicine that may interfere with completion of the study. Pregnant or breastfeeding women were also excluded.

Patients had the rights to decide to whether participate in or withdraw the study at any time. Their decisions did not affect their deserved treatments.

Participants recruited through advertisements in hospitals and schools were randomized by stochastic systems in computer and decided to receive control or EA treatment. All participants were blinded to the type of treatment method received until completion of the study.

2.2. Treatments. The total study period was shown in Figure 2. After two-week baseline assessment, each patient was treated with either deep EA or shallow EA for 8 weeks followed by 12 weeks follow-up period.

Each patient received total 28 treatments, including 5 times per week for the first two weeks and 3 times per week for the following six weeks.

Patients in EA group received EA at 6 acupoints, ST25 (Tianshu) and SP14 (Fujie) and ST37 (Shangjuxu), bilaterally. The physician inserted into ST25 and SP14 with HuaTuo 0.30 × 75 mm needles, deep to the parietal peritoneum without lifting and twisting. The two needles at ST25 and SP14 unilaterally were connected to an electric stimulator (HANS-200A, Nanjing Jisheng Co., China) for 30 min. The frequency was 2/15 Hz alternately. The current was strong enough (0.1 mA–1.0 mA) to produce a slight tremor in patients' abdominal muscles. HuaTuo 0.30 × 40 mm needles were inserted into ST37 with depth of 1 cun, lifted and twisted slightly three times to Deqi every 10 minutes for a total of 30 minutes. Patients in the control group received EA with same techniques and parameters, but with shallow puncture with depth of 2 mm and at points located one cun away from those 6 acupoints (on the median between Stomach Meridian of Foot Yang-ming and Spleen Meridian of Foot Tai-yin), respectively, without lifting and twisting, for 30 minutes.

2.3. Assessment. The primary outcome was CSBM (complete spontaneous bowel movements); the secondary outcomes consisted of spontaneous bowel movements (SBM), Bristol stool scores (BSS), hard defecation score, and Patient Assessment of Constipation Quality of Life (PAC-QOL). The participants filled the defecation diary every day during the entire experimental period.

Table 1: Patients demographics (mean ± SD).

	Control (n = 33)	EA (n = 34)	P
Sex (female (%))	81.82%	79.41%	0.803
Age (years)	37.00 ± 17.89	37.94 ± 18.06	0.768
Course (months)	106.21 ± 91.98	139.59 ± 112.68	0.289

Table 2: The cure rate.

	n	Cured	Not cured	Cure rate	P
Control	33	1	32	3.03%	0.014
EA	34	8	26	23.53%	

2.4. Statistical Analysis. All of statistical analysis was performed in both ITT analysis (intention-to-treat analysis) and PP analysis (per-protocol analysis). The data are expressed as the mean ± standard error (SEM) in each group. SPSS Win. Ver.14.0 software was used and $P < 0.05$ was considered as significance.

3. Results

3.1. Outcomes. One hundred and nine volunteers were filtered in this study, and 37 volunteers were excluded due to either failure to meet the Rome III criteria or being afraid of needle insertion or lacking of time to complete the experiment. Then 72 participants were divided into control group (n = 37) or EA group (n = 35) randomly; 67 participants completed all treatments and the follow-up visits. In control group, two participants lost contact, and the other two failed in blinding. One participant in EA group received another treatment of constipation (Figure 1).

At the 1st assessment (baseline, before treatment), there were no significant differences between the two groups, including gender, age, and disease course (Table 1).

At the 2nd assessment (after treatment of 8 weeks), CSBM and SBM were increased significantly in EA group (n = 34, 2.00 ± 1.67/week and 4.10 ± 2.29/week, resp.), compared to control group ($P < 0.05$, n = 33, 1.33 ± 1.09/week and 3.06 ± 1.53/week, resp., Figure 3). However, at the 3rd assessment (follow-up visits of 12 weeks), there was no difference between the two groups on CSBM (data not supplied).

Both treatment methods significantly increased BSS and PAC-QOL compared to the baseline ($P < 0.01$, resp.); however, no differences were found between the two treatment methods ($P > 0.05$) (Figures 4 and 5).

According to Rome III criteria, we consider CSAM ≧ 3 as a standard indicating the success of treatment. The cure rate of EA group was higher than that in control group ($P = 0.014$) (Table 2).

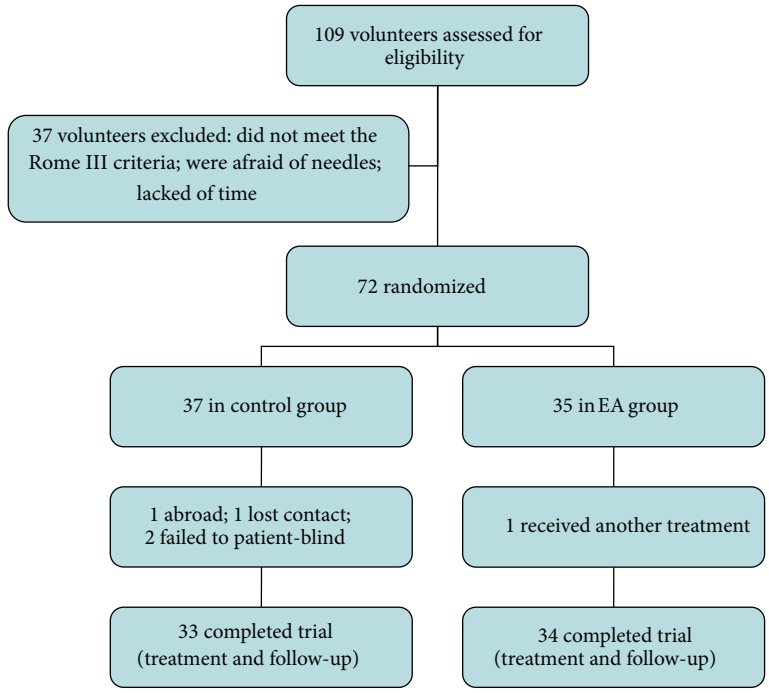

Figure 1: Trail flow chart.

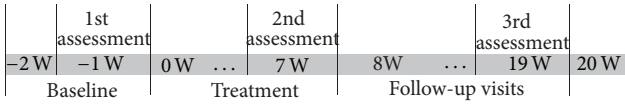

Figure 2: The total study period and the timepoint of evaluation.

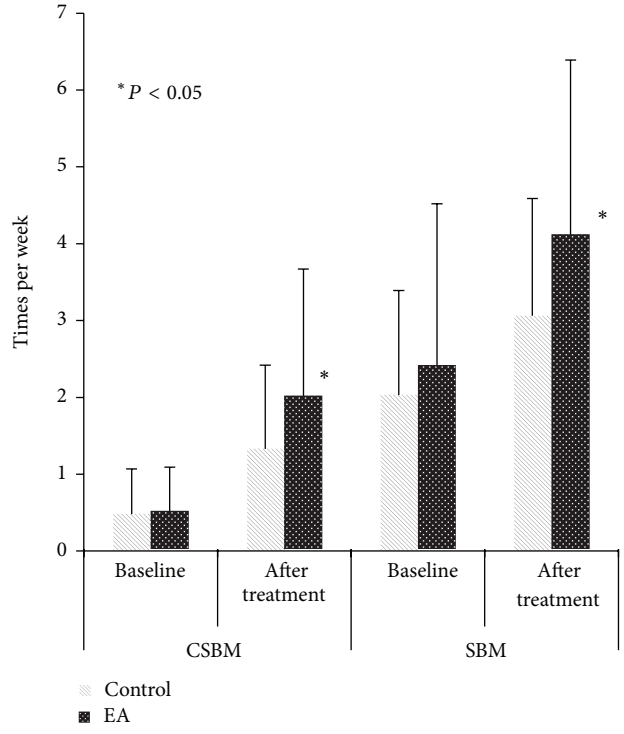

Figure 3: CSBM and SBM (mean ± SD).

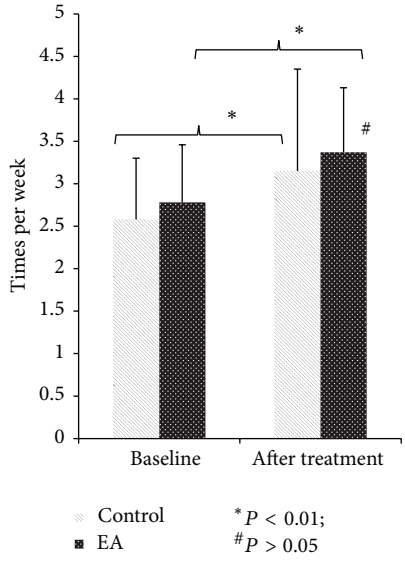

Figure 4: BSS (mean ± SD).

3.2. Safety. There were no serious adverse events reported. Local subcutaneous congestion appeared in two participants; one participant reported mild abdominal pain.

4. Discussion

Electroacupuncture (EA) is based on acupuncture, an ancient Chinese traditional medicine therapy, in which electric current is transmitted to needles inserted acupoints on skin.

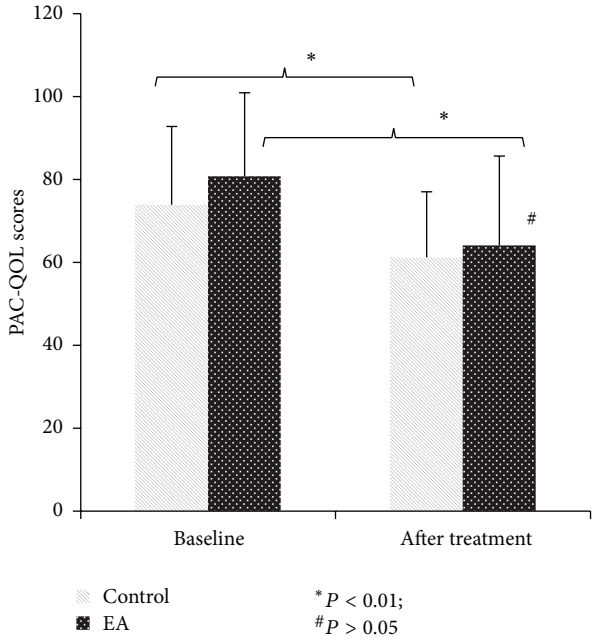

Figure 5: PAC-QOL score (mean ± SD).

During the past decade, EA has been reported to treat constipation by acupuncturists. However, evidences to efficacy and safety are deficiency because of less randomized controlled clinic trails reported.

In this study, EA showed effective on constipation. Times of spontaneous bowel movements per week were increased; properties of stool were improved so that evacuation became smooth; qualities of life of patients with constipation were taking a turn for the better.

Nonacupoints were active in control group, despite the fact that they locate at one cun away from normal acupoints and the middle of two meridians. In the literature, opinions on nonacupoints were controversial, especially the distance between nonacupoint and normal acupoint. Some researchers consider that acupoint is not located at a point on skin but in a field [14]; therefore the more proper name of acupoint is "acupuncture field" [15]. Moisberger recommend "a minimum distance of 6 cm between verum and sham points on face, hands and feet, and up to 12 cm for all other parts of the body" [15]. However, this is not feasible because there are so many acupoints throughout the body; it is understandable that all acupoints interfere with each other within the distance of 6 cm or 12 cm. In the current study, although using the shallow needle insertion, the control group also received EA treatment and therefore improved defecation frequency and constipation symptom scores.

The technique of deep puncture performed on acupoints ST25 and SP14 caused that EA group acted better than control group. Taking needles perpendicularly and slowly into skin of abdomen until penetrating the peritoneum had been proved effective for constipation [16]. Operative technique of puncture is deemed to be one of important factors which can affect acupuncture action. So the direction and depth of puncture should be required. Needles penetrated the peritoneum, stimulated intestine directly, and improved motility and at the same time avoided impairing organs due to without lifting and twisting. The safety of "deep acupuncture" on ST25 had been confirmed through study of anatomy and operation standard had been set up [17]. No obvious adverse events have been noted in the current study.

The mechanism of EA for treating constipation could be attributed to the improvement of colonic motility. It was reported that EA promotes contractility of distal colon in rats [18]. EA was also shown to accelerate colon motility and transit in rats [19]. Rectal distention, a common model to mimic feces stasis, has been shown to alter gastric slow waves and delay gastrointestinal transit. Using the rectal distention model, EA was shown to normalize the impaired gastric slow waves and improve antral contractions in dogs and improve upper and lower abdominal symptoms in healthy volunteers [20, 21]. These effects are believed to be mediated via cholinergic and opioid pathways [18–21].

In conclusion, it is effective and safe with EA to treat FC. There are deficiencies in this study, including small sample sizes and single blind. More rigorous studies with larger sample sizes are required.

Conflict of Interests

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

Authors' Contribution

Nili Da and Xinjun Wang contributed equally to this work.

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Research Article

Efficacy of Adaptive Biofeedback Training in Treating Constipation-Related Symptoms

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Biofeedback therapy is a well-known and effective therapeutic treatment for constipation. A previous study suggested that adaptive biofeedback (ABF) training was more effective than traditional (fixed training parameters) biofeedback training. The aim of this study was to verify the effectiveness of ABF in relieving constipation-related symptoms. We noticed that in traditional biofeedback training, a patient usually receives the training twice per week. The long training sessions usually led to poor compliance. This study proposes an intensive biofeedback therapy and compares intensive therapy with nonintensive therapy in patients with constipation-related symptoms. *Methods.* 63 patients with constipation-related symptoms were treated with ABF between 2012 and 2013. These patients were further divided into the intensive therapy and nonintensive therapy groups. *Results.* A total of 63 patients were enrolled in the study, including 24 in the nonintensive therapy group and 39 in the intensive therapy group. 100% ($N = 21$) of constipation patients achieved the primary efficacy endpoint (≥3 bowel movements/week). There was significant improvement in constipation-related symptoms after adaptive biofeedback. The intensive biofeedback therapy did not show better performance compared to nonintensive biofeedback therapy. *Conclusions.* This investigation provides support for the efficacy of biofeedback for constipation-related symptoms. The efficacy of intensive therapy is similar to nonintensive therapy.

1. Introduction

Chronic constipation is a common disorder characterized by defecation difficulty or decreased bowel movements (less than three times a week). The worldwide prevalence of chronic constipation varies from 12% to 17% [1]. It is more prevalent in females than males (prevalence rate of 2.2 : 1) and the prevalence increases with age [2]. Patients who reported persistent constipation have decreased health-related quality of life and higher level of depression [3]. Chronic constipation has a great economic and social impact, including laboratory tests, diagnostic procedures, and healthcare expenditures [4].

Constipation is primarily a functional disorder, and it could also be caused by medications, diseases of the colon, metabolic disturbances, and neurologic disorders. Constipation can be categorized into 3 subgroups (obstructed defecation, slow transit constipation, and normal transit constipation) [5, 6]. About 40% of constipation is due to obstructed defecation [7, 8]. Obstructed defecation (also known as dyssynergic defecation, pelvic floor dyssynergia, or outlet obstruction) is characterized by the lack of coordination between the abdominal and pelvic floor muscles during defecation. Obstructed defecation is caused by one of the following problems: impaired rectal contraction, paradoxical anal contraction, or inadequate anal relaxation.

Although currently available treatment options have been reported to be effective at improving patients' symptoms, the curative effect is still unsatisfactory. There is insufficient data

to support that lifestyle and diet change such as increased fiber and fluid intake can improve chronic constipation. Laxatives (including bulking agents, osmotic and stimulant laxatives, and stool softeners) have been approved to relieve the symptoms [9–11]. However, laxatives do not target the underlying pathophysiology, such as paradoxical anal contraction. Biofeedback therapy, an instrument-based learning process, can correct the incoordination of the abdominal, rectal, and anal sphincter pressures [12]. The efficacy of biofeedback therapy is reported to range from 44% to 100% in various clinical studies [13]. However, training requires complex processing and the training targets are fixed, meaning all patients receive the same training regardless of different anorectal motility and ability to achieve the training goal. A novel method of adaptive biofeedback (ABF) training reportedly changes the training targets and protocols according to patients' anorectal motility. This method of ABF has shown to be superior to the traditional biofeedback training [14].

The frequency and duration of traditional biofeedback training are variable in different clinical trials [15–18]. On average, patients are asked to receive treatment for 3 months at a frequency of twice per week. The inconvenience and lengthy duration of biofeedback treatment often lead to poor compliance. We propose an intensive biofeedback therapy once a day or once every other day. The aim of the present study was to confirm the efficacy of ABF and compare the efficacy of intensive therapy with nonintensive therapy in patients with constipation-related symptoms.

2. Materials and Methods

A retrospective cohort study was conducted on subjects who had been treated with ABF for constipation-related symptoms between April 2012 and September 2013. The results were compared between the intensive therapy and nonintensive therapy in terms of constipation-related symptoms. The subjects were selected in this study according to the following inclusion/exclusion criteria.

2.1. Inclusion and Exclusion Criteria. The study enrolled men and women, aged ≥ 18 years, with a history of constipation-related symptoms. Constipation-related symptoms are defined as follows: <3 bowel movements (BMs) per week on average, hard stools, low stool volume, sensation of incomplete evacuation, straining at defecation, or a need for manual maneuver to facilitate evacuation. Exclusion criteria included drug-induced constipation, metabolic, endocrine, neurological disorders, surgical obstruction, megacolon/megarectum, surgical obstruction, and pseudoobstruction. Other exclusion criteria were severe cardiovascular, renal, liver, or lung diseases.

2.2. Outcomes and Data Collection

2.2.1. Primary Outcomes. Patients rate the severity of constipation in terms of bowel movements with the three-point scale classification [0 = normal (≥3 BMs per week), 1 = mild (1-2 BMs per week), 2 = severe (<1 BMs per week)]. Criteria for therapeutic effects are being cured (BMs changed from severe or mild to normal), being effective (BMs changed from severe to mild), and having no effect (BMs did not change).

2.2.2. Secondary Outcomes. Secondary outcome measures usage of medications, defecation difficulty, hard stools, straining, incomplete bowel movement, low stool volume, manual maneuver to facilitate, abdominal bloating, and anus discomfort. Symptoms of defecation difficulty, hard stools, incomplete bowel movement, low stool volume are described on a 0–3 scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), manual maneuver to facilitate [0 = absent, 1 = mild (<1 time per week), 2 = moderate (1–3 times per week), 3 = severe (>3 times per week)].

2.2.3. Impact on Social Activities and Work. The impact on social activities and work is rated on a 0–2 scale where 0 = absent, 1 = mild (a mild effect on normal social activities and normal work), and 2 = severe (a severe effect). Criteria for therapeutic effects are being cured (change from severe or mild to absent), being effective (change from severe to mild), and having no effect (no change).

2.3. Adaptive Biofeedback Training. Biofeedback training for the treatment of constipation is to train the relaxation of anal sphincter, enhance the sensory perception, and improve the rectoanal coordination. Training of rectoanal coordination is to increase the pushing effort as reflected by an increase in intra-abdominal/intrarectal pressures and synchronized relaxation reflected by a decrease in anal sphincter pressure. However, the traditional biofeedback training algorithm uses the fixed training target, it cannot increase (or decrease) the training strength or duration based on patient's capacity. On the other hand, the adaptive biofeedback training (ABT) (Ningbo Maida Medical Device Inc. Ningbo, China.) method uses the training strength and duration based on patient's own capacity and trains the patient at strength slightly above his or her own threshold with the purpose to gradually increase the strength threshold until the targeted threshold is met. It was reported to have a better efficacy for the treatment of constipation than the traditional biofeedback training method. Each patient received a total of 16 training sessions with each training session lasting half an hour.

Intensive Therapy. Patients were asked to receive intensive biofeedback therapy once a day or once every other day.

Nonintensive Therapy. Patients received nonintensive training twice a week in the motility lab.

2.4. Statistical Analysis. The data are expressed as mean ± standard error. The paired-sample t-test was used to compare defecation difficulty, hard stools, straining, incomplete bowel movement, low stool volume, manual maneuver to facilitate, abdominal bloating, and anus discomfort before and after treatment with ABF. An independent t-test was used to compare the nonintensive therapy with the intensive therapy

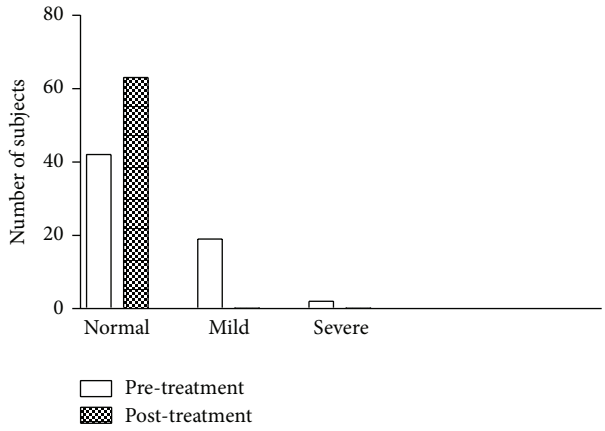

Figure 1: Effects of ABF on bowel movement (BM).

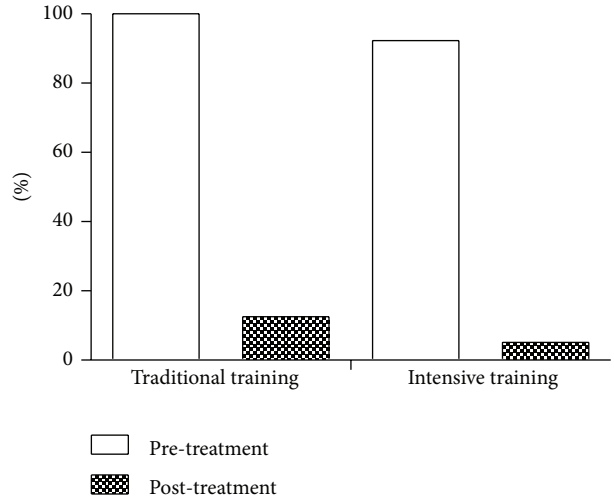

Figure 2: Usage of medications during the biofeedback training.

group. Data were considered statistically significant if $P < 0.05$.

3. Result

A total of 63 subjects met the inclusive criteria. 21 subjects had a long history of constipation defined as an average of <3 BMs per week. The mean age of the participants was 45.60 ± 16.60 and 42 (66.66%) were women and 21 were men. There was no significant difference in age and gender between the two treatment groups.

After adaptive biofeedback training treatment, all constipation patients ($N = 21$) reported a significantly greater number of weekly bowel movements (≥3 times) compared with the baseline (<3 times). The cure rate of nonintensive therapy ($N = 8$) and intensive therapy ($N = 13$) both reached 100%. None of the patients reported less than 3 BMs per week after the treatment (Figure 1). The usage of medications decreased considerably during the training period in both treatment groups compared to baseline. The medication usage at the start of treatment was 100% for nonintensive therapy group and 92.3% for intensive therapy group. During the treatment period, medication usage decreased to 12.5% for the nonintensive therapy group and 5.1% for the intensive therapy group (Figure 2).

As shown in Table 1, defecation difficulty, hard stools, and straining significantly improved with nonintensive therapy/intensive therapy compared with baseline ($P < 0.05$). Intensive therapy patients also reported significant improvements in incomplete BM. Intensive therapy also improved low stool volume ($P = 0.006$) and decreased manual maneuver frequency ($P = 0.048$). Both treatments significantly decreased abdominal bloating ($P < 0.05$). Nonintensive therapy, but not intensive therapy, significantly reduced the scores for anus discomfort (0 versus 0.48 + 0.87, $P = 0.011$; 0 versus 0.10 + 0.50, $P = 0.21$). However, there was no statistically difference between the two methods in all symptoms ($P > 0.05$).

Overall, 82.5% ($N = 52$) of subjects reported that constipation symptoms interfered with normal social activities

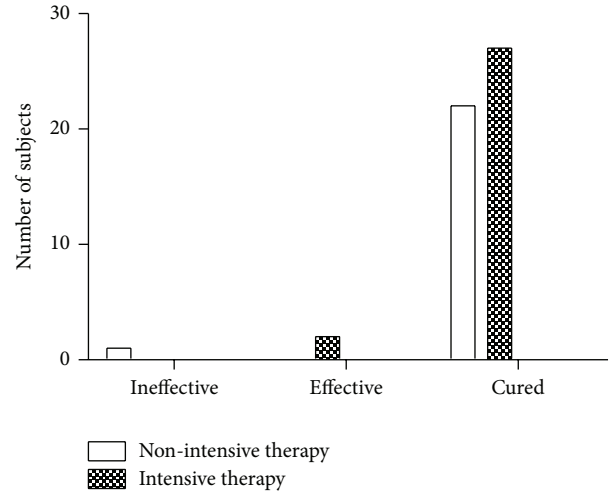

Figure 3: Improve the impact on social activities and work.

and normal work. The number of patients receiving either nonintensive therapy or intensive therapy who were cured was high (22 and 27, resp.). Only 1 patient with nonintensive therapy showed no improvement (Figure 3).

4. Discussion

The results of this study indicate that adaptive biofeedback training was effective in the treatment of patients with constipation-related symptoms. The adaptive biofeedback training was able to significantly increase weekly bowel movements. Patients also showed major improvement in defecation difficulty, hard stools and straining, incomplete BM, low stool volume, manual maneuver to facilitate, and abdominal bloating. In the current study, adaptive biofeedback training also reduced the impact on social activities and work created by constipation-related symptoms.

Table 1: Constipation-related symptoms before and after intensive therapy/nonintensive therapy.

	Intensive therapy		Nonintensive therapy	
	Before training	After training	Before training	After training
Defecation difficulty	1.18 + 1.12	0.13 + 0.41*	0.79 + 1.06	0.17 + 0.48*
Staining	0.44 + 0.97	0.05 + 0.22*	0.58 + 0.93	0*
Incomplete BM	0.41 + 0.82	0.03 + 0.16*	0.25 + 0.68	0
Low stool volume	0.67 + 1.01	0.26 + 0.50*	0.17 + 0.57	0.04 + 0.20
Hard stools	0.67 + 1.06	0.10 + 0.31*	1.04 + 1.08	0.13 + 0.45*
Manual maneuver to facilitate	0.23 + 0.71	0*	0.08 + 0.41	0
Abdominal bloating	0.46 + 0.88	0.03 + 0.16*	0.96 + 1.20	0.04 + 0.20*
Anus discomfort	0.10 + 0.50	0	0.50 + 0.89	0*

* $P < 0.05$ versus before training.

Our results are consistent with the study conducted by Xu et al. [14] who recently reported that adaptive biofeedback training was more effective in improving bowel movements than those of conventional fixed biofeedback training (3.4 ± 1.3 versus 2.6 ± 0.5, $P < 0.005$). In this study, twenty-one constipation patients (100%) had bowel movements of more than 3 times per week after ABF therapy. Chiarioni et al. [15] reported 82% of patients had ≥3 bowel movements per week at 12-month follow-up after fixed biofeedback training. Only 29% patients reported ≥3 bowel movements per week at 4 weeks of prucalopride therapy [19]. The ABF had a higher bowel movement response rate than fixed biofeedback training and laxative.

ABF significantly improved symptoms of constipation, such as defecation difficulty, incomplete BM, hard stools, and straining based on ROME III criteria [20]. Xu et al. [14] reported that ABF significantly improved these symptoms compared with fixed biofeedback training.

In addition, the impact of constipation symptoms on social activities and work was significantly decreased at the end of ABF. A growing evidence shows that constipation patients have a significantly impaired health-related quality of life compared with population norms [21–23]. Although this study did not use standard assessment tools to characterize quality of life, the results indicated that symptoms had an impact on social function. Other studies reported that fixed biofeedback training improved the quality of life scores compared with control group [18, 24].

In this study, we investigated the efficacy of intensive therapy compared to nonintensive therapy. In previous studies, patients were asked to receive nonintensive biofeedback training twice a week with a total of 4 to 6 sessions [25]. We proposed an intensive biofeedback therapy of which frequency was once a day or once every other day. There was no significant difference in constipation-related symptoms between the two treatment groups. Several randomized controlled trials had variable duration and number of biofeedback sessions, but the efficacy of therapy was similar [15–18, 26]. But the intensive biofeedback therapy had short duration and may have better compliance.

In conclusion, treatment with adaptive biofeedback training produced significant improvement in bowel movements. ABF also significantly improved symptoms associated with constipation. The intensive biofeedback therapy did not seem to be superior to nonintensive therapy.

Conflict of Interests

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

Authors' Contribution

Jing Tang and Zhihui Huang contributed equally to this paper.

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Research Article

Ameliorating Effect of Transcutaneous Electroacupuncture on Impaired Gastric Accommodation in Patients with Postprandial Distress Syndrome-Predominant Functional Dyspepsia: A Pilot Study

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Patients with functional dyspepsia (FD) have both reduced gastric accommodation and impaired gastric motility that are difficult to treat. The aim of this study was to investigate the therapeutic potential of transcutaneous electroacupuncture (TEA) for both of these disorders in FD patients. Acute experiments were performed in FD patients to study the effect of TEA and sham-TEA on gastric accommodation assessed by a nutrient drink test and gastric motility assessed by the measurement of the electrogastrogram (EGG). TEA or sham-TEA was performed via cutaneous electrodes at acupoints ST36 and PC6 or sham-points nonacupoints. It was found that (1) gastric accommodation (maximum tolerable volume) was reduced in FD patients compared with the controls ($P < 0.03$). TEA improved gastric accommodation in FD patients ($P < 0.02$). (2) Acute TEA significantly increased the percentage and power of normal gastric slow waves in the fed state assessed in the FD patients by the EGG in comparison with sham-TEA. (3) TEA increased vagal activity assessed by the spectral analysis of the heart rate variability in the fed state in FD patients. It was concluded that needleless method of transcutaneous electroacupuncture may have a therapeutic potential for treating both impaired gastric accommodation and impaired gastric motility in patients with FD.

1. Introduction

The prevalence of functional dyspepsia (FD) is high but the treatment options have been limited [1]. Patients with FD complain about symptoms of epigastric pain, abdominal fullness, early satiety, and abdominal discomfort. Pathophysiologies of FD include visceral hypersensitivity, reduced gastric accommodation, and impaired gastric motility, such as gastric dysrhythmia, antral hypomotility, and delayed gastric emptying [2].

Gastric accommodation is mediated by the vagal nerve. Upon food ingestion, the vagal nerve is activated and nitric oxide is released, resulting in a relaxation of the stomach. This relaxation reflex accommodates ingested food without causing an increase in gastric pressure [3]. Impaired gastric accommodation leads to early satiety and postprandial fullness, possibly attributed to weakening of the vagal nerve.

After the patients with GI disorder eat food, a series of indigestion symptoms of early satiety and abdominal distension will appear due to insufficient relaxation of proximal gastric and intragastric pressure increasing. About 40% to 70% of FD patients have proximal GI disorder [4]. Accordingly, treatment for impaired gastric accommodation is of great clinical significance [5, 6].

Common treatment options for FD include dietary measures, pharmacologic treatments, such as acid-suppression drugs, prokinetic agents, fundus relaxing drugs, and antinociceptive agents, and psychological interventions [7–16]. In

general, targeted therapies directed at the underlying pathophysiology are desirable. However, efficacy of the therapy is usually very limited due to multiple symptoms and pathophysiologies in individual patients. For example, a patient may have impaired accommodation and delayed gastric empting at the same time; in this case, prokinetic agents can be used to treat delayed gastric emptying but would worsen the symptoms related to gastric accommodation because available prokinetics often impair gastric accommodation. For the same reason, fundus relaxing drugs may be used for treating impaired accommodation; however, these drugs may delay gastric emptying because they relax muscles. The treatment approach to the patients with hypersensitivity to gastric distension has not been established. Antidepressants are commonly used in functional gastrointestinal disorders and were thought to exert a visceral analgesic rather than an antidepressant effect. However, studies of the effects of antidepressants on visceral sensitivity are rare, and the existing data on visceral sensitivity are controversial [14, 15].

Acupuncture has been used to treat gastrointestinal symptoms in China for thousands of years. The most commonly used acupuncture points (acupoints) for the treatment of gastrointestinal symptoms are Neiguan (PC6) and Zusanli (ST36). In clinical research, manual acupuncture is commonly replaced with electroacupuncture that is more reproducible. In a comparative study, electroacupuncture was found to be as effective as manual acupuncture in treating pain [17]. Electroacupuncture at ST36 and PC6 has been documented to increase the regularity of gastric slow waves and accelerate gastric emptying of liquids in animals [18]. In recent studies, electroacupuncture was reported to accelerate gastric emptying of solids and improve dyspeptic symptoms and gastric dysrhythmia in patients with FD and patients with diabetes [19, 20] and similar beneficial effects can be observed in patients with FD when electroacupuncture is applied without needles or a method called transcutaneous electroacupuncture (TEA) [21]. TEA is a completely noninvasive method which is readily accepted by patients. However, it is unknown whether TEA is able to treat both reduced gastric accommodation and impaired gastric motility in patients with FD.

The aims of this study were to investigate the therapeutic potential of TEA for patients with FD by assessing its acute effects on gastric accommodation assessed by a noninvasive nutrient drink test and gastric motility assessed by noninvasive electrogastrography as well as dyspeptic symptoms and to explore vagal mechanisms involved with TEA.

2. Materials and Methods

2.1. Subjects. Eight FD patients with postprandial distress syndrome and 8 healthy volunteers aged 21 to 65 years old were recruited in this study. Patients included fulfilled Rome III criteria for FD postprandial distress syndrome [1]. Patients who were unable to give informed consent; were taking prokinetic, anticholinergic, or dopaminergic agents during the experimental period; had a history of gastrointestinal surgery; were pregnant or preparing to conceive a child; had diabetes; and were allergic to skin preparation and familiar with acupoints and their functions were excluded from the study. Inclusion criteria of healthy volunteers include no history of supreme gastrointestinal diseases, including peptic ulcer disease, gastroesophageal reflux disease, and hepatobiliary and pancreatic diseases, a history of abdominal surgery, no history of alcohol abuse, no serious systemic illness and possible malignancy, and usually no dyspeptic symptoms, including upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper abdominal swelling, early satiety, nausea, vomiting, excessive belching, and heartburn. All general information including height, weight, address, and relating medical history is recorded and all the subjects had signed the informed consent prior to the study. The experimental protocol was approved by the ethical committee of Yinzhou People's Hospital and all the subjects signed the consent form before participation.

2.2. Experimental Protocol. All subjects were studied in the morning after a 12-hour fast. Each subject was studied for two sessions in a randomized order: TEA and sham-TEA sessions. The experiment protocol was as follows: 30-minute baseline recording, 30-minute TEA/sham-TEA treatment in the fasting state, and then a satiety drinking test conducted with a liquid meal of Ensure (0.95 kcal/mL) with TEA/Sham-TEA. After the completion of satiety drinking test, there was a 30-minute recovery period with TEA/sham-TEA. Electrogastrogram (EGG) and electrocardiogram (ECG) were recorded during the entire experimental period except during the satiety drinking test.

2.3. Transcutaneous Electroacupuncture. Acupoints ST36 (Zusanli) and PC6 (Neiguan) were used in the TEA session. ST36 is located at the place of 4-finger-breadth measuring down from the outer eye of the knee between the fibula and the tibia, 1-finger-breadth measurement beside the tibia; PC6 is located at the place of one-sixth of remote end and five-sixths of proximal end of the connection stripe between the transverse wrist crease and cubical crease. The stimulation was delivered by two portable neuromodulation devices at ST36 and PC6, respectively (SNM-FDC01, Ningbo Maida Medical Device Inc.). The stimulation parameters were chosen as 2s-on, 3s-off, 25 Hz, 0.6 ms, and amplitude of 2 mA to 10 mA depending on tolerance of the subject, which was shown to improve gastrointestinal symptoms in patients with diabetic gastroparesis [22]. In the sham-TEA group, the sham-acupoint for PC6 was located at about 15–20 cm away from PC6 (up to the elbow and outside coastal margin of the forearm not on any meridian) and the sham-point for ST36 was located at 10–15 cm down from and to the lateral side of ST36 not on any meridian. The stimulation parameters used for sham-TEA were the same as in the TEA.

2.4. Satiety Drinking Test. The gold-standard method of assessing gastric accommodation is the barostat method. However, this method is not well tolerated by patients due to intubation of a plastic bag into the stomach. Recently, the satiety drinking test has been used as a surrogate for the measurement of gastric accommodation [23]. A higher volume taken by the subject is indicative of a higher gastric

accommodation. In this method, after an overnight fast, the subject was instructed to take Ensure (0.95 kcal/mL) at a rate of 120 mL every 4 minutes (average 30 mL/min) until the subject reported to reach satiety (complete fullness). During the test, each subject was asked to score satiety at a 5-minute interval using following scores: 0: no symptoms; 1: initial satiety (threshold); 2: mild; 3: moderate; 4: severe; 5: maximum or intolerable satiety. When reaching score 5, the subject was asked to stop drinking and the total volume drunk was recorded, which reflected the maximum tolerable volume (MTV).

2.5. Assessment of Autonomic Function. The electrocardiogram (ECG) was recorded using a one-channel amplifier with a cut-off frequency of 100 Hz (Ningbo Maida Medical Device Inc., Ningbo, China) from two active ECG electrodes and one ground electrode. The two leads were attached to the right edge of the sternum and apex of the subjects and the ground to the right side of the abdomen. The heart rate variability (HRV) signal was derived from the ECG recording using a special program developed [24] by identifying R peaks, calculating and interpolating the R-R intervals so that the time interval between consecutive samples was equal and finally downsampling the interpolated data to a frequency of 1 Hz.

Overall power spectral analysis was applied to the HRV signal and the power in each frequency subband was calculated. The power in the low frequency band (0.04–0.15 Hz), LF, represents mainly sympathetic activity and part of parasympathetic activity. The power in the high frequency band (0.15–0.50 Hz), HF, stands purely for parasympathetic or vagal activity. For LF and HF, standard calculations were done, respectively, by LF/(HF + LF) and HF/(HF + LF) [25].

2.6. Recording and Analysis of Electrogastrogram (EGG). The gastric myoelectrical activity was recorded using a 4-channel electrogastrogram (EGG) device (MEGG-04A, Ningbo Maida Medical Device Inc., Ningbo, Zhejiang, China) via 6 cutaneous electrodes described as follows. First, the abdomen where electrodes were to be placed was cleaned with a special gel (Nuprep, Weaver and Company, Aurora, USA); then conductive gel (Ten20, Weaver and Company, Aurora, USA) was applied to the cleaned skin area to reduce skin-electrode impedance. After this, six cutaneous electrodes were placed on the abdominal skin surface based on a previously established method [2]. The subject was in a supine position for the EGG recordings and talking, reading, or sleeping was not allowed.

Established EGG parameters were derived from the EGG signals using a spectral analysis software package (Ningbo Maida Medical Device Inc., Ningbo, China) after a careful deletion of motion artifacts [26, 27]: (1) dominant frequent and power, representing the frequency and amplitude of gastric slow waves; (2) percentage of normal 2–4 cycles/min slow waves, representing the regularity of gastric slow waves; (3) postpreprandial ratio of EGG dominant power, standing for postprandial increase in gastric motility.

Table 1: Effects of acute TEA treatment on EGG in patients with functional dyspepsia in the study.

	Session	
	TEA	Sham-TEA
Dominant frequency (cpm)		
Fasting	3.02 ± 0.03	3.04 ± 0.06
Postprandial	2.84 ± 0.07	3.25 ± 0.10
Dominant power (dB)		
Fasting	33.98 ± 1.58	34.46 ± 1.75
Postprandial	42.35 ± 1.35	40.24 ± 1.47*
Percentage of normal slow waves (%)		
Fasting	82.6 ± 3.1	83.7 ± 2.7
Postprandial	85.42 ± 4.27	74.97 ± 6.60*
Postpreprandial power ratio	1.03 ± 0.03	0.92 ± 0.04

*$P < 0.05$.

2.7. Assessment of Dyspeptic Symptoms. Gastric cardinal symptom index was used to assess dyspeptic symptoms at baseline and after the acute TEA or sham-TEA [28]. These included upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper abdominal swelling, early satiety, nausea, vomiting, excessive belching, and heartburn. Each symptom was graded based on severity: grade 0: no symptoms; grade 1: mild; grade 2: moderate; grade 3: severe.

2.8. Statistical Analysis. Results are expressed as mean ± standard deviation. Paired Student's t-test was used to study the difference between TEA and sham-TEA and between baseline and after the acute treatment using SPSS 16.0 statistical software. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effects of TEA on Gastric Accommodation. FD patients showed a reduced gastric accommodation that was improved with acute TEA. The MTV was 725 ± 46 mL in the normal control group and 548 ± 38 mL in the FD patients ($P = 0.022$; see Figure 1(a)). Acute TEA increased the MTV in the FD patients to 663 ± 29 mL ($P = 0.007$, versus baseline), whereas the sham-TEA did not increase the MTV in patients with FD (549 ± 36 mL after sham-TEA ($P = 0.121$ versus 700 mL)). There was a difference ($P = 0.017$) in MTV in the FD patients after TEA and sham-TEA (Figure 1(b)).

3.2. Effects of TEA on Gastric Slow Waves. The EGG recording was found to be normal in 2 patients but abnormal in 6 patients with FD (percentage of normal slow waves below 65% in either fasting or fed state or this was a postprandial decrease in dominant power). The major EGG parameters in the TEA and sham-TEA sessions are shown in Table 1. TEA improved the percentage of normal 2–4 cycles/min slow waves in the fed state (Figure 2) and also increased the dominant EGG power in the fed state (Figure 3).

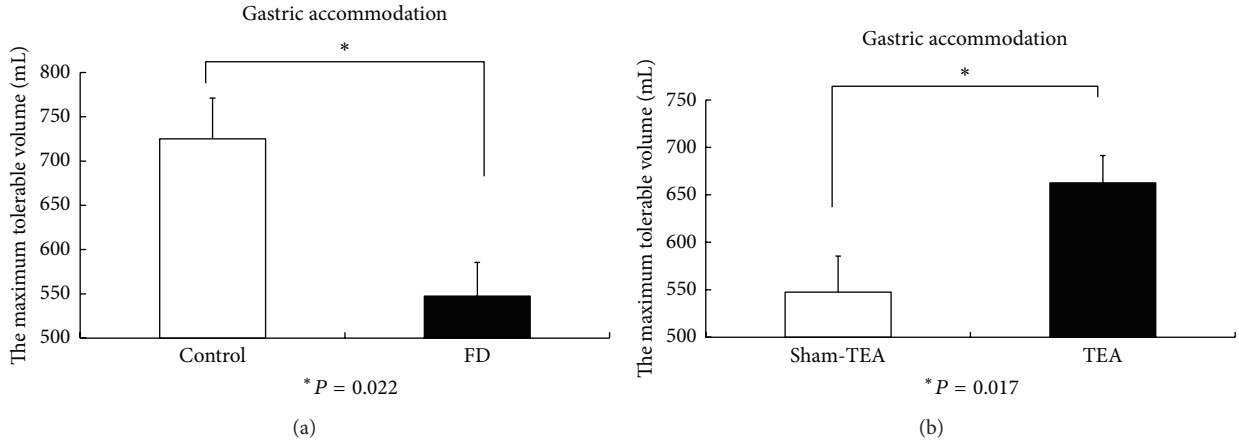

Figure 1: (a) The maximum tolerable volume (gastric accommodation) in normal controls and patients with FD. (b) The maximum tolerable volume after TEA and sham-TEA.

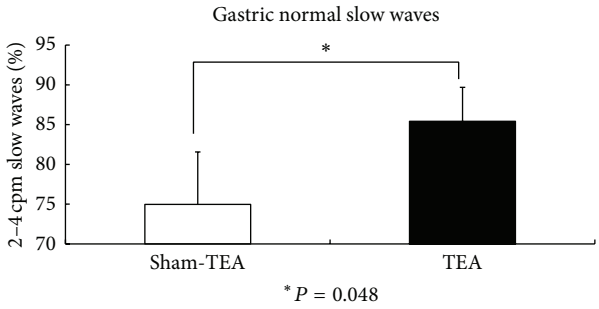

Figure 2: TEA improved the percentage of normal 2–4 cycles/min slow waves in the fed state.

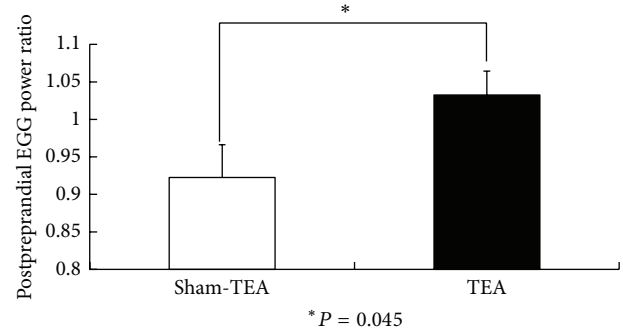

Figure 4: The comparison of postpreprandial EGG power ratio between sham-TEA and TEA.

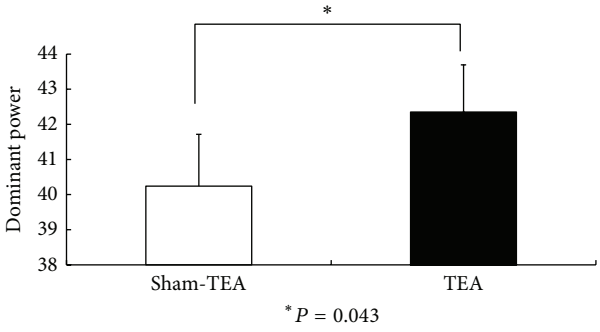

Figure 3: The comparison of EGG dominant power in the fed state after sham-TEA and TEA.

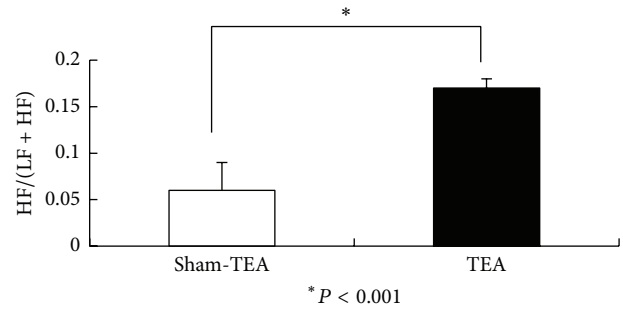

Figure 5: The vagal activity HF/(LF + HF) assessed by the spectral analysis of HRV in patients with FD treated with sham-TEA and TEA.

The postpreprandial EGG power ratio was significantly higher in the TEA sessions than in the sham-TEA session (Figure 4).

3.3. TEA Enhanced Vagal Activity. The acute TEA significantly increased the vagal activity in the 30 min postprandial period in patients with FD assessed by the spectral analysis of HRV. The HF/(LF + HF) was 0.17 ± 0.01 in the TEA session and 0.06 ± 0.03 in the sham-TEA session ($P < 0.001$) (see Figure 5).

3.4. Effects of Acute TEA on Dyspeptic Symptoms. Acute TEA improved the dyspeptic symptoms in the FD patients. The mean total symptom score was 23.5 ± 2.9 at baseline and decreased significantly to 11.9 ± 1.4 ($P = 0.007$ versus baseline) after TEA but was 21.9 ± 2.9 after sham-TEA

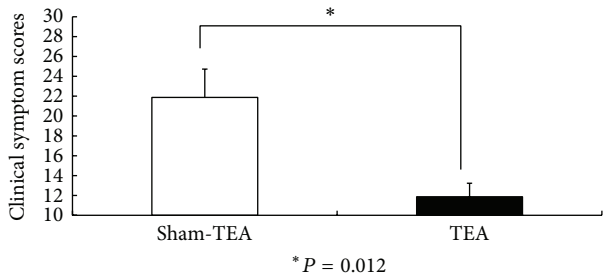

Figure 6: The clinical symptom scores in FD patients after TEA and sham-TEA treatment.

($P = 0.102$ versus baseline). There was a significant difference in the clinical symptom scores between the FD patients after true treatment and those after sham treatment (Figure 6).

4. Discussion

In this study, we found that acute TEA at the acupoints of ST36 and PC6 improved gastric accommodation and enhanced postprandial gastric slow waves in patients with FD (increased the amplitude and regularity of slow waves). A concurrent increase in vagal activity was also noted with the acute TEA, suggesting a vagal mechanism. Acupuncture or electroacupuncture has been used to treat the symptoms of upper abdomen, such as nausea and vomiting. Hu et al. [29] reported that electroacustimulation at point PC6 reduced significantly the severity of the symptoms of motion sickness. The number of emetic episodes induced by morphine [30] or cyclophosphamide [31] was significantly reduced by electroacupuncture at the PC6 point in ferrets. Electroacupuncture at both the PC6 and the ST36 points reduced the incidence of vomiting induced by vasopressin in dogs [32]. A few papers reported the effect of acupuncture or electroacupuncture on dyspeptic symptoms in patients with FD. In one study with FD patients, acupuncture was demonstrated to be effective in reducing dyspeptic symptoms [19].

While electroacupuncture has been proven effective in treating certain functional gastrointestinal diseases, the insertion of acupuncture needles is required and the treatment has to be done at a doctor's office. The method proposed in this study, TEA, did not require the insertion of any needles and the procedure could be done by the patient at his/her home. This was more attractive than electroacupuncture and was well accepted by the patients as the compliance of the therapy was 100%; none of the patients quitted the study. It is similar to transcutaneous electrical nerve stimulation except that the stimulation electrodes in this study were placed on the acupuncture points related to the targeting disorder. Liu et al. [33] found that a two-week treatment of TEA at ST36 and PC6 significantly improved dyspeptic symptoms and increased vagal activity in patients with FD. These findings were in agreement with the present study. However, the effect of TEA on gastric accommodation was not previously investigated.

Impaired gastric accommodation in FD is difficult to treat because it requires the use of muscle relaxant. The use of muscle relaxant, however, worsens impaired gastric motility that is common in FD. In this study, acute TEA significantly and substantially improved gastric accommodation while concurrently improving gastric motility assessed by electrogastrography. This is an attractive strength of the proposed method of TEA. As stated earlier, impaired gastric accommodation is associated with symptoms of early satiety and postprandial fullness and bloating. The TEA-induced increase in gastric accommodation could lead to improvement in these symptoms. Although exact mechanisms involved in the increase of gastric accommodation were unknown, the concurrent increase in vagal activity noted in this study was believed to play a major role.

Electrogastrography has previously been shown to be an accurate and reliable method for studying gastric myoelectrical activity. Several studies have reported EGG abnormalities in FD patients [34, 35]. Meanwhile, it is known that electroacupuncture may affect gastric myoelectrical activity. A number of studies have investigated the effect of electroacupuncture on the gastric slow waves. Ouyang et al. [18] showed that electroacupuncture at ST36 and PC6 increased the regularity of gastric slow waves in both the proximal and distal stomach. Chang et al. [20] found that electrical stimulation at ST36 increased the percentage of normal EGG frequency and decreased the percentage of tachygastrial frequency in diabetic patients. Electroacupuncture at ST36 and PC6 increased the percentage of regular slow waves, resulting in the normalization of dysrhythmia in healthy human [36]. However, Liu et al. [33] study showed that TEA at ST36 and PC6 points did not change the EGG parameters in the patients with FD, suggesting that TEA may not treat disorders induced by gastric myoelectrical disturbances. In this study, however, we found that acute TEA at the acupoints of ST36 and PC6 improved gastric slow waves in the postprandial state. It should be noted that in this study the EGG in the postprandial state was recorded after the maximum ingestion of a nutrient liquid meal. This was apparently different from the postprandial recording after a regular meal.

Altered HF and LF/HF in the spectral analysis of HRV in patients with FD have been previously reported [37, 38]. It has been proposed that the autonomic dysfunctions could play a role in the development of disturbed gastric motility and perception. Spectral analysis of the HRV is a noninvasive and simple method for the quantitative evaluation of autonomic activity [39, 40]. We used this method to evaluate the effect of acute TEA on HRV in patients with FD and found a significant increase in HF after the TEA treatment. This result is in good agreement with others reported previously [18, 33, 41]. Although we did not have proof that this was responsible for the improvement in dyspeptic symptoms, it was consistent with the hypothesis that the visceral effects of TEA are at least partially mediated by the autonomic nerve pathway.

In summary, acute TEA at ST36 and PC6 significantly improves gastric accommodation and postprandial slow waves as well as dyspeptic symptoms, possibly mediated via the vagal mechanisms. Chronic clinical studies are warranted to establish clinical role of this noninvasive method of TEA for treating FD.

Ethical Approval

This work was performed to the principles expressed in the Declaration of Helsinki. This study was approved by the ethical committee in the Yinzhou Affiliated Hospital. An informed consent was obtained from all patients and controls.

Conflict of Interests

The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this paper.

Authors' Contribution

The work presented here was carried out through collaboration between all authors. Jieyun Yin defined the research theme. Jieyun Yin and Yan Tan designed the methods and experiments. Feng Xu, Yan Tan, Zhihui Huang, Nina Zhang, and Yuemei Xu carried out the clinical experiments and Yan Tan analyzed the data. Yan Tan and Jieyun Yin interpreted the results and wrote the paper. All authors have contributed to and approved the paper. Feng Xu and Yan Tan contributed equally.

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Review Article

Complementary and Alternative Therapies for Chronic Constipation

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Chronic constipation, an ancient disease, is prevalent, and costly in the general population. Complementary and alternative therapies are frequently used for constipation. This review introduces various methods of complementary and alternative therapies, including acupuncture, moxibustion, massage, and herbal medicine. Efficacy, safety, influence factors, sham control design, and mechanisms of these therapies are discussed and evaluated. Acupuncture or electroacupuncture was found to be most commonly used for constipation among these complementary and alternative therapies, followed by herbal medicine. Although only a small number of clinical studies are flawless, our review of the literature seems to suggest that acupuncture or electroacupuncture and herbal medicine are effective in treating constipation, whereas findings on massage and moxibustion are inconclusive. More well-designed clinical trials are needed to improve and prove the efficacy of the complementary and alternative therapies for constipation; mechanistic studies that would lead to wide spread use and improvement of the methods are also discussed in this review.

1. Introduction

Chronic constipation (CC) is a complaining problem for many patients with or without other diseases. The prevalence of constipation in the general adult population ranges from 2% to 26.9%, with a mean of 15.4%, revealed by an integrative literature review of 11 population-based studies. Female gender was identified as the first associated factor in all of these studies, and the second most common associated factor was advanced age [1].

Physical and mental components of quality of life (QoL) scores have been consistently reported to be low in both adult and pediatric patients with CC; meanwhile the greatest influence is seen in secondary care studies [2]. The mean expenditures per hospital costs for constipation increased from $8869 in 1997 to $17,518 in 2010, whereas the total charges increased from $188,109,249 in 1997 to $851,713,263 in 2010 (adjusted for long-term inflation) [3].

The vast majority of CC belongs to functional constipation (FC). According to the Rome III criteria [4], a standardized definition of FC is presented as follows.

Rome III Functional Constipation Criteria

(1) It must include at least 2 of the following:

- (a) straining during at least 25% of defecations,
- (b) lumpy or hard stools in at least 25% of defecations,
- (c) sensation of incomplete evacuation for at least 25% of defecations,
- (d) sensation of anorectal obstruction/blockage for at least 25% of defecations,
- (e) manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor),
- (f) fewer than three defecations per week.

(2) Loose stools are rarely present without the use of laxatives.

(3) There are insufficient criteria for diagnosis of irritable bowel syndrome.

Criteria fulfilled for the previous three months with symptom onset at least 6 months prior to diagnosis.

This definition of FC is for adult patients. For child patients, there are other criteria [4] (as follows).

Rome III Functional Constipation Criteria

(1) It must include two or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of IBS:

(a) two or fewer defecations in the toilet per week,

(b) at least one episode of fecal incontinence per week,

(c) history of retentive posturing or excessive volitional stool retention,

(d) history of painful or hard bowel movements,

(e) presence of a large fecal mass in the rectum,

(f) history of large diameter stools which may obstruct the toilet.

(2) Criteria are fulfilled at least once per week for at least months prior to diagnosis.

CC is very general, including all kinds of constipation, whereas functional constipation is only one major part of it. CC is classified into outlet obstruction constipation (OOC), slow transit constipation (STC), and both. The OOC is characterized with impaired relaxation and coordination of abdominal and pelvic floor muscles during evacuation [5]. STC is defined as prolonged stool transit (>3 days) through the colon [6]. In fact, most of patients with STC are associated with outlet obstruction [7, 8]. It was reported that more than half of patients with STC simultaneously had some degree of outlet obstruction [9, 10].

Pharmacologic agents for CC are available. However, 28% of participants were dissatisfied with their laxatives. In a large sample survey, as high as 83% of respondents indicated that they were absolutely or probably interested in other treatment options and complementary/alternative therapies [11]. In another survey, Johanson and Kralstein reported that the causes of laxatives dissatisfaction included "does not work well" or "inconsistent results" and safety-related or adverse-effect concerns [12]. In children, the adherence rate to medical therapies of constipation was reported to be low, attributed to financial difficulties (23.2% of cases) and side effects (40.2%) [13].

This article reviews complementary and alternative therapies for CC, including acupuncture, moxibustion, massage and herbal medicine.

2. Acupuncture

Acupuncture is an ancient Chinese Traditional Medicine therapy in which acupoints on skin are manually stimulated by needles. It is usually termed hand-acupuncture. Electroacupuncture (EA) is a method in which electrical current is delivered to needles inserted into acupoints. Transcutaneous electroacupuncture (TEA) is similar to EA but the needles are replaced with electrodes. Auricular acupuncture (AA) is the one in which acupuncture is performed at acupoints on the skin of ear. All of the above methods had been used in the treatment of CC.

Clinic studies on acupuncture or EA for CC were searched in PubMed database from inception to October 2014. Keywords used in the search included "acupuncture" or "electroacupuncture" and "constipation". The language of publications was instructed as English or abstract in English. Seventeen reports yielded from this search were summarized in Table 1.

2.1. Quality Assessment of Acupuncture Trials for CC. Among the 17 articles, 11 of them were RCT's and 90% of the RCT studies were published after 2010. There were 6 high quality trials [14, 16, 17, 23, 24, 27] which could be assessed as 5 according to Jadad scoring system [31], but sample sizes of them were all small. A trial containing 553 samples was evaluated to have a Jadad score of less than 3 due to the flaw in design [15].

Multiple methods of the design for control were used in clinical studies on CC. The control groups in the literature included medications, other methods of stimulation, and acupuncture plus medications. Medications used in the control group included conventional medicine [15, 16, 23, 24] (Mosapride, Macrogol 4000, Lactulose) and Chinese herbal medicine [15, 22] (Fuzhengliqi mixture and Plantain and Senna Granule). Sham acupuncture [17, 27, 29], shallow acupuncture [16, 23, 24], regular electrical stimulation [19], and other methods of stimulation were performed as control methods. Combinational use of medications included EA plus Fuzhengliqi mixture [15], and EA plus Plantain and Senna Granule [22]. There was only one trial in which two kinds of stimulation methods, acupuncture and moxibustion, were used together [21].

The treatment duration [14–17, 22–24, 27] ranged from 4 weeks to 7 weeks, and the follow-up time [14–16, 22, 24, 26, 27] ranged from 4 weeks to 64 weeks. The primary outcome was the number of weekly spontaneous bowel movements. The secondary outcomes included opaque X-ray marker, patient's satisfaction, and clinical symptom score (such as weekly defecation frequency, defecation time, stool characteristics, straining and abdominal pain). The questionnaires used in trials included Bristol score, Cleveland Clinic Score, and Quality of Life. Some indicators about mechanisms of acupuncture for constipation also were measured, including plasma motilin [15], plasma panopioid [29], and heart rate variability [17].

2.2. Efficacy and Safety of Acupuncture for CC. Several systematic reviews, including meta-analysis, indicated that acupuncture for CC was effective and did not cause obvious adverse events [32–36].

The overall efficacy rate of hand-acupuncture for chronic functional constipation was 52.0% [21]. It improved weekly

Table 1: Articles of acupuncture or EA for CC.

Reference	Study design (participants)	Acupoints	Implementation of acupuncture	Key efficacy results	Adverse reactions
Wu et al., 2014 [14]	RCT (n = 104) adult	ST25, BL25, LI11, ST37	EA1: ST25, BL25 EA2: LI11, ST37 EA3: ST25, BL25, LI11, ST37 C: Mosapride citrate	Weekly frequency of defecation, defecation difficulty life, and quality score were all improved significantly in the four groups; in follow-up, weekly frequency of defecation of LI11 and ST37 (EA2) was superior to the other three groups	NA
Zhang et al., 2013 [15]	RCT (n = 553) adult	ST25, ST37, ST36, BL25, TE6	EA: 2 Hz/200 Hz D: Fuzhengliqi mixture EA + D: both of above C: Mosapride and Macrogol 4000	All groups decreased the defecation interval, stool property, constipation symptom grade, accompanying symptom grade, and GITT; EA + D was better than others; EA could keep long-term effect	No
Peng et al., 2013 [16]	RCT (n = 128) adult	ST25	EA-deep: 20 to 65 mm in depth EA-shallow: 5–8 mm depth D: lactulose oral liquid	All groups increased the weekly defecation frequency; EA-deep could keep long-term effect	No
Chen et al., 2013 [17]	RCT (n = NA) adult female	ST36, ST37, ST25, ST28, CV4, CV6	EA Sham-EA	EA improved constipation symptoms and increased autonomic nervous system activities, sham-EA not	NA
Zhou et al., 2012 [18]	RCT (n = 200) elder	AT3, 4i, AT3, AT4, CO7, CO17, AH8, CO18, Constipation Point	AT: according to the pattern/syndrome differentiation C: solid points	The effective rate: AT 92.0%, C 76.0%	NA
Xu et al., 2012 [19]	RCT (n = 64) adult	TE6, ST25, ST36, ST37	EA: Hwato neuro and muscle stimulator C: regular electronic stimulator	The effective rate of short term: EA 54.6%, C 29.0%	NA
Anders et al., 2012 [20]	Retrospective case series study (n = 10) children	Quchi (LI11)	Fixed indwelling acupuncture needles (0.9 mm in length)	After a median of 3 days of HIC, all children defecated within 2 h. Local constipation therapy was not required	No
L.-J. Wang and L.-L. Wang, 2011 [21]	RCT (n = 100) adult	Group 1: ST25, SP15, CV6, CV4, ST36, ST37, SP6. Group 2: BL33, BL34, BL5, BL23, BL20 Alternatively	HA: punctured by hands HA + moxibustion: grain-shaped moxibustion was given at CV6, ST36, BL25, BL20, and others with puncture	The total effective rate: HA + moxibustion as 74.0% (37/50) versus 52.0% (26/50)	NA
Guo et al., 2011 [22]	RCT (n = 378) adult	ST25, ST37, ST36, BL25, TE6	EA: 2 Hz/100 Hz D: Plantain and Senna Granule EA + D: both of the above	All groups decreased the scores of defecation cycle, stool property, constipation symptom grade, accompanying symptom grade, and GITT; EA + D was better than others; EA and EA + D could keep long-term effect	No
Wang et al., 2010 [23]	RCT (n = 95) adult	ST25	EA-deep: 45 mm in depth EA-shallow: 5 mm in depth D: lactulose oral liquid	EA-deep and EA-shadow were significantly superior to D group in increasing number up to 4 and improved CCS. EA-deep worked faster than EA-shadow	NA
Wang et al., 2010 [24]	RCT (n = 95) adult	ST25	EA-deep EA-shallow D: Duphalac	EA-deep was similar to EA-shallow in number up to 4 and CCS, and its efficacy remained much longer	NA
Jin et al., 2010 [25]	Before-after study (n = 90) adult	Group 1: ST25, CV6, ST37; Group 2: BL33, BL34, BL25 Alternatively	EA: BL33, BL34, ST25, T37	The scores of defecation frequency, difficulty degree of defecation, defecation time, endless sensation of defecation, stool quality, awareness of defecation, and QoL were obviously improved after treatment. The total effective rate was 67.7% (61/90)	NA
Ding et al., 2009 [26]	Before-after study (n = 30) adult	Group 1: ST25, SP15, SP14, CV6, CV4, ST36, ST37; Group 2: BL25, BL23, BL31, BL32, BL33, BL34, Ex-HN1 Alternatively	Deep needling was applied on acupoints of abdominal and back region and moxibustion was put on Ex-HN1	Reduced laxative, scores for awareness, and QoL. Increased frequency of defecation	No

Table 1: Continued.

Reference	Study design (participants)	Acupoints	Implementation of acupuncture	Key efficacy results	Adverse reactions
Zhang et al., 2007 [27]	RCT EA SA	TE6	EA: EA at Zhigou SA: EA at nonacupoint	EA could obviously improve CCS and CTT, decrease cathartics, effective rate of 94.4%	No
Zhu et al., 2003 [28]	Before-after study (n = 188) adult	ST25, ST36, ST37, BL25, BL57	HA	Total effective rate of 100%	NA
Broide et al., 2001 [29]	CCT-self (n = 17) child	NA	Treated by five weekly placebo acupuncture sessions, followed by 10 weekly true acupuncture sessions	The frequency of bowel movements increased only after 10 true acupuncture sessions	NA
Klauser et al., 1993 [30]	CCT-self (n = 8) adult	LI4, ST25, LE3, BL25	EA: 10 Hz	Stool frequencies and CCT were not altered	Two patients dropped out because symptoms worsened

RCT: randomized controlled trial; CCT: controlled clinical trial; HA: hand-acupuncture; EA: EA; AT: auriculotherapy; SA: sham acupuncture; D: drug; HA + D: hand-acupuncture + drug; EA + D: EA + drug; C: control; PE: patient's endurance; MA: mean age; PO: by mouth; CCS: Cleveland Constipation Score; number up to 4: the number of constipation patients whose defecation was up to 4 times per week; BMs, bowel movements; GITT: gastrointestinal transit time; TGITT: total gastrointestinal transit time; M-ITT: mouth-intestine transit time, CTT: colonic transit time; RCTT: right colonic transit time; LCTT: left colonic transit time; RSTT: rectosigmoid colonic transit time; MTL: motilin; QoL: quality of life; CI: confidence interval; QD, every day; BID: twice per day; TID: triple per day; NA: not acquirable.

Table 2: Acupoints appeared ≥3 times for CC in these 17 articles.

Acupoints	Times appeared
Tianshu (ST25)	13
Shangjuxu (ST37)	9
Dachangshu (BL25)	8
Zusanli (ST36)	7
Zhigou (TE6)	5
Qihai (CV6)	4
Guanyuan (CV4)	3
Zhongliao (BL33)	3
Xialiao (BL34)	3

spontaneous defecation times, abdominal pain, evacuation difficulty, endless sensation of defecation, obstruction sense of anus, laxative prescription dependence, and quality of life [21, 32], as well as psychological symptoms score [21].

The overall efficacy rate of EA for chronic functional constipation raged from 54.6 to 94.4% [15, 19, 27]. EA increased the frequency of weekly defecation and the number of persons who had defecation 4 times or more a week (responder) [16, 23], decreased stool property, constipation symptom grade, accompanying symptom grade, and gastrointestinal transit time (GITT) [15, 22, 24, 27].

Several articles reported that acupuncture or EA outperformed conventional medicine, such as lactulose [16, 23, 24] and Plantain and Senna Granule [22]. This was different with the conclusion drawn from a systematic review which indicated that acupuncture was probably as effective as conventional medical therapy in the change of bowel movements and colonic transit activity [32]. This difference might be attributed to the small sample sizes in these trials. A trial including 553 patients reported that the effective rate of EA was not different from Fuzhengliqi mixture or Mosapride combined with Macrogol 4000 in short term but was superior to them in long term because constipation symptoms recurred in the two control groups [15].

Zhou et al. performed an RCT study and reported that the effective rate of AA for functional constipation was 92% [18]. However, the reliability of this conclusion was low due to small sample size and lack of control. It was indicated in a systematic review that no conclusion should be made on the effectiveness of acupuncture due to significant methodological flaws [34].

Acupuncture for the treatment of pediatric patients with hospital-induced constipation was evaluated in a pilot study for the feasibility and acceptability with encouraging results [20].

2.3. Most Popular Acupoints for CC. Acupoints used more than 3 times for CC in the 17 articles included ST25, ST37, BL25, ST36, TE6, CV6, CV4, BL33, and BL34 (Table 2). These acupoints usually are considered as representative choices adopted by doctors and researchers. The top five acupoints being used most frequently for treating CC are discussed here.

ST25 is on the upper abdomen, laterally to the umbilicus above the small intestine according to World Health Organization (WHO) standard acupoint locations [37]. EA at ST25 was reported to enhance small intestinal motility in rodent model of slow transit constipation [38]. However, in normal or fasted rats, EA at ST25 was found to produce inhibitory effects on jejunum electrical and mechanical activities [39, 40]. These findings seem to suggest that EA at ST25 exerts different effects under different conditions.

ST36 and ST37 are located on the anterior aspect of the leg and above of tibialis anterior muscle. ST36 is above ST37 [37]. Acupuncture stimulation of ST36 was reported to increase intragastric pressure and gastric peristaltic frequency in rats with gastric hypomotility [41]. In patients after abdominal surgery, ST36 was able to shorten the time of first flatus passage and improve gastrointestinal functions [42]. Significant acceleration of colonic transit with EA at ST36 was mediated via the sacral parasympathetic efferent pathway [43]. Acupuncture at ST37 was reported to alter rectal motility and the effect appeared one hour after needling [44].

BL25 is located on the lumbar region, at the same level as the inferior border of the spinous process of the fourth lumbar vertebra (L4), laterally to the posterior median line [37]. Acupuncture at BL25 reduced early postoperative inflammatory small bowel obstruction [45], improved symptoms of ulcerative colitis [46], and irritable bowel syndrome [47].

TE6 is located on the posterior aspect of the forearm, midpoint of the interosseous space between the radius and the ulna, proximal to the dorsal wrist crease [37]. EA at TE6 and ST36 was effective for adhesive ileus, remarkably improved abdominal pain and distention, and accelerated intestinal peristalsis [48].

The above discussion indicates that acupuncture or EA at all of the top five acupoints improves gastrointestinal motility. According to the anatomy of the nervous system, tibial nerve, L4 spinal nerve, and posterior interosseous nerve are under ST36 and ST37, BL25, and TE6, respectively. Therefore, acupuncture effects of these four acupoints are probably mediated via these nervous pathways. Special acupuncture technique is required on ST25 to get a better therapeutic effect. In this technique, the needle is inserted perpendicularly and slowly till penetrating the peritoneum, about 20–65 mm in depth [16]; direct intestinal stimulation might be implicated with this technique.

2.4. Influence Factors of Acupuncture for Constipation. There are several factors influencing the effective rate of acupuncture for CC [21, 27]. These include acupoint group, operative technique of puncture, stimulation parameters, and treatment interval.

Various acupoint groups had been used in clinical trials. All of acupoints for CC can be classified into four categories according to their locations: abdomen acupoints (ST25, ST28, CV4, CV6, SP15), lumbosacral acupoints (BL25, BL20, BL23, BL33, BL34), crus acupoints (ST36, ST37, BL57, SP6), and forearm acupoints (TE6, LI11, LI4). Acupoint groups result in the combination coming from at least one kind

of acupoints. Abdomen acupoints plus crus acupoints or forearm acupoints are counted as acupoint group regularly [14, 17, 19, 21, 22, 25, 26, 28, 30]. Lumbosacral acupoints are taken as a group usually [21, 25]. One trial used three kinds of acupoints simultaneously: abdomen, lumbosacral, and crus [15]. In five trials, only one acupoint was used [16, 20, 23, 24, 27]. No studies are available in the literature comparing different acupoint groups. Studies of searching optimal acupoint group are needed.

ST25, the most frequently used acupoint, was dealt with through a special operative technique of puncture which was named as deep-puncture technique [16, 23, 24]. Here is the deep-puncture technique of ST25: needle is inserted perpendicularly and slowly till penetrating the peritoneum, about 20–65 mm in depth [16]. Using the deep-acupuncture technique, the number of functional constipation patients whose defecation was up to 4 times per week was increased, compared with the shallow-acupuncture technique during the second treatment week [23]. However, at the forth treatment week there was no difference between the two techniques in the number of responders, the defecation interval, stool property, constipation symptom grade, accompanying symptom grade, or GITT [16, 23]. At the 6-month follow-up, deep-acupuncture was reported to be still effective, whereas the shallow-acupuncture became ineffective [24]. The standard definition and operation about "deep-acupuncture" of ST25 was studied in the fields of anatomy and safety [49]. In acupuncture theory, the operative technique of puncture is considered as one of key factors that affects the outcomes of acupuncture. Therefore, the direction and depth of needling are required. This technique was applied in puncturing ST25 for constipation, but not for other acupoints and other diseases.

There are 11 trials which adopted EA for constipation among the 17 articles. The parameters used in EA treatment seem to be important. Different stimulation frequencies were used in these studies, including 2 Hz/200 Hz [15], 1 Hz/20 Hz [19], 2 Hz/100 Hz [22], and 10 Hz [30]. In rough, EA frequency can be divided into low-frequency (1 Hz, 2 Hz, 10 Hz, etc.) and high-frequency (100 Hz, 200 Hz, etc.). In acupuncture analgesia, high- and low-frequency of EA could facilitate the release of endogenous opioid peptides. The effect of low-frequency EA was found to be mediated by the κ opioid receptor, whereas high-frequency EA was reported to be mediated by the δ and μ opioid receptors [50]. However, it is unclear whether the EA frequencies for analgesia are applicable to EA for constipation and more studies are needed to determine the best EA stimulation frequency for constipation.

In addition to the stimulation frequency, the frequency of treatment (treatments per week) is also an important factor. Five treatments per week seemed to be most popular in the previous studies [15, 16, 22–24]. Most of acupuncturists believe that efficacy induced by acupuncture can be maintained for one or two days and thus require patients to receive treatment every day or every other day. However, one of major problems with clinical acupuncture is that the treatment is administrated infrequently, such as 1 or 2 times per week, yielding insignificant or inconsistent results [30].

2.5. Sham Acupuncture Design. Sham acupuncture was used as control in two of the articles [17, 27]. Sham acupuncture design is based on two key points: one is the use of nonacupoints and the other is nonneedle. For blindfolding patients, sham needles were glued on skin. It looks like being inserted; however, this is exposed easily for experienced patients due to different feelings between the needle being inserted at the acupoint and the one placed on the surface of acupoint. Sham acupuncture at nonacupoints refers to needle manipulation at points that are not on any meridian or acupoints. Different from the specific technique of acupuncture, which can induce a higher intensity of *de qi* that substantially improves the therapeutic effect, acupuncture that does not induce *de qi* can also be regarded as sham acupuncture. This method of sham design was used in acupuncture for Bell's palsy, a recent RCT completed by Xu et al. [51], and appreciated by John Fletcher who is Editor-in-Chief of Canadian Medical Association Journal. Fletcher considered that results of that trial were reasonable because every patients received acupuncture, but with valid or invalid technique [52]. What calls for special attention is that valid or invalid technique should be defined according to different diseases and types of acupuncture. For example, EA-shallow being regarded as control in some trials [16, 23, 24] should not be designed as sham control, unless electric current was shut off.

2.6. Mechanisms of Acupuncture for Constipation. Despite the fact that acupuncture for constipation has been proved effective in clinical studies [32], enhancing contractility in the distal colon [53], and accelerating colonic transit [43] in animal studies, mechanisms involved in these effects are still unclear. A lower level of motilin was noted in patients of functional constipation and found to be elevated with acupuncture at ST36 and ST37 [54]. EA at bilateral ST25 was reported to increase colonic smooth muscle thickness and number of Cajal cells considerably [38]. Vagal and parasympathetic mechanisms have also been implicated in the accelerative effect of acupuncture or EA on colon motility [55]. Overall, little is known on the mechanisms involved in the effect of acupuncture on constipation. More studies are needed to reveal possible pathways, such as neural pathway, endocrine pathway, opioid pathway, and/or serotonic pathway.

3. Moxibustion

Moxibustion is a traditional therapy in Chinese Medicine to stimulate acupoints with burning moxa made from dried mugwort. Little has been reported in the literatures on the management of CC with moxibustion. A systematic review [56], published in 2010, only included 3 RCTs with a total of 256 patients, and no randomization or blinding (two in Chinese and one in Korean). Given that the methodological quality of these trials was poor, the review reported that there was insufficient evidence to suggest that moxibustion was an effective treatment for constipation [56].

In PubMed database, RCTs of moxibustion for CC were searched from its inception to October 2014 with keywords including "constipation" plus "moxibustion," resulting in only

one high quality RCT published in 2011 in English. This trial was randomized, sham-controlled, patient blinded, and pilot clinical [57]. The trial noted that moxibustion treatment appeared safe but showed no positive effect on constipation [57].

However, this conclusion does not stand up to be scrutinized due to the design of sham control. Sham moxibustion used in this trial [57] was given with adding insulation below the moxa pillar in order to prevent the transfer of heat from patients. The sham moxa pillar looked similar to real moxa pillar on its appearance and burning procedure and that the smoke from moxa could be smelled and the burning could be observed. This method of sham moxibustion seems well established as blinded to the participants [58, 59]. However, sham moxibustion would be recognized easily by experienced patients and thus patients with previous experience of moxibustion should be excluded from a controlled study [59].

Studies of moxibustion for constipation have been so limited that no mechanistic research has been published. Long-term, larger sample size, rigorously designed, and mechanism studies are desired.

4. Massage

Massage is the manipulation of activating deeper and superficial layers of connective tissues and muscles using various techniques. It has been practiced for thousands of years in many ancient civilizations [60].

Seventeen clinic articles were derived from the PubMed search with keywords "massage" and "constipation" [61–77]. Among them, there are only 3 articles with a Jadad score ≥3 [31]. In spite of this, the 3 articles were in lack of sham control and blind method and of very small sample size. In brief, these 17 studies showed that massage increased defecation frequency [63, 65, 66, 76], relieved abdominal pain syndrome [66], and decreased Gastrointestinal Symptoms Rating Scale [66] and Constipation Assessment Scale [71] but could not decrease laxative use [66].

Various mediums have been used in manipulation of massage, but it is unclear which methods are better. Aroma oil, which is often used in massage, did not seem to be more effective than the meridian massage [65]. Massage may work on constipation in children and seniors. A study indicated that massage was beneficial to hospitalized children with constipation due to brain injury [61]. But it is not recommended because of the lack of sufficient evidence according to an integrative review of the literature [78]. Abdominal massage using essential oils seems helpful for constipation in the elderly [71].

It is difficult for massage to design a method of sham or blind technique. Various techniques of massage have been developed through thousands of years originated from different ancient civilizations. Up till now there is no well-recognized standard technique for massage. Therefore, technique of sham or blind massage could not be defined.

Abdominal massage was performed in patients with constipation and healthy volunteers with negative results. Neither in patients, nor in healthy controls, did the abdominal massage alter stool frequency or colon transit measured by radiopaque markers [75].

There are a number of advantages with massage. Firstly, despite the fact that the trials about massage for constipation were various in terms of designs, patient samples, and types of massage used, there were no adverse side effects. Secondly, massage can be self-administrated or administrated by patients since it is easily learnt [77]. Thirdly, expenditure and cost-effectiveness could be reduced greatly since it can be self-administrated [79].

Overall, the experience of abdominal massage is appreciated by consumers, not only feeling embraced and in safe hands but also improving their bowel habits [62].

5. Herbal Medicine

Constipation, as an ancient disease, has been treated with many kinds of herbal medicines in the human history. According to quantity of herbal medicines, it can be divided into two types: single herb and multiple herbs. According to active ingredient of single herb, it also can be divided into two types: bulk laxative and stimulant laxative.

5.1. Single Herb Medicine

5.1.1. Bulk Herbal Laxative. Psyllium and *Ficus carica* are frequently used bulk laxatives. Psyllium increased stool frequency and improved stool consistency but was not effective on colon transit or anorectal motility [80]. Similar results were reported in CC patients with Parkinson's disease [81]. Psyllium increased more stool water content and weight, more total stool output, and higher O'Brien rank-type scores than docusate sodium according to a multicenter, randomized, double-blind, and parallel-design study in which 170 subjects with chronic idiopathic constipation were treated for 2 weeks [82]. About the efficacy of Psyllium for constipation, a general understanding is that its high fiber and mucilaginous content contribute to a laxative action. Gut-stimulatory effect of Psyllium, mediated partially by 5-HT_4 (5-hydroxytryptamine 4) receptor and muscarinic receptor activation, was beneficial as complement actor [83]. However, high dose Psyllium was effective on diarrhea resulting from its inhibitory effect on the gut possibly mediated by activation of nitric oxide-cyclic guanosine monophosphate pathways and blockade of Ca^{2+} channels [83].

Ficus carica was not used in clinic trials despite the fact that it is considered as laxative in some countries. *Ficus carica* paste for loperamide-induced constipation in rats increased pellet number, weight, water content, tension, and peristalsis of intestinal ileum, as well as thickness and mucin area in the distal colon [84]. No abnormal symptoms were observed on serum and whole blood parameters [84]. Similar results were obtained in constipated beagles induced by a high-protein diet and movement restriction [85]. The ameliorating effect on constipation was believed to be attributed to cellulose, one of the main components of *Ficus carica* [84, 85]. Cellulose improved fecal excretion by increasing water content and

bulk, elevating viscosity and shortening fecal transit time [86].

5.1.2. Stimulant Herbal Laxative. Anthranoid-containing laxatives, the most frequent in stimulant herbal laxatives, include senna, aloe, rheum officinale, and cascara.

Anthraquinones are effective components in this kind of stimulant herbal laxatives. Glycosides, naturally occurring from senna, aloe, rheum officinale, and cascara, pass unchangedly through the small intestine and are split into active ingredient rhein-anthrone by the colonic microbiota [87]. They were reported to improve stool frequency and consistency in a number of clinical studies [88–90]. Pseudomelanosis coli or melanosis coli which are a dark-brown discoloration of colon mucosa would be induced by anthraquinone in 9–12 months [91] and would disappear over weeks to months after termination of the use of anthraquinone [92]. It is controversial whether there is a link between pseudomelanosis coli and colorectal cancer.

5.2. Multiple Herbs Medicine. Multiple herbs medicine means two or more of single herb medicines are used in combination. For example, Psyllium and senna as a group occurs in a lot of over-the-counter brands. Agiolax, a representative sample, comprising *Plantago ovata* 52 g, ispaghula husk 2.2 g, and *Tinnevelly senna* Pods 12.4 g per 100 g granules, was proved superior to lactulose in measurement of mean daily bowel frequency, stool consistency, and ease of evacuation in a double-blind crossover study [93]. The expansion of Psyllium and stimulation of sennosides under safe and recommended doses are perfect in cooperation.

5.3. Chinese Herbal Medicine. Chinese herbal medicine for constipation is complex on its formation. Usually, it comprises not only multiple herbal laxatives but also some other herbs which contribute to relieve side effect of stimulant herbal laxatives, for example, Ma Zi Ren Pill [94–96] and CCH1 [97].

Ma Zi Ren Pill, who's other name is Hemp Seed Pill, comprises six herbs: Semen Cannabis Sativae, Radix Paeoniae, Semen Pruni Armeniacae, Fructus Immaturus Citri Aurantii, Radix et Rhizoma Rhei, and Cortex Magnoliae. According to the Chinese traditional medicine theory, it moistens the intestines, relaxes the bowel, and promotes the movement of Qi [95]. An 18-week prospective, randomized, double-blind, placebo-controlled clinical study on 120 subjects documented that Ma Zi Ren Pill increased complete spontaneous bowel movement and decreased straining at evacuation and no serious adverse effects were noted [95].

CCH1 comprises six herbs: *Panax* ginseng C. A. Meyer, Zingiber officinale Rosc., *Glycyrrhiza uralensis* Fisch., *Atractylodes macrocephala* Koide, *Aconitum carmichaelii* Debx., and Rheum tanguticum Maxim [97]. A randomized, double-dummy, double-blind, and placebo-controlled trial on 120 participants showed that CCH1 was superior to lactulose in spontaneous bowel movements [97]. Another high quality trial showed that efficacy of CCH1 could be proved, but maintenance effect needs further trial [98].

The two Chinese herbal medicines were tested in high quality trials. However, the evidence and reliability of many others are compromised by methodological flaws [99]. Further randomized, placebo-controlled, double-blind trials need to be promoted and reported in detail [99].

6. Conclusion

Among the four kinds of complementary and alternative therapies for constipation discussed in this review, the efficacy of acupuncture and herbal medicine has been indicated. Well-designed high quality studies are needed to investigate the efficacy of moxibustion and massage for constipation. Since constipation is a chronic and highly prevalent disease, convenient and cost-effective therapies are needed. Therefore, complementary and alternative medicine is expected to play a more important role in the future. Novel and innovative therapies of complementary and alternative medicine are needed in treating constipation. To increase the efficacy of existing methods, combinational methods may be explored. Equally, if not more importantly, mechanistic studies are needed in order to improve and disseminate the application of the available complementary and alternative therapies for constipation.

Conflict of Interests

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

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Review Article

Mindfulness-Based Therapies in the Treatment of Functional Gastrointestinal Disorders: A Meta-Analysis

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Background. Functional gastrointestinal disorders are highly prevalent and standard treatments are often unsatisfactory. Mindfulness-based therapy has shown benefit in conditions including chronic pain, mood, and somatization disorders. *Objectives*. To assess the quality and effectiveness reported in existing literature, we conducted a meta-analysis of mindfulness-based therapy in functional gastrointestinal disorders. *Methods*. Pubmed, EBSCO, and Cochrane databases were searched from inception to May 2014. Study inclusion criteria included randomized, controlled studies of adults using mindfulness-based therapy in the treatment of functional gastrointestinal disorders. Study quality was evaluated using the Cochrane risk of bias. Effect sizes were calculated and pooled to achieve a summary effect for the intervention on symptom severity and quality of life. *Results*. Of 119 records, eight articles, describing seven studies, met inclusion criteria. In six studies, significant improvements were achieved or maintained at the end of intervention or follow-up time points. The studies had an unclear or high risk of bias. Pooled effects were statistically significant for IBS severity (0.59, 95% CI 0.33 to 0.86) and quality of life (0.56, 95% CI 0.47 to 0.79). *Conclusion*. Studies suggest that mindfulness based interventions may provide benefit in functional gastrointestinal disorders; however, substantial improvements in methodological quality and reporting are needed.

1. Introduction

Functional gastrointestinal disorders (FGIDs) have a high prevalence, a significant impact on patients' wellbeing and are costly to the health care system [1]. Patients with these disorders report a marked impact on quality of life and an average of 30 sick days per year per person, constituting a substantial health care burden [2].

The pathophysiology underlying FGIDs is unclear as they lack any discernable organic or structural pathology. Current knowledge suggests the involvement of factors such as abnormal gut motor function, increased visceral perception, abnormalities in central pain processing, and disruption of the gut microbiota as well as genetic and psychological factors [1]. Psychiatric disorders are frequent comorbidities in patients with FGIDs and recent prospective study evidence suggests that the relationship is bidirectional [1].

Of the FGIDs, the most common is irritable bowel syndrome (IBS), affecting 7–10% of the population worldwide. It is characterized by recurring abdominal pain or discomfort and diarrhea or constipation [1].

Standard treatment for IBS is targeted at symptom control through the use of laxatives, antidiarrheal agents, antispasmodics, and antidepressant medications. Studies report that less than 50% of patients with IBS are satisfied with the standard medical treatment and many turn to alternatives. Studies of complementary and alternative medicine use in IBS populations have reported rates of 21–51% [2].

Treatment and burden of other FGIDs such as functional abdominal pain, vomiting, and dyspepsia are less well understood, although there is considerable categorical overlap with IBS. Similarly to IBS, other FGIDs are associated with high rates of complementary and alternative medicine usage. Pharmacological treatments for other FGIDs, aimed at targeting receptors with enteric and central nervous system effects, are similarly in the early stages of development [3–5].

Because of the significant involvement of emotional, cognitive, and neurological factors in IBS, a number of

studies have investigated psychological interventions including cognitive behavioural therapy (CBT), hypnotherapy, and relaxation exercises. An early review suggested that all of these interventions have shown benefit [2].

A more recent addition to this list of interventions is mindfulness-based therapy (MBT), a form of psychotherapeutic treatment which uses meditation practices to assist patients in the cultivation of nonjudgemental awareness of the present moment. This involves monitoring of cognition, emotion, perception, and sensations and the development of nonreactivity to difficult or negative aspects of these experiences [6]. The use of mindfulness as a therapeutic tool began in the late 1970s with the development of the mindfulness-based stress reduction (MBSR) program as a treatment for chronic pain [7]. The MBSR program has been combined with CBT in the development of mindfulness-based cognitive therapy (MBCT). It was developed for the prevention of major depressive disorder relapse [7], however evidence to support its use in anxiety and active depression continues to emerge [8]. The programs typically consist of 8 weekly 2.5 hour group sessions involving various forms of meditation, group discussion, and other exercises; one day of meditation retreat and approximately one hour of daily home practice [9].

In addition to the treatment of mental health concerns, there is an expanding body of research supporting the use of mindfulness-based interventions for stress, pain, and somatization disorders such as fibromyalgia and chronic fatigue syndrome [7].

A review article exploring the neural mechanisms of mindfulness and meditation found significant structural and functional changes within the brain both during, and resulting from, mindful states and practices [10]. Based on patterns of cortical thickening, meditation is associated with structural changes in brain regions related to sensory, cognitive, and emotional processing [11].

Because of the significant involvement of emotional factors in IBS, it was initially suspected that the benefit of psychological interventions was achieved through improvement of comorbid psychological distress [6]. A recent study utilized a number of assessment tools to explore some hypothesized mechanisms for the benefit exerted by MBT on IBS. The results of their analysis revealed that several cognitive processes are involved. MBT led to a decrease in reactivity to thoughts, emotions and physical sensations which led to a decrease in visceral sensitivity. The decreased visceral sensitivity was related to a decrease in IBS symptom severity and an improvement in quality of life. Additionally, nonreactivity was associated with a decrease in pain catastrophizing which predicts improvement in quality of life and increased reinterpretation of pain sensations predicted reductions in IBS severity [6].

Previous reviews studying the use of MBT in FGIDs have combined it with other psychotherapeutic interventions or with other disorders [7, 12]. A recent systematic review and meta-analysis investigated the use of mindfulness-based therapy in the treatment of somatization disorders including fibromyalgia, chronic fatigue, and IBS [7]. In the time since this review was completed, additional clinical trials have been published. The review examined efficacy outcomes at the end of treatment only and did not discuss risk of bias or other elements describing the quality of reporting of the studies. A synthesis which includes these components is essential to provide context to the findings as well as provide guidance for future research.

This review will discuss the effectiveness of mindfulness therapy at improving symptom severity and quality of life measures in patients diagnosed with FGIDs compared to waitlist or active control groups. The review will explore the effectiveness at the end of the intervention as well as after a follow-up period. Additionally, the quality of the studies will be assessed to describe the current state of reporting and study bias in the existing literature.

2. Methods

The PRISMA statement was used to guide the conduct and reporting of this meta-analysis [13].

2.1. Systematic Literature Searches. Systematic literature searches were performed using the Pubmed, EBSCO, and Cochrane databases. The following search terms were used: mindfulness, MBCT, MBSR, mindfulness-based cognitive therapy, mindfulness-based stress reduction, mindful, functional gastrointestinal, functional bowel, colonic disease functional, colonic disease, functional abdominal pain, recurrent abdominal pain, abdominal pain, IBS, irritable bowel, spastic colon, irritable colon, constipation, diarrhea, bloating, distention, gastroesophageal reflux, GERD, dysphagia, and functional dyspepsia. Studies in any stage of publication from database inception onward in English were considered. The purpose of this strategy was to be inclusive of the existing literature and noting that previous reviews did not identify a large base of non-English publications. The last date searched was May 29, 2014.

The search results were combined and duplicates were removed. A screen of article titles and abstracts was performed to identify clinical trials that utilized mindfulness-based interventions for the treatment of FGIDs. After reviewing the full-text articles, those with control groups, randomization, and an adult population with FGID symptoms were included.

2.2. Data Collection. Data was extracted by one reviewer. Data for the following study variables was extracted: study size and percent female participants, participant diagnosis, intervention and duration, control, follow-up, symptom severity at the end of the intervention and at follow-up, and quality of life assessment at the end of the intervention and at follow-up. The principle summary outcome measures for synthesis were the changes in symptoms severity between baseline, end-of-intervention, and follow-up. Corresponding authors of included studies were contacted regarding missing or unclear data, though notably this did not result in any additional information beyond what was originally published. Two attempts to contact authors via email were made before ceasing attempts at correspondence.

2.3. Data Analysis. Effect sizes (Cohen's d) were calculated for relevant validated outcome measures (effect on IBS severity at end of intervention, effect at postintervention follow-up, and quality of life) from individual studies using reported mean, standard deviation and group size. A random effects model (DerSimonian-Laird (DL)) was assumed to account for the small number of studies with pool-able data (n = 5-6), small sample sizes, and high degree of variance within the studies. Studies were weighted based on sample size in order to generate a pooled point estimate and 95% confidence interval for effect size. Heterogeneity was assessed using the I^2 statistic; Cochran Q is reported as an inference of combinability of studies. Kendall's tau and Egger's test will be reported to assess for power and risk of bias affecting the cumulative result. Statistical analysis and figure generation (funnel and forest plots) were accomplished using StatsDirect (version 3.0.119) software.

2.4. Quality Analysis. Assessment of study quality was conducted using the Cochrane Risk of Bias [22] and the CONSORT checklist for reporting trials of nonpharmacologic treatments [23]. Assessment was completed by two reviewers independently and any discrepancies were discussed until a consensus was reached.

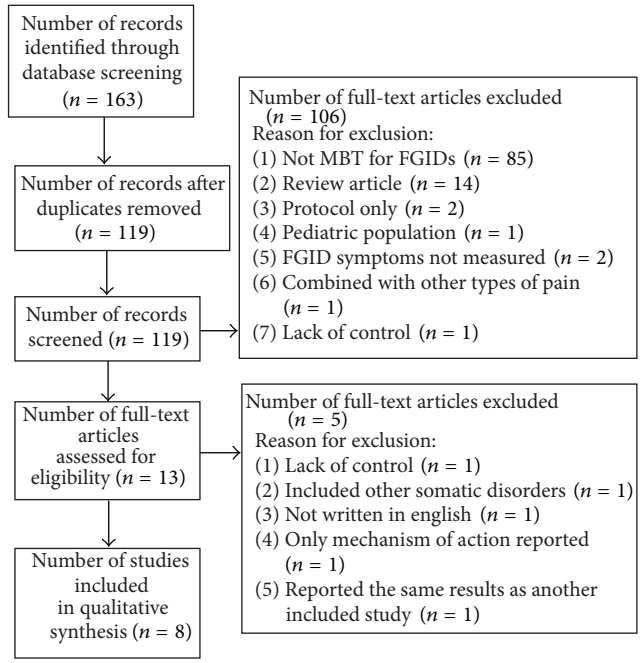

Figure 1: PRISMA flow chart showing number of screened, included, and excluded studies.

3. Results

3.1. Literature Search. The literature search yielded 119 unique records (Figure 1). After these records were screened based on title and abstract, 106 studies were excluded. The reasons included the following: did not assess the use of mindfulness in FGIDs (85), review articles (14), protocol only (2), uncontrolled design (1), pediatric population (1), other types of pain included (1), outcomes limited to cost effectiveness (1), and outcomes limited to psychological symptoms (1). Of the 13 full-text articles assessed for eligibility, eight articles reporting the results of seven randomized controlled trials met the criteria for inclusion in this analysis. The reasons for exclusion were a lack of adequate control (1), combination with other somatic disorders (1), not written in English (1), only mechanism of action outcomes reported (1), and reporting the same results as another included study (1).

3.2. Efficacy—End of Intervention. Of the seven studies included in this review, five (71.4%) reported significant improvements in IBS symptom severity at the end of the intervention compared to waitlist or comparison intervention (Table 1). One study did not report end-of-intervention results [24]. One study, which included patients with inflammatory bowel disease (IBD) who were in remission and experiencing IBS-like symptoms, showed a nonsignificant trend towards improvement compared to waitlist control. These patients represented a subgroup analysis within the study and, thus, had a small sample size [14].

3.3. Efficacy—Follow-Up. Data from a follow-up time point was reported in all eight publications. These follow-up periods ranged from two to 18 months after the end of the intervention. The study of IBD patients continued to show a trend towards improvement that did not reach significance [14]. The study that only reported data from the follow-up assessment showed significant improvement [21]. The other six studies reported that participants maintained improvement in the severity of their IBS symptoms. Among these, one showed a nonsignificant trend towards further improvement [19]. One study that showed maintenance of improvement showed improvement in the control group resulting in a loss of statistical significance [20]. During the follow-up period the participants did not receive further treatment with mindfulness-based therapy; however the programs taught participants skills and exercises which they were encouraged to continue using. Two studies assessed for the use of additional treatments during the follow-up period and found no significant difference in the outcomes reported by those who had sought additional treatment and those who had not [17, 18].

3.4. Efficacy—Quality of Life. Five studies utilized the irritable bowel syndrome quality of life instrument (IBS-QOL) as a secondary outcome and of these, 80.0% (n = 4) reported a significant improvement at end-of-intervention. Between the end-of-intervention and the follow-up assessment, significant further improvement was seen in two of these studies while the other two studies showed maintenance of improvement. One study demonstrated a significant improvement in IBS-QOL in both the intervention group and the wait list control group that was maintained at follow-up [20]. The study reporting long-term follow-up data only showed maintenance of QOL improvement.

The study that enrolled IBD patients used an objective biomarker for the assessment of intestinal inflammation [14];

Table 1: Characteristics and outcomes of studies included in systematic review.

Study	N, % female	Population	Intervention & duration	Control	Follow-up	IBS severity at end-of-intervention	IBS severity at follow-up	Quality of life
Berrill et al. 2014 [14]	38, 77%	IBD with IBS-type symptoms	MCT; 16 weeks	Waiting list (TAU)	8 and 12 months	Decrease in IBS-SS but did not reach statistical significance (32.5% vs. 6.8% reduction, $P = 0.219$)	Decrease in IBS-SS but did not reach statistical significance (30.0% vs. 0% reduction, $P = 0.213$)	Not assessed
Gaylord et al. 2011 [15]	75, 100%	IBS	Mindfulness-based stress and pain management program; 8 weeks	Support group	3 months	Significantly greater improvement in IBS-SS (26.4 vs. 6.2% reduction, $P = 0.006$)	Improvement maintained (38.2 vs. 11.8% reduction, $P = 0.001$)	Significant improvement in IBS-QOL at follow-up only ($P = 0.027$)
Ljótsson et al. 2010 [16]	85, 85%	IBS	ICBT, 10 weeks	Online closed discussion forum	3 months	Significant improvement in diary symptom ratings (pain, diarrhea, constipation, and bloating) and GSRS-IBS (42% reduction vs. 12% increase, $P < 0.001$)	Improvement in GSRS-IBS maintained	Significant improvement in IBS-QOL post treatment ($P = 0.001$); further significant improvement at follow-up ($P = 0.04$)
Ljótsson et al. 2011 [17]	Long term follow-up of Ljótsson et al. (2010) [16]				15–18 (mean = 16.4) months		Improvement in GSRS-IBS maintained ($P < 0.05$)	Significant improvement in IBS-QOL ($P < 0.05$), maintained at follow-up; no difference between those who did/did not seek additional care for IBS
Ljótsson et al. 2011 [18]	61, 74%	IBS	ICBT, 10 weeks	Online closed discussion forum before crossing over	12 months	Significantly larger improvement in GSRS-IBS (30.5% reduction vs. 2.8% increase) (Cohen's d 0.77 (0.19–1.34 95% CI))	Improvement in GSRS-IBS maintained	Significantly greater improvement in IBS-QOL (Cohen's d 0.79 (0.20–1.35 95% CI)); further improvement at follow-up ($P = 0.04$)
Ljótsson et al. 2011 [19]	195, 79%	IBS	ICBT, 10 weeks	Internet-based stress management	6 months	Significantly larger improvement in GSRS-IBS (23.6% vs. 13.1% reduction) (difference in score of 4.8 (1.2–8.4 95% CI))	Significantly larger improvement in GSRS-IBS (difference in score of 5.9 (1.9–9.9 95% CI)); nonsignificant trend towards continued improvement	Significantly larger improvement in IBS-QOL (difference in score of 10 (4.5–15.6 95% CI)), maintained at follow-up (difference in score of 6.2 (0.2–12.2 95% CI))

Table 1: Continued.

Study	N, % female	Population	Intervention & duration	Control	Follow-up	IBS severity at end-of-intervention	IBS severity at follow-up	Quality of life
Zernicke et al. 2013 [20]	90, 90%	IBS	MBSR; 8 weeks	TAU waitlist	6 months	Significantly greater improvement in IBS-SS (30.7 vs. 5.2% reduction $P < 0.0001$ among completers, 16.9% vs. 3.5% using ITT)	Improvement maintained; some improvement seen in TAU group leading to no statistically significant difference ($P = 0.17$)	IBS-QOL improved in both groups posttreatment and follow-up ($P < 0.001$)
Zomorodi et al. 2014 [21]	48, 44%	IBS and healthy controls	MBSR or CBT, 8 weeks	No psychological intervention	2 months	Not provided	Significantly greater improvement in IBS questionnaire vs. CBT or control (35.0% vs. 5.8%, $P < 0.05$)	Not assessed

GSRS-IBS: gastrointestinal symptom rating scale—IBS version.
ICBT: internet-based cognitive behavior therapy which includes exposure, mindfulness, and acceptance.
IBS-SS: irritable bowel syndrome severity score.
IBDQ: inflammatory bowel disease questionnaire.
IBS-QOL: irritable bowel syndrome quality of life instrument.
MCT: multiconvergent therapy-combination of mindfulness meditation and CBT.
MBSR: mindfulness-based stress reduction.
TAU: treatment as usual.

however none of the other studies used objective tests for the assessment of FGID symptoms as primary or secondary outcome measures. All of the assessment tools relied on validated patient/self-report outcome measures.

Two studies [18, 19] used a linear mixed-effects model to observe the difference in rates of change between the MBT and control intervention over time amid significant interaction effects between group and time were seen ($P <$ 001).

3.5. Quality Assessment. Quality assessment of the studies included in the review revealed strengths as well as weaknesses and opportunities for the introduction of bias. The Cochrane risk of bias assessment showed overall unclear or high risk of bias for the included studies (Table 2).

The most significant contributor to risk of bias was a lack of blinding of participants, facilitators, and outcome assessment. In three studies, the mindfulness intervention was compared with a support group or another psychological intervention and the participants were not aware of their allocation in the study; however, the remaining studies used a waitlist control or treatment-as-usual comparison and in these cases, the participants were aware that they were receiving the intervention being tested. In all studies, personnel who were administering the therapy were not blinded, although this is acknowledged as an inherent challenge in psychological interventions.

Another area that presented a risk of bias is incomplete outcome data. In many studies the rate of withdrawal was the same in the intervention and control groups and intention to treat analyses were utilized; however, in many cases the dropout rates were large, ranging from 10 to 44%. One study failed to report outcome measures at the end of the intervention and only reported data from the follow-up assessment. Two studies failed to describe their funding source. Some studies lacked clarity in their description of random sequence generation ($n = 1$) and allocation concealment ($n = 3$).

Assessment of the studies using the CONSORT checklist of items for reporting trials of nonpharmacologic treatment also highlighted strengths and weaknesses (Figure 2). The majority of studies included adequately reported background information, study objectives, sample size determination, randomization method, statistical analysis methods, participant flow, recruitment dates, baseline data, numbers analyzed, outcomes, additional analyses, interpretations, generalizability, and overall evidence. Partially complete information was reported in most titles and abstracts. There was limited reporting of the inclusion criteria for study sites and intervention providers as well as the location of data collection. Additionally, only two studies completely described standardization of the intervention and assessment of adherence to the protocol. None of the studies reported adverse event data or results of how the interventions were implemented. As previously stated, the details of allocation concealment were often incomplete or absent, as well as information about blinding of participants and personnel. Of the eight studies, four reported registration in an open access clinical trial registry.

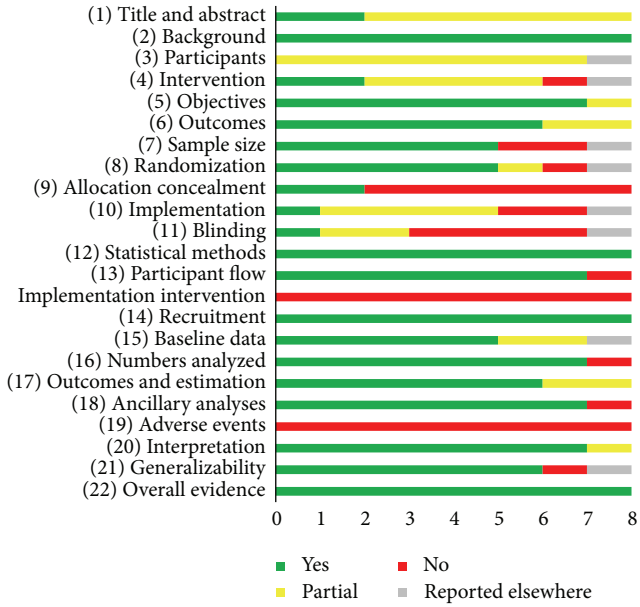

Figure 2: CONSORT checklist of items for reporting trials of nonpharmacologic treatments.

Overall, the studies included had deficiencies in reporting and significant risk of influence of bias.

3.6. Meta-Analysis. Six studies reported IBS severity at end of intervention data that was amenable to calculation of effect size; five studies contained data available for pooling for each of IBS severity at postintervention follow-up and quality of life.

Mild-moderate heterogeneity existed between studies with respect to effects of MBT on IBS severity at end of intervention ($I^2 = 49.9\%$, 95% CI = 0% to 78.2%; Cochran $Q =$ 9.982 $P = 0.076$), on IBS severity at postintervention follow-up ($I^2 = 23.3\%$, 95% CI = 0% to 71.8%; Cochran $Q = 5.216$ $P = 0.266$), and on QOL ($I^2 = 30.4\%$, 95% CI = 0% to 74%; Cochran $Q = 5.747$ $P = 0.219$).

Funnel plots (Figure 3), Kendall's tau, and Egger's test for bias are suggestive of low power, low likelihood for unpublished or unreported studies, and not statistically significant for bias across IBS severity at end-of-intervention, (Kendall's tau = 0.333 $P = 0.469$; Egger = 1.901, 95% CI = −4.376 to 8.182 $P = 0.448$), on IBS severity at postintervention follow-up (Kendall's tau = 0.4 $P = 0.483$; Egger = 1.256, 95% CI = −3.988 to 6.501, $P = 0.501$), and on QOL (Kendall's tau = 0 $P = 0.817$; Egger = 1.345, 95% CI = −6.742 to 9.432, $P = 0.633$).

Forest plots (Figure 4) outline a statistically significant pooled effect size for IBS severity at end of intervention (Pooled $d = 0.596$, 95% CI = 0.334 to 0.858), on IBS severity at postintervention follow-up (Pooled $d = 0.352$, 95% CI = 0.112 to 0.593), and on QOL (Pooled $d = 0.564$, 95% CI = 0.340 to 0.789) using random effects model. No major difference in findings was observed using a fixed effects model for pooling data (data not reported).

Table 2: Cochrane risk of bias assessment of studies included in systematic review.

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall
Berrill et al. 2014 [14]	Low	Low	High	Unclear	High	Low	Low	High
Gaylord et al. 2011 [15]	Low	Unclear	Low*	Low	Unclear	Low	Low	Unclear
Ljótsson et al. 2010 [16]	Low	Low	High	Unclear	Low	Low	Unclear	High
Ljótsson et al. 2011 (long term) [17]	As Ljótsson et al. 2010 [16]	As Ljótsson et al. 2010 [16]	As Ljótsson et al. 2010 [16]	As Ljótsson et al. 2010 [16]	Low	Low	Low	High
Ljótsson et al. 2011 (Acceptability) [18]	Low	Low	High	Unclear	Unclear	Low	Low	High
Ljótsson et al. 2011 (Internet) [19]	Low	Low	Low*	Unclear	Low	Low	Low	Unclear
Zernicke et al. 2013 [20]	Low	Unclear	High	Unclear	Unclear	Low	Low	High
Zomorodi et al. 2014 [21]	Unclear	Unclear	Low*	Unclear	Unclear	High	Unclear	High

Low*: study participants were blind; however due to the nature of a psychological intervention, those providing the intervention were not blind.

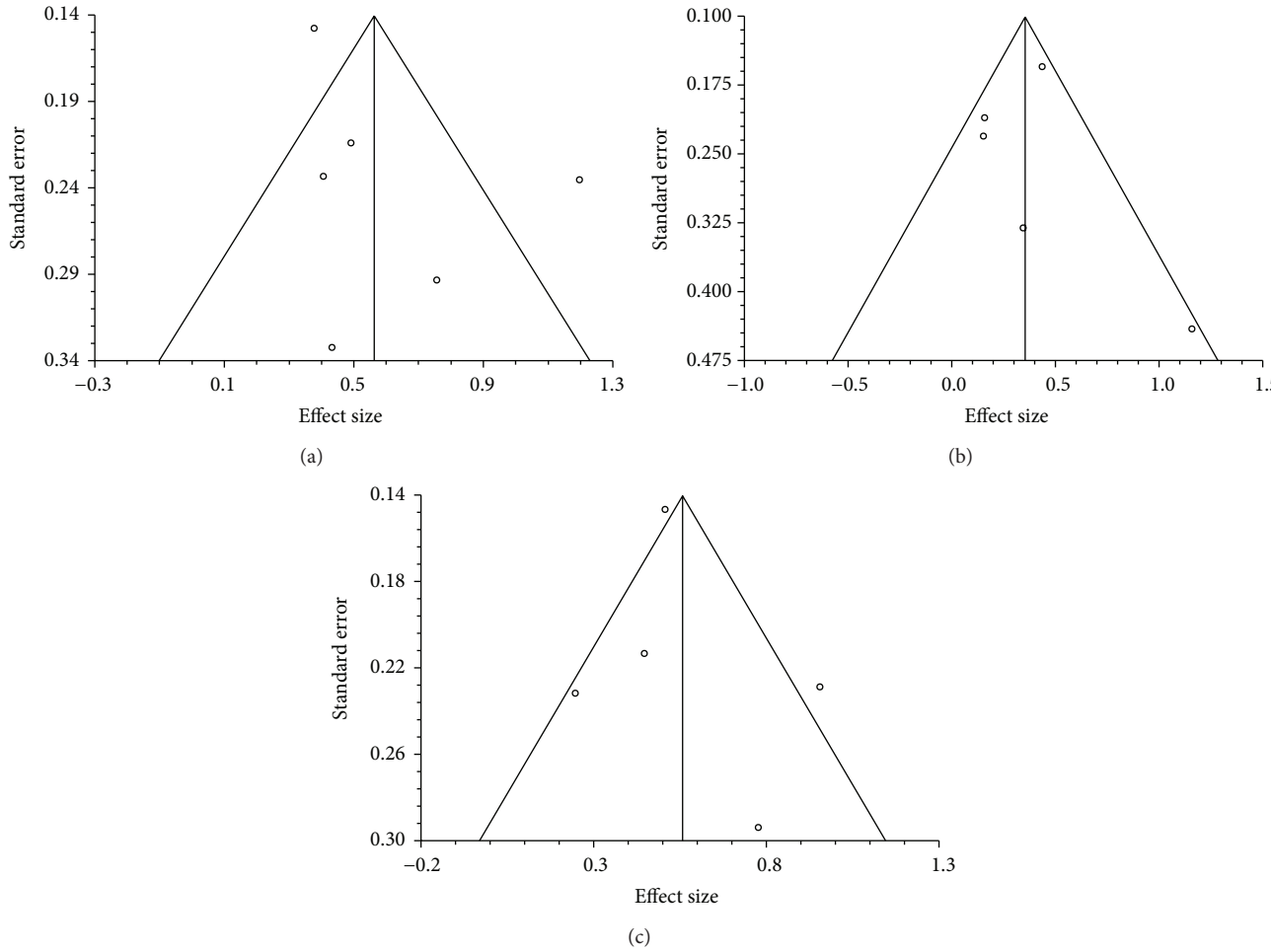

Figure 3: Funnel plots for IBS severity at end of intervention (a), IBS severity at postintervention follow-up (b), and quality of life (c).

4. Discussion

The results of the studies reviewed suggest that MBT may be an effective treatment for FGIDs achieving both a reduction of symptom severity and an improvement in quality of life. The mean decrease in symptom severity ranged from 23 to 42%. Though the sample size is small, this suggests some consistency in effectiveness observed amongst studies. A previous meta-analysis suggests that the variability of effectiveness of mindfulness therapies is no greater than that observed in other pharmacological or cognitive behavioural therapies across disorders [24]. In Zernicke et al. [20], the mean decrease of 30.7% amongst completers equated to 50% of participants achieving a clinically meaningful reduction in their IBS symptoms (i.e., a reduction of 50 points on the IBS Severity Scale).

4.1. Duration of Effect. Additionally, the results suggest that the improvement achieved during treatment is lasting and may even lead to continued improvement. All of the studies that yielded statistically significant improvement in symptom severity at end-of-intervention demonstrated maintenance of that improvement at follow-up. In addition, three studies observed statistically significant improvement in quality of life between end-of-intervention and follow-up. Lasting effects have been observed in previous studies using MBT. One study, which sought to investigate the long-term effects of MBCT in the treatment of depression, found that improvements achieved during treatment were maintained for up to 59.8 months of follow-up [25]. The lasting effects of MBT are likely related to changes in the way participants attend to moment-by-moment cognition, emotion, perception, and sensations—the development of trait or dispositional mindfulness [6].

4.2. Quality. Quality assessment of the studies revealed some strengths, but largely weaknesses and deficiencies. Overall, the current literature has not responded to challenges relating to increased quality in design, conduct, and reporting that may impact credibility in the field of mindfulness or other psychological interventions [26].

Some of the studies used active control groups including support groups, discussion forums, cognitive behavioral therapy, and stress-management training. This allowed for

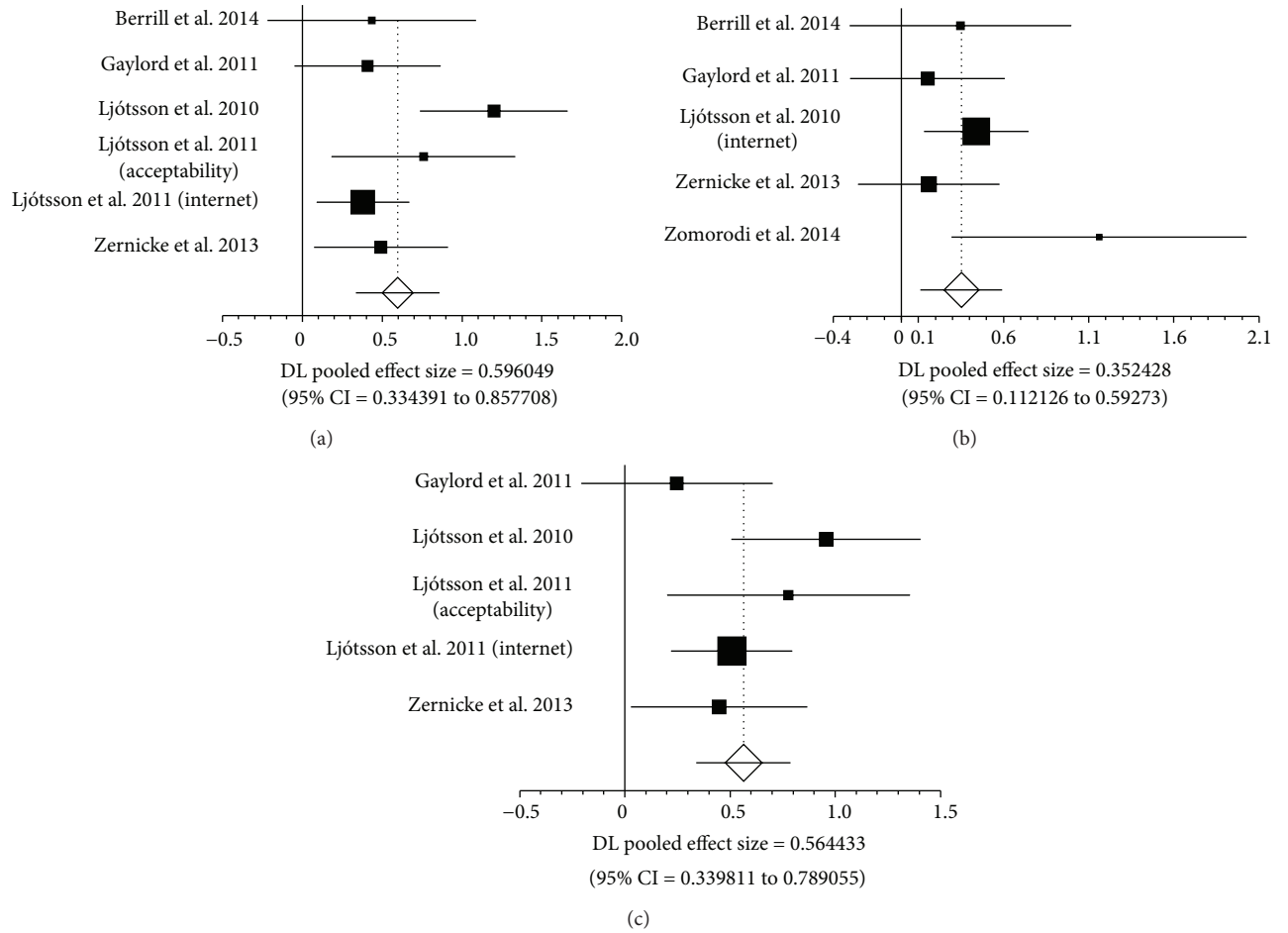

Figure 4: Forest plots for effect size on IBS Severity at end of intervention (a), IBS severity at postintervention follow-up (b), and quality of life (c).

participant blinding as well as insight into the mechanism of the effect. In all cases the mindfulness based therapy showed superior efficacy to the other interventions suggesting that the therapeutic benefit is specific to the material covered rather than nonspecific factors such as peer-support, attention, or the expectation effect. However, a major challenge in the study of psychological interventions is the inability to blind all study personnel to participant allocation. Some studies took steps to help conceal allocation and preserve blinding amongst outcome assessors; however no studies took into account blinding of the individuals facilitating the interventions or other steps that might help manage expectation and performance bias.

Another area that posed a risk of bias is incomplete outcome data due to dropouts. MBT requires a large amount of participant involvement and time, often including weekly group sessions and daily home practice. This may have contributed to the high dropout rates observed. Many studies utilized intention to treat analysis to account for these occurrences however some articles did not address this or report the specific manner in which intention to treat analysis was done.

A major limitation to this review is a relatively small number of studies with (qualitatively) significant heterogeneity in their methodology. The follow-up time period varied from two to 18 months. Additionally, the type of intervention varied. Of the seven studies reviewed, three were conducted by the same research group using a unique methodology called internet-based cognitive behaviour therapy (ICBT) which includes mindfulness and acceptance-based exercises in combination with exposure. While it is accessible over the internet, it is not available to the public at this time. In contrast, MBSR and MBCT programs are offered in hospitals, universities and health clinics worldwide.

Most of the studies reviewed enrolled patients with a diagnosis of IBS. The one study that included participants with IBD in remission and IBS-like symptoms was the only study that failed to yield a statistically significant improvement in IBS symptoms. The patients with IBS-type symptoms in this study were a subset of a larger patient population and as a result there was a small sample size which may have contributed to the failure to reach statistical significance. Alternatively, it may be that patients without organic gastrointestinal disease are more responsive to MBT.

Many of the studies had a high percentage of female participants. While there is a risk that this may limit the generalizability of the results it is known that IBS is more prevalent among women [7].

The studies reviewed demonstrated benefits in the placebo groups; however, this is a common finding among trials involving patients with IBS and other subjective complaints. A meta-analysis of the placebo effect in IBS found a range of 16–71% improvement (27) and a randomized controlled trial using open-label placebo for the treatment of IBS demonstrated a statistically significant benefit (28).

Although a statistically significant finding was demonstrated on pooled effect sizes, the low power, small number of studies, and overall high risk of bias in study design or completeness of reporting suggest that this should be interpreted with some discretion.

5. Conclusions

Analysis of these studies suggests that mindfulness-based interventions may be useful in improving FGID symptom severity and quality of life with lasting effects; however, substantial improvements in methodological quality must be implemented in future studies in order to fully assess its impact. Due to absence of reporting of adverse events, no definitive conclusions can be drawn with respect to safety. Future studies would benefit from use of established criteria for reporting clinical trials using nonpharmacological interventions, registration of studies in an open-access clinical trial registry, and improvements in blinding to decrease the risk of bias.

Conflict of Interests

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

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Research Article

Effects and Mechanisms of Transcutaneous Electroacupuncture on Chemotherapy-Induced Nausea and Vomiting

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Nausea and vomiting are one of the major complications of chemotherapy for cancers. The aim of this study is to investigate the emetic effects and mechanisms involving serotonin and dopamine of needleless transcutaneous electroacupuncture (TEA) at Neiguan (PC6) and Jianshi (PC5) on chemotherapy-induced nausea and vomiting in patients with cancers. Seventy-two patients with chemotherapy were randomly divided into sham-TEA group (sham-TEA, $n = 34$) and TEA group ($n = 38$). TEA was performed at PC 6 and PC 5 (1 h, bid) in combination with granisetron. Sham-TEA was delivered at nonacupoints using the same parameters. We found the following. (1) In the acute phase, the conventional antiemetic therapy using Ondansetron effectively reduced nausea and vomiting; the addition of TEA did not show any additive effects. In the delayed phase, however, TEA significantly increased the rate of complete control ($P < 0.01$) and reduced the nausea score ($P < 0.05$), compared with sham-TEA. (2) TEA significantly reduced serum levels of 5-HT and dopamine in comparison with sham-TEA. Those results demonstrate that needleless transcutaneous electroacupuncture at PC6 using a watch-size digital stimulator improves emesis and reduces nausea in the delayed phase of chemotherapy in patients with cancers. This antiemetic effect is possibly mediated via mechanisms involving serotonin and dopamine.

1. Introduction

Chemotherapy is an important component of comprehensive treatments for cancers. Nausea and vomiting are one of the major complications of chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) lead to a variety of adverse clinical consequences, including noncompliance with therapy, undermining of the efficacy of therapy, and unwillingness or even refusal of therapy [1–3].

Antiemetics include 5-HT_3 receptor antagonists, glucocorticoids, dopamine receptor antagonists, benzodiazepine class of drugs, antipsychotic drugs, and marijuana. Among them, 5-HT_3 receptor antagonists are most widely used [4]. Introduction of 5-HT_3 receptor antagonists in the early 1990s represents major advance in the management of acute CINV. Common adverse events of 5-HT_3 receptor antagonists include mild headache, transient increase in hepatic transaminase level, and constipation [5]. The major problems with the 5-HT_3 receptor antagonist are (1) lack of efficacy in treating delayed emesis and (2) lack of efficacy in treating nausea in both acute and delayed phases [6]. According to the functional living index, nausea was reported to have a stronger negative impact on patients' daily life than vomiting [7]. Neither clinical evidence nor the ratio of cost/effectiveness justifies the use of the 5-HT_3 antagonist beyond 24 hours after chemotherapy for prevention of delayed emesis. Therefore, the outcome of the treatment for CINV is unsatisfactory and there is still an urgent need for the development of novel therapies for CINV, especially delayed CINV.

Acupuncture has been used to treat nausea and vomiting in China for thousands of years. The most commonly used acupoints for the treatment of gastrointestinal symptoms are

Neiguan (PC6), Zusanli (ST36), and Jianshi (PC5). A large number of studies have demonstrated that acupuncture or electroacupuncture (EA) can effectively reduce nausea and vomiting under various conditions, such as postsurgery [8–10], pregnancy [11, 12], and motion sickness [13]. Dundee et al. reported that acupuncture treatment might also significantly reduce CINV [14, 15]. Acupuncture and EA are performed by acupuncturists or doctors due to the insertion of needles into the acupoints and therefore the patient can receive the treatment only in clinics or hospitals. To make the therapy readily available at patient's home, a needleless self-administrated method of transcutaneous electroacupuncture (TEA) was proposed in this study.

The aim of this study was to investigate the emetic effects and mechanisms involving serotonin and dopamine of the proposed needleless TEA at PC6 and PC5 on CINV in patients with cancers.

2. Material and Methods

2.1. Study Population. The study was conducted according to the Declaration of Helsinki and approved by the ethical committee of the Zhejiang Provincial Hospital of Traditional Chinese Medicine (TCM). Patients meeting the inclusion and exclusion criteria scheduled for CINV from July 2011 to September 2012 in Zhejiang Provincial Hospital of TCM were divided into two groups: sham-TEA (17 female, 17 male) and TEA group (12 females, 26 males). Written informed consent was obtained from all subjects before the study.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (1) ages 18–80 years with confirmed diagnosis of cancer; (2) either being naive to chemotherapy or having received only moderately or highly emetogenic chemotherapy; (3) being scheduled to receive one cycle of moderately or highly emetogenic chemotherapy ($\geq$50 mg/m^2 cisplatin, >1500 mg/m^2 cyclophosphamide, and >250 mg/m^2 Carmustine); (3) Karnofsky's score $\geq$60; (4) white blood cell $\geq 3 \times 10^9$/L and adequate hepatorenal function, aspartate aminotransferase <100 IU/l, alanine aminotransferase <100 IU/l, and creatinine clearance $\geq$60 mL/min; and (5) being scheduled to stay at hospital for chemotherapy.

Exclusion criteria included the following: (1) receiving concurrent radiotherapy of the upper abdomen or cranium; (2) vomiting or $\geq$grade 2 nausea (the National Cancer Institute—Common Terminology Criteria for Adverse Events v3.0 (CTCAE)) not clear to me; (3) severe uncontrolled complications; (4) unstable metastases in the brain; (5) uncontrolled pleural effusion or ascites; (6) gastrointestinal obstruction; (7) unwillingness or inability to accept acupuncture treatment, such as wrist disability or hematonosis; (8) contraindications to 5-HT$_3$ receptor antagonists; (9) history of convulsions or seizure disorder; and (10) inability to understand or cooperate with study procedures.

2.3. Treatment Regimens. At the beginning of the study, patients who met all entry criteria were assigned to either TEA or sham-TGEA group according to a computer generated randomization schedule. The patients in the TEA group were treated with TEA at acupoints PC 6 and PC 5, whereas the patients in the sham-TEA group were treated with the same electrical stimulation at sham-points (neither on acupoints nor on any meridians). Sham-point 1 was at the lateral end of the transverse cubital crease, 2 cun (50 mm) from the bicipital muscle of arm; sham-point 2 was at medial end of the transverse cubital crease, condylus medialis humeri. The treatment was given twice daily each lasting one hr using a special watch-size stimulator (SNM-FDC01, Ningbo MaiDa Medical Device Inc., Ningbo, China) with the following parameters: monophasic, rectangular-wave pulses with pulse width of 0.3 ms, frequency of 20 Hz, and amplitude of up to 10 mA (individually adjusted according to the tolerance of the subject). The stimulation was delivered intermittently with on-time of 0.1 s and off-time of 0.4 ms. This set of parameters was previously used in animals to exert antiemetic [16] and analgesic effects [17]. Both groups received granisetron (3 mg iv bid) during the three-day treatment.

2.4. Clinical Efficacy. Nausea and vomiting were noted starting from administration of moderately or highly emetogenic chemotherapy up to 3 days. Patients recorded the date and time of episodes of emesis and the degree of nausea in diaries. The definition of an emetic episode was as follows: one episode of vomiting or a sequence of episodes in very close succession not relieved by a period of at least one min relaxation; any number of retching episodes in any given 5 min period; or an episode of retching lasting <5 min combined with vomiting not relieved by a period of relaxation of at least 1 min [18]. Nausea was classified into four grades (0: none; 1: mild; 2: moderate; and 3: severe). Any use of rescue medications was recorded, including drug name, dose, and time of administration. Rescue medication was administered for an emetic event or nausea upon request of the patient. The patients' diaries were checked daily by research staff for accuracy and completion.

Clinical efficacy was assessed as follows: (1) the proportion of patients with complete response (CR): no emesis and no rescue medications during the acute phase (0–24 h) after chemotherapy; (2) the proportion of patients with CR during the delayed phase (24–72 h) after chemotherapy; (3) the proportion of patients with complete control (CC): no emetic episode, no rescue medication, and no more than mild nausea during the delayed phase (24–72 h) after chemotherapy.

2.5. Mechanistic Measurements. Blood samples were collected at 6 AM on day 1 and day 3 after overnight fasting using tubes with EDTA and Aprotinin, centrifuged at 4200 g and 4°C for 10 min, and stored at 4°C until extraction. Plasma levels of 5-HT and dopamine were determined with the corresponding commercial ELISA kits (Beifang Institute of Biology and Technology, Beijing Rigorbio Science Development Co., Ltd., Beijing, China).

2.6. Safety Measurements. Vital signs (body temperature, heart rate, and respiratory rate), 12-lead electrocardiogram,

blood tests (white blood cell, aspartate aminotransferase, alanine aminotransferase, and creatinine clearance), and urinalysis were assessed on days 1 and 3. Safety was also assessed by recording adverse events (AEs) up to 14 days after the therapy. AEs were assessed using common terminology criteria for adverse events (CTCAE) v4.0 by the investigators for intensity [19, 20].

2.7. Statistical Methods. All data are presented as mean ± SEM. Student's t-test was used to determine the difference between before and after the treatment in any measurement (nausea score, 5-HT, or dopamine level) and the difference in any measurement between the two treatments (SPSS 17.0 for Windows-standard version; SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare the clinical efficacy of the two treatment methods (TEA versus sham-TEA). Statistical significance was assigned for $P < 0.05$.

3. Results

3.1. Effects on Nausea and Vomiting. TEA improved vomiting in the delayed phase although it did not in the acute phase. The average number of vomiting episodes was 0.85 ± 0.26 with sham-TEA and 0.82 ± 0.20 with TEA ($P = 0.9$) in the first 24 hours (acute phase) ($P = 0.9$). In the delayed phase, however, this number was significantly lower with TEA than sham-TEA ($P = 0.046$ for the second day and $P = 0.68$ for the third day) (see Figure 1).

The nausea scores during the delayed phase (48 h, 72 h) were 1.88 ± 0.10 and 1.68 ± 0.10 in the sham-TEA group and 1.21 ± 0.15 and 1.26 ± 0.15 in the TEA group, respectively (Figure 2). The differences between two groups were significant ($P = 0.001$ and 0.025, resp.). No significant difference was noted in the rate of complete response between the two groups, neither in the acute phase nor in the delayed phase.

The rate of complete control was significantly increased with TEA during the second day as shown in Table 1 ($P = 0.008$ for the second day and $P = 0.3$ during the third day).

3.2. Mechanisms Involving Serotonin and Dopamine. TEA significantly reduced circulating 5-HT and dopamine. At baseline, no difference was noted in serum 5-HT and dopamine levels between the TEA and sham-TEA groups. After the treatment, however, the serum levels of 5-HT and dopamine were significantly reduced ($P = 0.03$ and $P = 0.02$, resp.) (Figures 3 and 4).

3.3. Adverse Events. Safety was assessed in all patients. Laboratory examinations (white blood cell, aspartate aminotransferase, alanine aminotransferase, and creatinine clearance) and electrocardiogram were found normal after the treatment in all patients (both groups) except one who had allergic reaction of medical adhesive tape judged to be unrelated or unlikely related to TEA.

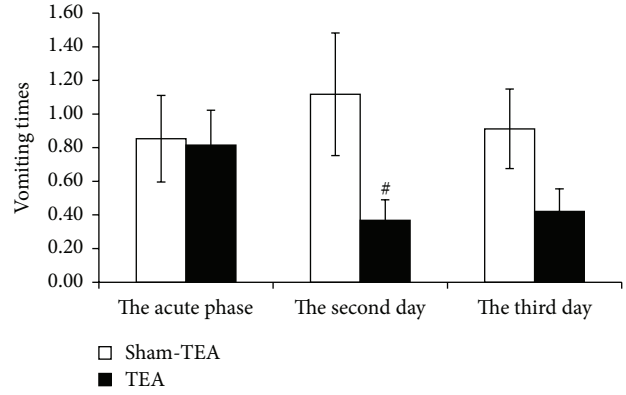

Figure 1: Effect of TEA on vomiting times. TEA significantly reduced the vomiting times on the second day after chemotherapy compared to sham-TEA group and reduced it on the third day after chemotherapy, but the difference was not significant ($^{\#}P < 0.05$).

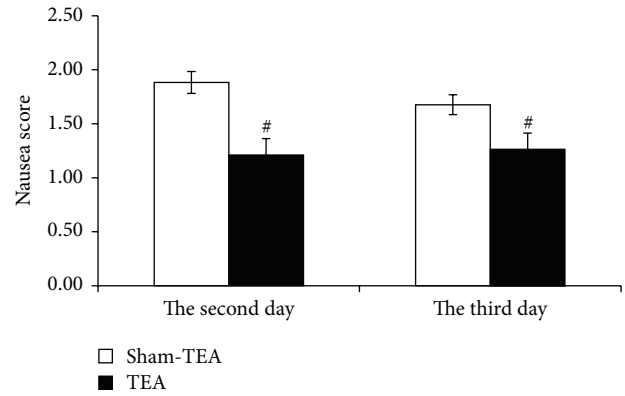

Figure 2: TEA reduced the nausea scores at both 48 h and 72 h after chemotherapy. TEA reduced substantially the nausea scores by 55.5% at 48 h and significantly by 32.7% at 72 h compared to sham-TEA group ($^{\#}P < 0.05$).

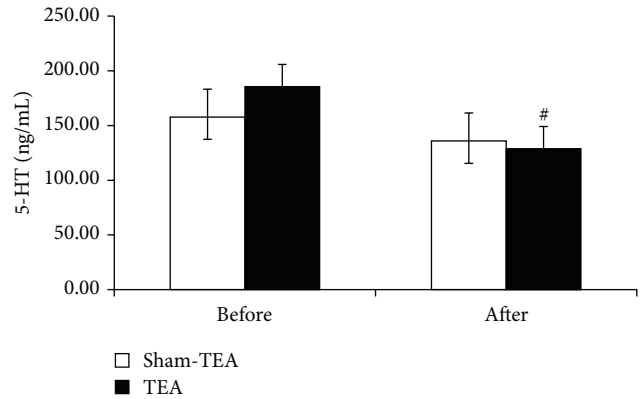

Figure 3: Effect of TEA on serum levels of 5-HT before and after the treatment. TEA significantly reduced the serum level of 5-HT compared to sham-TEA ($^{\#}P < 0.05$).

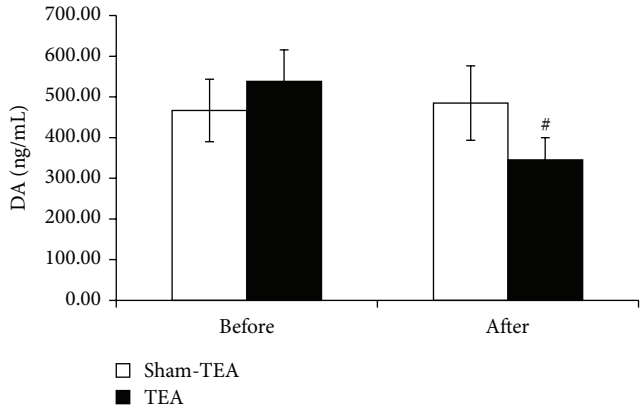

Figure 4: Effect of TEA on serum levels of DA before and after the treatment. There are significant differences of serum level of DA between TEA and sham-TEA ($^{\#}P < 0.05$).

Table 1: Patients with the CC rates in delayed emesis (48 h; 72 h; case%).

The second day		The third day	
Sham-TEA	TEA	Sham-TEA	TEA
8 (23.6%)	21 (55.3%)$^{\#}$	12 (35.3%)	18 (47.4%)

The rate of complete control was significantly increased with TEA during the second day compared to sham-TEA ($^{\#}P < 0.01$).

4. Discussion

In this study, we found that TEA at PC6 and PC5 reduced nausea and vomiting in the delayed phase of chemotherapy in patients with cancers. This antiemetic effect was possibly mediated via mechanisms involving serotonin and dopamine.

Various methods of acupuncture have been applied for treating CINV, such as manual acupuncture, acupressure, electroacupuncture, auricular acupuncture, and pharmacopuncture. Dundee et al. were the first ones who reported the antiemetic effect of acupuncture on CINV [14, 15]. Recently it was reported that acupressure also exerted an antiemetic effect on CINV in patients with breast cancers [21]. Auricular acupuncture was applied to treat CINV in children with cancers who underwent chemotherapy and shown to be effective but not different from sham stimulation [22]. A recent review on pharmacopuncture (medications delivered via the acupoints) analyzed 22 studies involving about 2500 patients but failed to provide a confirmative conclusion due to high risk of bias and clinical heterogeneity [23]. Although acupuncture and its variations are promising in treating CINV, no definitive conclusions could be made from studies reported in the literature due to poor study design and high risk of bias. In a recent systematic review of acupuncture in cancer care, a total of 2,151 publications were screened; it was concluded that acupuncture was an adequate complementary therapy for CINV but additional studies were needed [24].

In this study, a needleless method of TEA was introduced and a placebo controlled clinical trial was designed to investigate the antiemetic effect of TEA on CINV in patients with cancers. A special set of parameters was used based on a previous study in our lab with gastric electrical stimulation showing an antiemetic effect in dogs treated with cisplatin and an analgesic effect in rats with gastric hypersensitivity [16, 17]. Using these special settings we found that TEA was able to significantly improve delayed emesis and nausea during the second day of the treatment. No significant effect was noted in the acute phase, attributed to the fact that Ondansetron effectively controlled emesis during the first day of the chemotherapy. Previously, acupuncture and electroacupuncture were shown to improve gastric motility and symptoms of upper abdomen, such as nausea and vomiting. In canine study we found that electroacupuncture at PC6 reduced vasopressin-induced nausea and vomiting mediated via the vagal mechanism [25]. Ouyang et al. reported that electroacupuncture at points PC6 and ST36 significantly accelerated gastric emptying in dogs also mediated via the vagal mechanism [26]. Clinically, there is evidence that acupuncture at PC6 and ST36 improved dyspeptic symptoms including nausea and vomiting and accelerates solid gastric emptying in patients [27]. These findings seem to suggest that electroacupuncture or TEA is capable of improving nausea and vomiting of different causes.

To the best of our knowledge, this was the first study investigating and demonstrating the antiemetic mechanisms of TEA involving 5-HT and dopamine. Serotonin and dopamine are two main neurotransmitters known to induce CINV. Many drugs of chemotherapy can cause emesis and nausea via upregulation of 5-HT and dopamine, and antagonists of serotonin and dopamine are commonly used in CINV [28, 29], and antagonists of serotonin are more common than antagonists of dopamine in treatment of CINV. Ondansetron, a 5-HT_3 antagonist, was used in this study as the primary antiemetic. It effectively reduced the number of vomiting times to an average level of 1. Interestingly, TEA was found to reduce circulating 5-HT in comparison with sham-TEA. Exact mechanisms involved in the reduction of 5-HT with TEA deserve further investigation. In gastrointestinal motility study, electroacupuncture was found to accelerate gastric emptying mediated via the 5-HT mechanism [18]. It was reported that electroacupuncture on the lumbar and hindlimb segments decreased the dopamine and serotonin levels which were increased by restraining stress in the dorsal raphe nucleus, indicating that electroacupuncture applied to the lumbar and hindlimb segments has an antistress effect via mediation of the levels of serotonin and dopamine [30]. However, different subtypes of 5-HT receptors are believed to be involved in the antiemetic effect and the prokinetic effect of acupuncture. The prokinetic effect of acupuncture is believed to involve 5-HT_4 mechanism, whereas the antiemetic effect of acupuncture is believed to involve 5-HT_3 mechanisms [29, 31]. In addition, a reduction in circulating dopamine was also noted after the treatment of TEA. This reduction might also play a role in the antiemetic effect of TEA. The mechanism involving dopamine was reported in the effect of acupuncture on drug addiction [32]; it was, however, first

reported in this study regarding the effect of acupuncture on CINV.

Traditional acupuncture or electroacupuncture treatment needs to be done in clinics and needle should be pierced into points. In this study, TEA did not require the insertion of any needles and the patient's activity was not restricted. So TEA seems to be more attractive than acupuncture or electroacupuncture and will be well received by patients. In this study, the compliance of the therapy was 100%; none of the patients quitted the study. Typically, acupuncture or electroacupuncture is performed a few times weekly due to required visits to doctor's office. This substantially reduces the efficacy and consistency of the therapy. With the TEA method, the treatment can be self-administrated at home and thus could be performed daily or a few times daily, which would greatly increase the efficacy of the therapy.

5. Conclusions

In conclusion, a needleless method of transcutaneous electroacupuncture is proposed in this study. The needleless TEA is effective in reducing delayed nausea and vomiting in patients undergoing chemotherapy, possibly mediated via the downregulation of serotonin and dopamine.

Conflict of Interests

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

Authors' Contribution

Xing Zhang and Hai-feng Jin are cofirst authors; they contributed equally to the work.

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Research Article

Therapeutic Effects of Biobran, Modified Arabinoxylan Rice Bran, in Improving Symptoms of Diarrhea Predominant or Mixed Type Irritable Bowel Syndrome: A Pilot, Randomized Controlled Study

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Background. Recently, it was revealed that low grade mucosal inflammation and/or immune imbalance of the lower digestive tract is one of the mechanisms involved in symptom generation in patients with irritable bowel syndrome (IBS). Biobran, arabinoxylan compound derived from rice bran, has been reported to have several biological actions such as anti-inflammatory and immune modulatory effects. So we investigated the therapeutic effects of Biobran in patients with IBS. *Method*. Forty patients with diarrhea predominant or mixed type IBS were randomly assigned to either a Biobran group for treatment with Biobran or a placebo group. Therapeutic efficacy and IBS symptoms were assessed subjectively by the patients after 4 weeks of administration. *Results*. The global assessment was effective in 63.2% of the Biobran group and in 30% of the placebo group ($P < 0.05$, Biobran group versus placebo group). Biobran group showed a significant decrease in the score of diarrhea and constipation and in CRP value. However, no significant changes were observed in the placebo group. *Conclusion*. The administration of Biobran improved IBS symptoms. It is likely that anti-inflammatory and/or immune modulatory effects of Biobran might be useful in IBS patients.

1. Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder [1] in which abnormal discomfort or pain is associated with defecation or a change in bowel habit and with features of disordered defecation. Many studies [2–8] in Western countries and Japan have estimated the prevalence of IBS to be between 10% and 30% in the adult population. Furthermore, IBS is a chronic problem that affects all aspects of daily life and has a significant negative impact on quality of life (QOL). It is widely accepted that various factors contribute to the development of IBS symptoms. Although disturbed gastrointestinal motility, sensory hypersensitivity, and psychosomatic factors have been proposed as the possible reasons behind IBS [9], no final mechanisms have been agreed upon to date. Many IBS treatments are currently available, ranging from specifically designed drugs such as 5-HT_3 antagonist and antidepressants to nonpharmacological therapies including hypnotherapy. Most of them are unsatisfactory, and new approaches to find the underlying pathogenesis are desirable.

Recently, there has been a general agreement that low grade mucosal inflammation and/or immune imbalance of the lower digestive tract are one of the mechanisms involved

in symptom generation in IBS patients. Several studies [10–14] have reported inflammation in mucosal biopsies of the colon, rectum, and terminal ileum in IBS patients. These studies have shown that IBS patients have an increased number of inflammatory cells, including lymphocytes, dendritic cells, and mast cells in their mucosa, and 1/2 of IBS patients have microscopic inflammation compatible with microscopic colitis. Furthermore, IBS may occur in about 7%~30% of patients recovering from acute enterocolitis, a condition called postinfective IBS (PI-IBS) [15–17].

Modified arabinoxylan rice bran (Biobran) is highly water-soluble modified rice bran, composed of polysaccharides, mainly arabinoxylan hemicelluloses. It has been sold as a functional food for more than 10 years in over 40 countries, including some in North America, Europe, and Japan. Biobran has shown a range of immune modulatory activities. Some studies have reported that oral Biobran intake enhances natural killer (NK) cell activity in healthy humans and aged mice [18, 19] and the proliferation of lymphocytes (T and B cells) [20] and induces a significant increase in some of cytokines, that is, IFN-α, IL-6, IL-8, and IL-10 [21]. In addition, Biobran enhances phagocytosis of *E. coli* and causes a significant induction of cytokines by neutrophils and monocytes and a reduction of the toxicity of chemotherapeutic agents [22, 23].

Not many studies have examined the effect of immune modulation on IBS symptoms. The aim of this study is to investigate the therapeutic effects of Biobran in IBS patients.

2. Methods

2.1. Study Design and Patients. This pilot study was a randomized, double-blind, placebo-control trial. Patients aged >20 years who had IBS, as defined by the Rome III criteria for diarrhea predominant IBS (IBS-D) or mixed IBS (IBS-M), were recruited for this study. The patients had recurrent abdominal pain or discomfort associated with loose or watery stools for at least 2 days per week within the preceding 3 weeks. Study patients had to undergo colonoscopy or colonography within 1 year of enrollment to show that there was no organic abnormality to explain the symptoms. Patients who reported the following conditions were excluded: (1) gastrointestinal organic lesions such as peptic ulcer, Crohn's disease, ulcerative colitis, and pancreatitis; (2) history of major abdominal surgery; (3) evidence of cardiovascular, gastrointestinal, metabolic, psychological, or malignant disease; and (4) pregnancy, lactating, or attempting to conceive. Patients who were using medications that could alter gastrointestinal function 2 weeks prior to enrollment were not eligible for this study. Patients taking nonsteroidal anti-inflammatory drugs, steroids, or antibiotics were also excluded, as well as those regarded as unsuitable by the investigators of this study. If concomitant medications had been prescribed for coexisting diseases before obtaining informed consent, they were continued during the study period without changing the dosage and dosage timing. Other concomitant therapies believed to affect the evaluation of this study were prohibited until the end of the study.

Patients were randomly assigned using computerized random numbers between 1 and 40 to receive either 1 g of Biobran powder (3.52 kcal, carbohydrate 752 mg, protein 115 mg, lipid 0 mg, dietary fiber 25 mg, moisture 44 mg, Daiwa Pharmaceutical Co. Ltd., Tokyo, Japan) or placebo twice a day for a 4-week period. This dose of Biobran is a common use for functional food. The placebo powder included dietary fiber and was identical to Biobran in volume, color, and taste. Each IBS symptom was assessed at baseline and weekly intervals following treatment. Gastrointestinal-specific QOL and anxiety were evaluated by a self-reported questionnaire before and at the end of treatment. All aspects of the protocol were approved by the Medical Ethical Committee of the Nagoya City University Graduate School of Medical Sciences (number 211-2). Written informed consent was obtained from all patients prior to the study in accordance with the Declaration of Helsinki.

2.2. Symptom Assessment. At the end of treatment, the subjective global therapeutic efficacy was assessed by the patients. The patient's subjective global assessment of the therapeutic efficacy in terms of its condition after treatment was evaluated according to 5 categories: (1) markedly improved, (2) slightly improved, (3) unchanged, (4) not so good, and (5) deteriorated. Categories 1 and 2 were defined as effective; and categories 3, 4, and 5 were defined as not effective. To evaluate the patients' QOL and anxiety state, a gastrointestinal-specific QOL questionnaire, the Gastrointestinal Symptom Rating Scale (GSRS) [24], and a psychological test questionnaire, the State-Trait Anxiety Inventory (STAI) [25], were completed by the patients at baseline and following the 4-week treatment. The GSRS includes 15 items and uses a 7-point Likert scale ranging from "no discomfort" to "very much discomfort." The 15 items were combined into 5 symptom clusters: reflux, abdominal pain, indigestion, diarrhea, and constipation. A higher score in a GSRS cluster indicates greater discomfort. The STAI questionnaire, consisting of 40 questions, 20 questions for state and 20 for trait anxiety trait, was converted to a scoring system standardized for a Japanese population.

2.3. Laboratory Test. A blood sample was collected from all patients before and following 4 weeks of treatment. The complete blood count, blood picture, C-reactive protein (CRP), proportion of B cell to T cell in peripheral blood lymphocytes, and NK cell activity were used to evaluate the changes of inflammation and immunological activity. T cell, B cell percentage in lymphocytes, and NK cell activity were measured by flow cytometry [26] and ^{57}Cr-released assay [26], respectively. Plasma catecholamines, adrenalin and noradrenalin, were also examined as stress markers by high performance liquid chromatography (HPLC) [27].

2.4. Study End Point and Statistics. The primary end point of this study was the subjective global assessment of the efficacy of Biobran following the 4 weeks of treatment.

The secondary outcomes were change in total and each GRSR abdominal symptom score, change in STAI score, and change in value of each laboratory test.

Values were presented as mean ± SD. The differences in mean values between the Biobran and placebo group were compared by the Student's t-test or U-test. The IBS symptom scores were assessed with the analysis of covariance. Scores of GSRS and STAI and values of the laboratory test between baseline and following the 4-week treatment were compared using the Wilcoxon ranks test or paired t-test, as appropriate. The global assessment categorical variables were evaluated by the chi-squared test. A P value < 0.05 was considered statistically significant.

3. Results

This study was performed from 2006 to 2007. Forty patients, aged 49.2 ± 15.1 years, were enrolled in this study with randomization of 20 patients each to Biobran and placebo. IBS subtypes according to the Rome III criteria were 28 IBS patients with IBS-D and 12 IBS-M patients. Table 1 shows the baseline characteristics of the patients (Table 1). There were no significant differences in age, gender, duration of disease, or the number of IBS subtypes between the Biobran and placebo groups. One patient in the Biobran group was excluded from the endpoint analysis, because he did not visit the hospital following the 4-week treatment (Figure 1).

3.1. Symptom Assessment and Efficacy of Treatment. The global assessment was effective in 63.2% of the Biobran and 30% of the placebo group ($P = 0.0465$) (Table 2).

Baseline values and changes in GSRS and STAI scores before and after 4 weeks of treatment are shown in Table 3. There were no significant differences in all GSRS scores of both baseline and after 4 weeks of treatment between the Biobran and placebo groups. Significant improvement in the total and category for reflux, diarrhea, and constipation of GSRS scores was observed after Biobran administration. However, no significant changes were observed in total or any of the items in the GSRS scores in the placebo group. In addition, no significant change in the STAI score was observed after Biobran or placebo administration (Table 3).

3.2. Laboratory Test. The changes in the values of hematological and serological examinations are shown in Table 4. No significant differences were observed in all baseline values of these data except the platelet count between the Biobran and placebo groups. After the intake of Biobran, the percentage of neutrophil was significantly lower than in placebo group, whereas B-cell percentage in Biobran group was higher than in placebo group. The lymphocyte ratio in peripheral white blood cells (WBCs), B-cell percentage in lymphocytes, and NK cell activity after Biobran intake were significantly increased when compared with the baseline values. In addition, the neutrophil ratio in the WBC and serum CRP values showed a significant decrease in contrast to the baseline value in the Biobran group. These changes were not observed after placebo intake. The placebo group showed a significant decrease in the peripheral blood platelet count. No significant changes were observed in the values of the serum catecholamine concentration in either of the 2 groups.

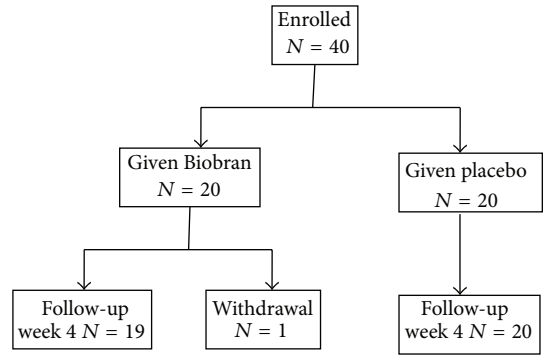

Figure 1: Flow diagram of study subjects.

Table 1: Clinical characteristics of subjects.

	Biobran ($n = 19$)	Placebo ($n = 20$)
Age (years)	48.8 ± 14.7	49.6 ± 16.0
Gender (M/F)	9/10	11/9
IBS subtype		
IBS-D	14	13
IBS-M	5	7
Duration of disease (years)	17.8 ± 11.8	15.8 ± 10.1

Values are mean ± SD.
IBS, irritable bowel syndrome.
IBS-D, irritable bowel syndrome with diarrhea.
IBS-M, mixed type irritable bowel syndrome.

3.3. Adverse Events. There were no adverse effects in either the Biobran or placebo groups.

4. Discussion

We have demonstrated the therapeutic effects of anti-inflammatory and immune modulatory treatments by Biobran administration in patients with IBS. This has been manifested by Biobran ability to improve IBS symptoms where subjective assessment of Biobran was effective in more than 60% of patients. In addition, Biobran treated patients showed increase in lymphocyte ratio and NK cell activity. The GSRS scores in both diarrhea and constipation concerning IBS after Biobran intake were significantly improved when compared with the baseline values.

It is widely accepted that low grade inflammation and immunological alterations play important roles in the development of IBS symptoms [13, 14]; IBS is believed to be associated with an activated adaptive immune response. In an inflammatory environment in the gut mucosa, increased epithelial permeability [28, 29] can allow antigens to enter easily and may lead to an increase in various immune cells and abnormal gut flora. These gut dysfunctions and activation of the digestive immune system may affect gastrointestinal

Table 2: The global assessment to treatment of either Biobran or placebo.

	Biobran ($n = 19$)	Placebo ($n = 20$)
Markedly improved	4 (21.1%)*	2 (10.0%)
Slightly improved	8 (42.1%)*	4 (20.0%)
Unchanged	6 (31.6%)	11 (55.0%)
Not so good	1 (5.3%)	2 (10.0%)
Deteriorated		1 (5.0%)

*$P = 0.0465$ versus placebo.

Table 3: Changes in values of Gastrointestinal Symptom Rating Scale (GSRS) and State Trait Anxiety (STAI) between baseline and after 4 weeks of treatment.

	Baseline	Treatment	P
GSRS			
Total dimension			
Biobran	3.21 ± 0.93	2.60 ± 0.96	<0.001
Placebo	2.93 ± 0.68	2.77 ± 0.75	N.S.
Reflux			
Biobran	2.33 ± 1.35	1.71 ± 1.17	0.013
Placebo	1.66 ± 0.90	1.55 ± 0.90	N.S.
Abdominal pain			
Biobran	2.33 ± 1.35	1.71 ± 1.17	N.S.
Placebo	1.66 ± 0.90	1.55 ± 0.90	N.S.
Indigestion			
Biobran	3.21 ± 0.93	2.60 ± 0.96	N.S.
Placebo	2.93 ± 0.68	2.77 ± 0.75	N.S.
Diarrhea			
Biobran	4.88 ± 1.98	3.51 ± 2.02	<0.001
Placebo	4.39 ± 1.59	3.95 ± 1.40	N.S.
Constipation			
Biobran	3.87 ± 1.73	3.20 ± 1.67	0.024
Placebo	3.68 ± 1.82	3.28 ± 1.67	N.S.
STAI			
State			
Biobran	3.21 ± 0.93	2.60 ± 0.96	N.S.
Placebo	2.93 ± 0.68	2.77 ± 0.75	N.S.
Trait			
Biobran	3.21 ± 0.93	2.60 ± 0.96	N.S.
Placebo	2.93 ± 0.68	2.77 ± 0.75	N.S.

Values are mean ± SD; No significant changes between Biobran and Placebo.

Table 4: Changes in values of hematological and serological examinations between baseline and after 4 weeks of treatment.

	Baseline	Treatment	P
White blood cell ($\times 10^2$)			
Biobran	59.9 ± 17.0	58.7 ± 15.8	N.S.
Placebo	63.8 ± 18.3	60.7 ± 14.7	N.S.
Neutrophil (%)			
Biobran	58.1 ± 8.1	54.3 ± 6.8*	0.039
Placebo	60.5 ± 8.3	60.3 ± 7.9	N.S.
Lymphocyte (%)			
Biobran	32.0 ± 7.4	35.5 ± 6.2**	0.022
Placebo	29.8 ± 7.0	30.3 ± 7.5	N.S.
Hemoglobin (g/dl)			
Biobran	13.6 ± 1.2	13.8 ± 1.3	N.S.
Placebo	14.0 ± 1.9	13.8 ± 2.1	N.S.
Platelet count			
Biobran	19.5 ± 5.7	21.9 ± 4.7	N.S.
Placebo	23.2 ± 5.5	21.4 ± 5.2	0.011
CRP (g/dl)			
Biobran	0.12 ± 0.10	0.10 ± 0.13	0.042
Placebo	0.32 ± 0.47	0.25 ± 0.36	N.S.
NOR			
Biobran	445.8 ± 166.1	508.6 ± 179.5	N.S.
Placebo	412.6 ± 183.0	389.3 ± 140.1	N.S.
T cell (%)			
Biobran	87.9 ± 3.6	86.9 ± 4.7	N.S.
Placebo	87.1 ± 4.6	86.9 ± 3.7	N.S.
B cell (%)			
Biobran	5.28 ± 2.49	6.44 ± 2.75	0.042
Placebo	5.84 ± 2.52	5.28 ± 2.87	N.S.
NK cell activity (%)			
Biobran	31.7 ± 12.5	40.3 ± 15.7	0.002
Placebo	36.2 ± 15.4	35.6 ± 15.7	N.S.
Th1/Th2			
Biobran	9.92 ± 5.60	10.05 ± 5.99	N.S.
Placebo	8.71 ± 5.31	10.24 ± 7.21	N.S.

Values are mean ± SD; *$P = 0.0184$ versus Placebo; **$P = 0.0384$ versus Placebo.
CRP, C reactive protein; NOR, Noradrenalin.

motility and visceral sensitivity, which have been proposed as the pathophysiological factors of IBS.

In this study, the results of the laboratory tests revealed the anti-inflammatory and immune modulatory effects of Biobran. After Biobran intake, NK cell activity increased and the CRP value showed a significant decrease when compared with the levels before intake. In addition, significant increase in the ratio of lymphocytes in WBCs and the B-cell percentage in lymphocytes was also observed, as well as a significant decrease in the neutrophil ratio. Ghonum et al. have shown that Biobran is a potent biological response modifier that works through stimulation of different arms of the immune system, such as NK, T, and B cells [18–21]. These previous data on Biobran support our result. A significant decrease in platelet count, however, was observed only in the placebo group. The reason for this effect may be partly due to higher baseline values in the placebo group than in the Biobran group. However, no data are available to explain this result.

A few clinical trials [30–33] have suggested that treatment with various probiotic bacteria can improve IBS symptoms. The intestinal microflora plays an important role in the health of the host [34–36] and possesses an immune modulatory capacity. Probiotic bacteria offer a means of modifying the enteric microflora and their therapeutic effects may influence the immune response [34, 37] by modulating mucosal

balance in the intestinal tract. In our study, oral Biobran intake increased the percentage of lymphocyte and enhanced NK cell activity, indicating that Biobran has immune modulatory effects in IBS patients. In addition, Biobran, which is a polysaccharide derived from rice bran, may influence the microflora in the digestive tract. However, the precise biological Biobran functions are not well understood. Further studies are needed to clarify the mechanisms of the beneficial effects of Biobran in IBS patients.

The potential of Biobran to directly mediate psychological stress and the autonomic nervous system was considered low. Psychological factors are important in the pathogenesis of IBS. The concentration of serum catecholamines including noradrenalin rises under psychological stress and the prevailing state [38, 39] of sympathetic nervous activity. In this study, no changes in either the STAI scores or values of serum catecholamine resulting from Biobran intake were observed, suggesting that there is no direct relationship between the effect of Biobran and psychological stress.

The first limitation of this study was that the sample size was small because of pilot study and that there was no data for some of cytokines such as IL in subjects before and after the intake. We could not investigate the correlation between the profile of immune cells and IBS symptom severity.

In conclusion, this is the first study to examine the anti-inflammatory and/or immune modulatory effects in IBS patients. We detected a significant improvement in symptoms in the cases of Biobran treatment when compared with that of the placebo. These data provide a novel application for Biobran in treatment of IBS patients. To confirm our results, further trials should be encouraged in a more generalized population.

5. Conclusion

Immune modulatory effects of Biobran, modified arabinoxylan rice bran, are probably useful in improving IBS symptoms.

Abbreviations

IBS: Irritable bowel syndrome
QOL: Quality of life
PI-IBS: Postinfectious IBS
NK cell: Natural killer cell
IFN: Interferon
IL: Interleukin
GSRS: Gastrointestinal Symptom Rating Scale
STAI: State-Trait Anxiety Inventory
CRP: C-reactive protein
HPLC: High performance liquid chromatography
IBS-D: IBS with diarrhea
IBS-M: Mixed IBS.

Conflict of Interests

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

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Research Article

Traditional Japanese Medicine Daikenchuto Improves Functional Constipation in Poststroke Patients

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Poststroke patients with functional constipation, assessed by the Rome III criteria, from 6 hospitals were recruited in a study on the effects of the traditional Japanese medicine Daikenchuto (DKT) on constipation. Thirty-four patients (17 men and 17 women; mean age: 78.1 ± 11.6 years) were randomly assigned to 2 groups; all patients received conventional therapy for constipation, and patients in the DKT group received 15 g/day of DKT for 4 weeks. Constipation scoring system (CSS) points and the gas volume score (GVS) (the measure of the intestinal gas volume calculated from plain abdominal radiographs) were recorded before and after a 4-week observation period. The total score on the CSS improved significantly in the DKT group compared to the control ($P < 0.01$). In addition, scores for some CSS subcategories (frequency of bowel movements, feeling of incomplete evacuation, and need for enema/disimpaction) significantly improved in the DKT group ($P < 0.01$, $P = 0.049$, and $P = 0.03$, resp.). The GVS was also significantly reduced in the DKT group compared to the control ($P = 0.03$). DKT in addition to conventional therapy is effective in treating functional constipation in poststroke patients. This study was a randomized controlled trial and was registered in the UMIN Clinical Trial Registry (no. UMIN000007393).

1. Introduction

There were over 1.34 million cerebrovascular patients in 2008 reported by the Japanese Ministry of Health, Labour, and Welfare [1]. Constipation is one of the complications seen in poststroke patients. Stratified by stroke severity on the National Institutes of Health Stroke Scale, the reported incidence of constipation in poststroke patients is 38.9% to

88.2% [2]. Functional constipation is thought to originate from decreased gastrointestinal motility as well as from decreased autonomic nervous system efficiency, impaired physical activity, abdominal muscle weakness secondary to hemiplegia, and diet [3]. Conventional therapy to control constipation involves the use of laxatives or stimulant purgatives, and these drugs are often used in the long term in chronic constipation patients [4]. However, patients can develop a tolerance to laxatives or stimulant purgatives, and paralytic ileus occasionally occurs in the clinical setting, even with conventional therapy [5].

DKT has historically been used to treat gastrointestinal dysfunction with abdominal coldness and pain in many East Asian countries, including Japan and China [6]. Recently, it has also been used to prevent ileus after gastrointestinal surgery and to treat irritable bowel syndrome [7]. Horiuchi et al. reported that DKT significantly improved abdominal bloating and pain and reduced intestinal gas volume in patients with intractable functional constipation [8]. Physiological reactions to the administration of DKT have been reported as promoting gastrointestinal motility [9–13] and increasing intestinal blood perfusion [14–19]. DKT's effectiveness in treating defecation disorders in patients with cerebrovascular disease is commonly observed in the clinical setting. Potential mechanisms underlying the physiological responses to DKT have been investigated in animal models and include elevated levels of plasma vasoactive intestinal polypeptide [14, 17, 20], substance P [14, 17, 21, 22], motilin [23–25], and acetylcholine [10, 11, 13, 26–28], which promote gastrointestinal motility, as well as calcitonin gene-related peptide (CGRP) [14, 15, 17, 21] and adrenomedullin [15, 16, 29, 30], which increase intestinal blood flow. Poststroke patients are at risk for arteriosclerosis and often experience abdominal pain accompanied by a cold sensation in the abdomen associated with low blood perfusion in the mesenteric arteries. DKT has been used to treat defecation disorders with abdominal coldness and pain caused by decreased intestinal motility and blood flow. We previously reported that administration of DKT increased blood flow in the superior mesenteric artery and promoted intestinal peristalsis in healthy subjects [18, 19]. Sato et al. reported that DKT significantly increased plasma CGRP levels in healthy subjects [21]. Therefore, plasma CGRP may be a useful biomarker to evaluate the effects of DKT on intestinal blood flow.

This study aimed to investigate the efficacy of DKT in treating functional constipation in poststroke patients. In addition, this study investigated the impact of DKT therapy on CGRP concentration.

2. Methods

2.1. Subject Eligibility Criteria. Eligible patients were aged 20 to 99 years of both genders, had been diagnosed with functional constipation according to the Rome III criteria [31], and remained stable over a 6-month period from the onset of cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage. Patients received nutrition orally or through a nasogastric or gastrostomy tube. Patients with concurrent diabetes were required to have an HbA1c (NGSP) less than 9%.

2.2. Subject Exclusion Criteria. Patients meeting or diagnosed with any of the following criteria were excluded: risk of intestinal adhesion following abdominal surgery, inflammatory bowel disease, or malignant gastrointestinal disease; hypoxic encephalopathy or myelopathy; history of interstitial pneumonia; liver and/or kidney dysfunction; cancer; and neurodegenerative disease, such as Parkinson's disease or spinocerebellar degeneration. However, patients who underwent laparoscopic cholecystectomy or underwent percutaneous endoscopic gastrostomy were not excluded because the invasiveness of the operation was minimal.

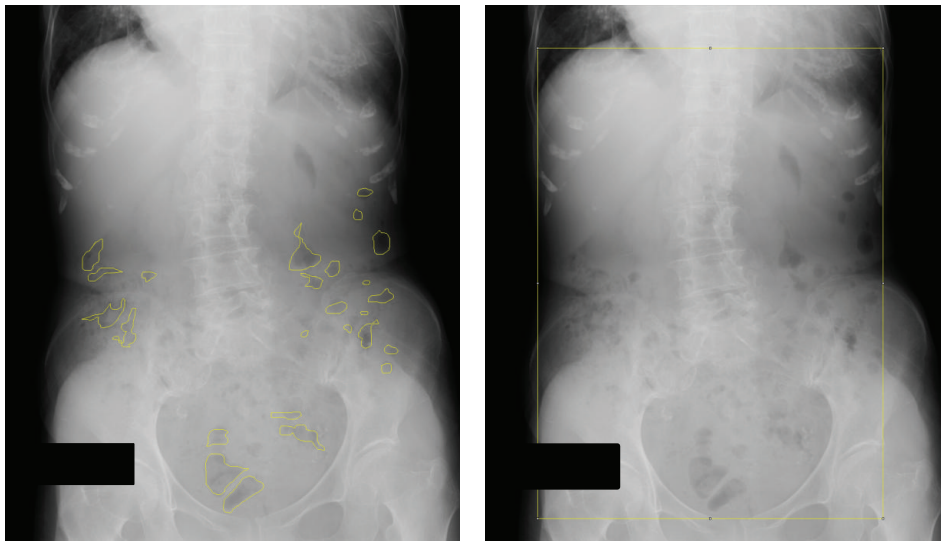
2.3. Patient Recruitment. From September 2012 to December 2013, eligible subjects were recruited from 6 hospitals: National Yonezawa Hospital, Ishinomaki Rehabilitation Hospital, National Hachinohe Hospital, Hikarigaoka Spellman Hospital, Miyagi Rifu Ekisaikai Hospital, and Wakuya Medical and Welfare Center.

2.4. Logistics. Subjects were randomly assigned to the DKT group or the control group. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Tohoku University Hospital and the 6 collaborating hospitals. Written informed consent was obtained from all patients or their families.

2.5. Trial Methods. The study protocol included an intention to treat analysis. The control group underwent conventional therapy for constipation, such as laxative administration, enemas, and disimpaction. In addition to conventional therapy, the DKT group continuously received 5.0 g of Daikenchuto extract granules (TJ-100, Tsumura & Co., Tokyo, Japan) 3 times a day before meals for 4 weeks. Each clinical parameter was measured before and after the 4-week trial. Fifteen grams of TJ-100 (DKT) extract granules contains a dried herbal extract mixture in the following proportions: Ginseng radix (Araliaceae, *Panax ginseng* C.A. Meyer, Radix) (3.0 g), processed ginger root (Zingiberaceae, *Zingiber officinale* Roscoe, rhizoma) (5.0 g), *Zanthoxylum* fruit (Rutaceae, *Zanthoxylum piperitum* De Candolle, pericarpium) (2.0 g), and saccharum granorum (the candy produced from maltose) (10.0 g). This formulation is registered in the Japanese Pharmacopoeia Sixteenth Edition [32]. The production and supply processes for TJ-100 comply with good manufacturing practice standards for Kampo products and have been approved by the Japanese Ministry of Health, Labour, and Welfare.

2.6. Evaluation of Clinical Symptoms

2.6.1. Activities of Daily Living. The Barthel Index was recorded for each patient at study enrollment to assess activities of daily living [33].



(a) (b)

Figure 1: Estimation of gas volume score (GVS). Plain abdominal radiographs obtained from fasting subjects were converted to digital data. The data were read using ImageJ, an image analysis program, and intestinal gas was traced using the program. (a) Tracing image and pixel count of the gas was 3,533 in this patient. (b) The window of abdominal area. The rectangular area was measured as the area between the inferior right side margin of the diaphragm, the inner costal margin, and the superior border of the pubic symphysis. The pixel count of the rectangular area was calculated as 92,968 in (b). GVS was calculated as (a)/(b)%; therefore, the GVS of this image is "$3,533/92,968 = 0.038(3.8\%)$."

2.6.2. Clinical Constipation Scores. Clinical scores for constipation were recorded before and after the 4-week trial period using the constipation scoring system (CSS, see the appendix) [34]. Questionnaires concerning constipation were administered to patients; however, if the patients could not completely answer the question, their families or nurses evaluated the questions depending on the objective findings (i.e., painful evacuation effort or abdominal pain before defecation was evaluated by family members or nurses using the patients' facial expressions; feeling of incomplete evacuation was evaluated with abdominal fullness after defecation). Because it was difficult to evaluate Q5 ("Time: minutes in lavatory per attempt") in the CSS for bedridden subjects using diapers, we removed Q5 from the statistical analysis. Evaluations before and after the administration of DKT were performed by the same family member or nurse with blinding of DKT administration.

2.6.3. Plain Abdominal Radiography. Plain abdominal radiographs of fasting patients in a supine position were obtained before and after the trial period. The gas volume score (GVS) was calculated by Koide's method [35] using ImageJ [36] (Figure 1).

2.6.4. Blood Sampling. General blood counts and biochemistry tests were performed in fasting patients before and after the trial period to assess potential adverse effects. Blood sample portions were stored in EDTA-2Na tubes. Samples were centrifuged (3000 rev/10 min), and 0.5 mL of plasma was collected and stored at −20°C. The concentration of plasma CGRP was quantified using the Human CGRP Elisa Kit (MyBioSource, Inc., San Diego, USA) tested by SRL, Inc., Tokyo, Japan.

2.6.5. Statistical Analysis. Statistical analysis was performed using SPSS software (ver. 16, SPSS Japan Inc., Tokyo, Japan). Baseline comparisons of group differences were conducted using the independent samples t-test for continuous variables and the chi-square test for categorical variables. Measurement of the mean and standard deviation (SD) was performed at baseline and at the endpoint for all parameters. Comparisons between the DKT and control groups were performed by two-way analysis of variance (ANOVA). Changes within groups before and after the trial period were compared using the paired t-test when the intergroup difference was significant. Correlation between age and the CSS points was analyzed by coefficient of product-moment correlation (Pearson correlation coefficient). P values <0.05 were considered significant.

3. Results

From September 2012 to December 2013, 34 subjects (17 men and 17 women; mean age: 78.1 ± 11.6 years) at 6 hospitals participated in the study. Patients were randomly assigned to 2 groups (control group or DKT group). The demographic characteristics, CSS, and GVS of each group at baseline are shown in Table 1. There was no significant difference between groups in characteristics, the way of nutrition intake, CSS, or GVS at baseline.

Table 1: Baseline population demographics of DKT and control groups.

	Group		P^*
	DKT[a]	Control	
N	17	17	
Sex			0.73
Female	9	8	
Male	8	9	
Age (y)	77.5 ± 11.9	78.7 ± 12.1	0.78
Height (cm)	156.3 ± 12.1	154.1 ± 9.3	0.56
Body weight (kg)	48.4 ± 10.2	48.3 ± 9.4	0.99
Diagnoses, N			0.31
Brain infarction	10	14	
Cerebral hemorrhage	4	2	
Subarachnoid hemorrhage	3	1	
Illness duration (y)	7.8 ± 6.1	4.8 ± 4.2	0.15
Barthel Index	2.1 ± 3.1	1.2 ± 2.8	0.39
The way of nutritional intake			0.14
Orally	5	1	
Through nasogastric tube	2	5	
Through gastrostomy tube	10	11	
CSS total[b] (points)	8.0 ± 3.1	8.1 ± 3.7	0.96
CGRP (pg/mL)	408 ± 482	262 ± 170	0.25
GVS (%)	16.3 ± 6.7	14.4 ± 7.8	0.44

[a]DKT, Daikenchuto; CSS, constipation scoring system; CGRP, calcitonin gene-related peptide; GVS, gas volume score.
[b]CSS total: not including point of Q5.
*Significance designated at $P < 0.05$.

3.1. Changes in Clinical Constipation Scores. All 34 subjects completed the CCS questionnaire before and after the observation period, and results are summarized in Table 2. There was no significant correlation between age and the CSS points on the baseline ($n = 34$) ($r = 0.12$, $P = 0.49$). Significant differences in the CSS scores were observed between the 2 groups (two-way ANOVA, $P < 0.01$). In the DKT group, the CSS scores significantly improved from 8.0 ± 3.1 to 6.0 ± 3.1 points (paired t-test, $P < 0.01$). There was no significant correlation between age and the changes of the CSS scores for subjects in DKT group ($n = 17$) ($r = -0.16$, $P = 0.53$). The control group did not show any significant improvement (Table 2). CSS subcategory findings are summarized for both groups in Table 3. Among the CSS subcategories, there were significant differences between the DKT and control groups using two-way ANOVA for the following questions: Q1 (frequency of bowel movements; $P < 0.01$), Q3 (feeling of incomplete evacuation; $P = 0.03$), and Q6 (need for drugs/enema/disimpaction; $P = 0.02$). In the DKT group, the constipation scores significantly decreased over the trial period for Q1 ($P < 0.01$), Q3 ($P = 0.049$), and Q6 ($P = 0.03$). The control group, however, did not show any significant changes (Table 3). Overall, the average change of 1 point in the score for Q1 means an improvement in defecation frequency from "once per week" to "2 times per week" or "less than once per week" to "once per week" in the clinical setting.

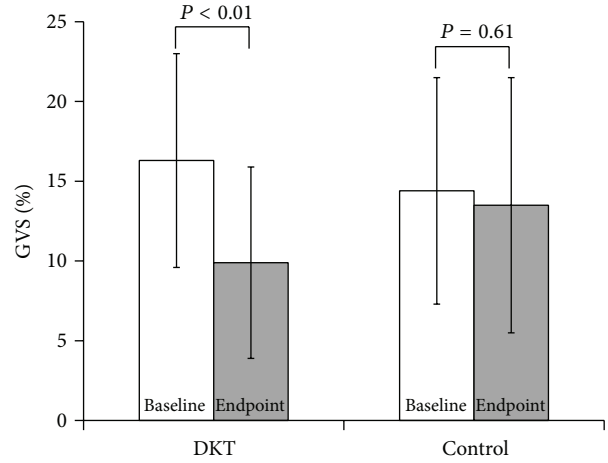


Figure 2: Changes in the gas volume score (GVS). Two-way ANOVA showed a significant difference between the groups ($P = 0.03$). In the DKT group, the GVS significantly improved from 16.3 ± 6.7% to 9.9 ± 6.0% (paired t-test; $P < 0.01$), and in the control group it changed from 14.4 ± 7.1% to 13.5 ± 8.0% with no significance (paired t-test; $P = 0.61$).

The average change of 0.4 points in the scores for Q3 and Q6 means that digital assistance or enemas were no longer necessary for approximately 30% of the patients in the DKT group.

3.2. Changes in Gas Volume Score. Figure 2 summarizes changes in the GVS before and after the observation period for both groups. There was a significant difference between the 2 groups (two-way ANOVA; $P = 0.03$), and the intragroup comparison revealed a significant decrease in the DKT group from 16.3 ± 6.7% to 9.9 ± 6.0% ($P < 0.01$) while the control group did not show any significant changes ($P = 0.61$). Representative abdominal radiographs of a patient before and after DKT administration show reduced intestinal gas volume (Figures 3(a) and 3(b)). In this case, DKT administration reduced the GVS from 26.0% to 12.3%.

3.3. Changes in Plasma Calcitonin Gene-Related Peptide Concentrations. In the DKT group, the initial and final CGRP concentrations were 409 ± 482 pg/mL and 452 ± 574 pg/mL, respectively. In the control group, the initial and final values were 270 ± 172 pg/mL and 251 ± 118 pg/mL, respectively. There was no significant difference between the 2 groups in plasma CGRP (two-way ANOVA; $P = 0.08$).

3.4. Adverse Effects. Notable adverse effects, such as itching, gastrointestinal symptoms, other subjective symptoms, and abnormalities in blood counts and blood biochemistry, were not observed during and after DKT administration.

4. Discussion

This study shows that DKT in addition to conventional therapy for functional constipation significantly improved

Table 2: Clinical constipation scores in both groups at baseline and endpoint.

	DKT[a] group ($N = 17$)		Intragroup difference	Control group ($N = 17$)		Intragroup difference	Intergroup difference
	Baseline	Endpoint[b]	P^*	Baseline	Endpoint	P	P
CSS total[c] (points)	8.0 ± 3.1	6.0 ± 3.1	<0.01	8.1 ± 3.7	8.2 ± 3.7	0.33	<0.01

[a]DKT, Daikenchuto; CSS, constipation scoring system.
[b]Endpoint: after the 4-week trial period.
[c]CSS total: not including point of Q5.
*Significance designated at $P < 0.05$.

Table 3: Constipation scoring system (CSS) subcategory scores in both groups at baseline and endpoint.

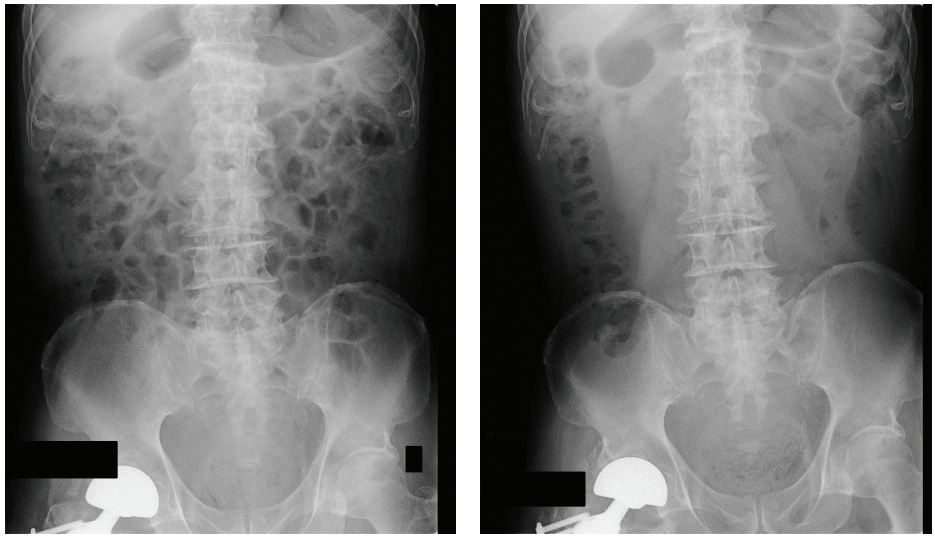
	DKT[a] group ($N = 17$)		Intragroup difference	Control group ($N = 17$)		Intragroup difference	Intergroup difference
	Baseline	Endpoint[b]	P^*	Baseline	Endpoint	P	P
Q1 (points)	2.2 ± 1.5	1.2 ± 1.4	<0.01	2.1 ± 1.4	2.1 ± 1.5	0.33	<0.01
Q2 (points)	0.5 ± 0.9	0.3 ± 0.7	—	0.6 ± 0.9	0.6 ± 0.9	—	0.07
Q3 (points)	1.2 ± 1.2	0.8 ± 1.0	0.049	1.5 ± 1.3	1.6 ± 1.4	0.33	0.03
Q4 (points)	0.4 ± 0.8	0.4 ± 0.7	—	0.7 ± 0.9	0.7 ± 0.9	—	0.33
Q5 (points)	—	—	—	—	—	—	—
Q6 (points)	1.8 ± 0.5	1.4 ± 0.8	0.03	1.7 ± 0.7	1.7 ± 0.7	1.00	0.02
Q7 (points)	0.1 ± 0.2	0.1 ± 0.2	—	0.1 ± 0.2	0.1 ± 0.2	—	1.00
Q8 (points)	1.9 ± 1.1	1.9 ± 1.1	—	1.5 ± 0.9	1.5 ± 0.9	—	1.00

Intragroup difference was calculated using the paired t-test only when the intergroup difference was significant.
[a]DKT, Daikenchuto.
[b]Endpoint: after the 4-week trial period.
*Significance designated at $P < 0.05$.

the CSS scores and significantly reduced the GVS in post-stroke patients. The incidence of adverse effects associated with DKT extract, such as gastrointestinal discomfort and liver dysfunction, has been reported as 1.9% in prior studies [37], but no adverse effects were observed during the 4-week treatment period in the present study. Functional constipation has a complex pathophysiology, and intestinal function is controlled by the autonomic nervous system; consequently, therapeutic protocols are limited in poststroke patients [38, 39]. Several clinical studies of DKT therapy for constipation have been reported, but almost all of these were limited to healthy subjects or were case series. The present study was a prospective randomized controlled trial for functional constipation in patients with stroke-related morbidity and therefore could show stronger evidence than previous reports of the clinical effects of DKT.

In a prior clinical study, it was reported that DKT extract improved colorectal function in patients diagnosed with Parkinson's disease [40]. Another study reported that administration of DKT to patients with chronic intractable constipation improved abdominal bloating and pain symptoms [8]. The present study similarly found improvement in clinical constipation scores and GVS. Numerous studies have investigated the active ingredients and mechanisms underlying the improved intestinal motility. Intestinal contraction may be induced by DKT through the cholinergic nervous system via serotonin receptors [13, 27, 28], motilin activity [23, 24], and the transient receptor potential vanilloid type 1 channel [11, 41]. Satoh et al. reported that *Zanthoxylum* fruit and maltose, ingredients in DKT, improved delayed propulsion in the small intestine. *Zanthoxylum* fruit also improved delayed propulsion in the distal colon. Endogenous cholecystokinin secretion resulting from maltose administration may play a role in the effect of DKT [42]. These reports describe the possible mechanisms through which DKT promotes intestinal movement and explain some aspects of the improvement in the CSS scores and the reduction of GVS noted in our study.

Some studies reported that DKT extract increased CGRP in healthy subjects [21, 25]. In another report, DKT did not change CGRP levels in patients with constipation secondary to palliative morphine therapy for cancer [24]. In the present study, changes in CGRP did not reach statistical significance. Several mechanisms may explain this lack of change in CGRP levels in the DKT group. Plasma CGRP is notably unstable [43]. An elevation following DKT administration may have been obscured by factors such as testing procedures, individual differences, daily fluctuations, and day-to-day variations. Furthermore, although some studies confirmed elevated CGRP immediately after DKT administration [21, 25], the CGRP level may be too unstable to be used as a target factor for evaluating the effects of DKT. DKT is thought to affect the promotion of intestinal motility and intestinal blood flow. Increase in intestinal blood flow is believed to be mediated through adrenomedullin and CGRP or through the transient receptor potential ankyrin 1 channel [16, 29, 30]. The mechanisms promoting intestinal motility and blood flow



(a) (b)

Figure 3: (a) Plain abdominal radiograph of an 86-year-old man prior to Daikenchuto administration. The gas volume score (GVS) was calculated as 26.0%. (b) Plain abdominal radiograph of an 86-year-old man after 4 weeks of Daikenchuto administration. The gas volume score (GVS) was calculated as 12.3%.

have complex interactions, which may be altered further by disease pathology, environment, and individual differences. The present results of improved constipation following DKT administration are overall consistent with the findings of prior studies, despite the lack of significant change in CGRP levels.

4.1. Limitations. The small sample size is the first limitation of the present study. The CGRP level tended to differ between the groups (ANOVA, $P = 0.08$); a larger sample size could determine the significance of this difference. In addition, participants were limited to hospitalized patients; therefore, patients who were hemiplegic, yet stable enough to receive outpatient care, were not included. As a result, the population was skewed toward patients with low activities of daily living. Third, there are no objective parameters for abdominal coldness at present. Ultrasound assessment of blood flow in the superior mesenteric artery was nearly impossible in poststroke patients with constipation owing to the presence of intestinal gas. Finally, the placebo effect of oral administration cannot be overlooked. A randomized double-blind comparative study using a placebo would be ideal and would eliminate the placebo effect. DKT includes 4 crude herbs and has a sweet and hot flavor. It will be difficult to produce a placebo without bioactivity that has a smell and flavor similar to DKT. Accordingly, the present study did not use a placebo control but rather compared the effects of DKT administration plus conventional treatment to conventional treatment alone.

5. Conclusions

Administration of DKT extract in conjunction with conventional therapy to treat functional constipation in poststroke patients improved clinical constipation scores and reduced intestinal gas volume. Results of this study show that DKT is effective for defecation control in poststroke patients.

Appendix

Constipation Scoring System (CSS) [34]

Minimum score, 0; Maximum score, 30, the numbering starting from zero represents the scores.

(1) Frequency of bowel movements

- (0) 1-2 times per 1-2 days
- (1) 2 times per week
- (2) Once per week
- (3) Less than once per week
- (4) Less than once per month

(2) Difficulty: painful evacuation effort

(3) Completeness: feeling incomplete evacuation

(4) Pain: abdominal pain

- (0) Never
- (1) Rarely
- (2) Sometimes
- (3) Usually
- (4) Always

(5) Time: minutes in lavatory per attempt

- (0) Less than 5

(1) 5–10
(2) 10–20
(3) 20–30
(4) More than 30

(6) Assistance: type of assistance

(0) Without assistance
(1) Stimulative laxatives
(2) Digital assistance or enema

(7) Failure: unsuccessful attempts for evacuation per 24 hours

(0) Never
(1) 1–3
(2) 3–6
(3) 6–9
(4) More than 9

(8) History: duration of constipation (yr)

(0) 0
(1) 1–5
(2) 5–10
(3) 10–20
(4) More than 20

Conflict of Interests

All authors declare no personal competing financial or non-financial interests in this study; however, Tohoku University Graduate School of Medicine received a grant from Tsumura Co. Ltd., the manufacturer of TJ-100.

Authors' Contribution

Takehiro Numata took part in planning the study, performed the data analysis, and wrote the paper. Shin Takayama and Koh Iwasaki were the original proposers of the study and were involved in developing the protocol and paper preparation. Muneshige Tobita, Shuichi Ishida, Dai Katayose, Mitsutoshi Shinkawa, Takashi Oikawa, and Takanori Aonuma took part in recruiting subjects and laboratory management in their hospitals. Soichiro Kaneko, Junichi Tanaka, and Seiki Kanemura helped to plan the study and provided advice related to writing the paper. Tadashi Ishii and Nobuo Yaegashi were responsible for the study design and execution and assisted in writing the paper. All authors read and approved the final paper.

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