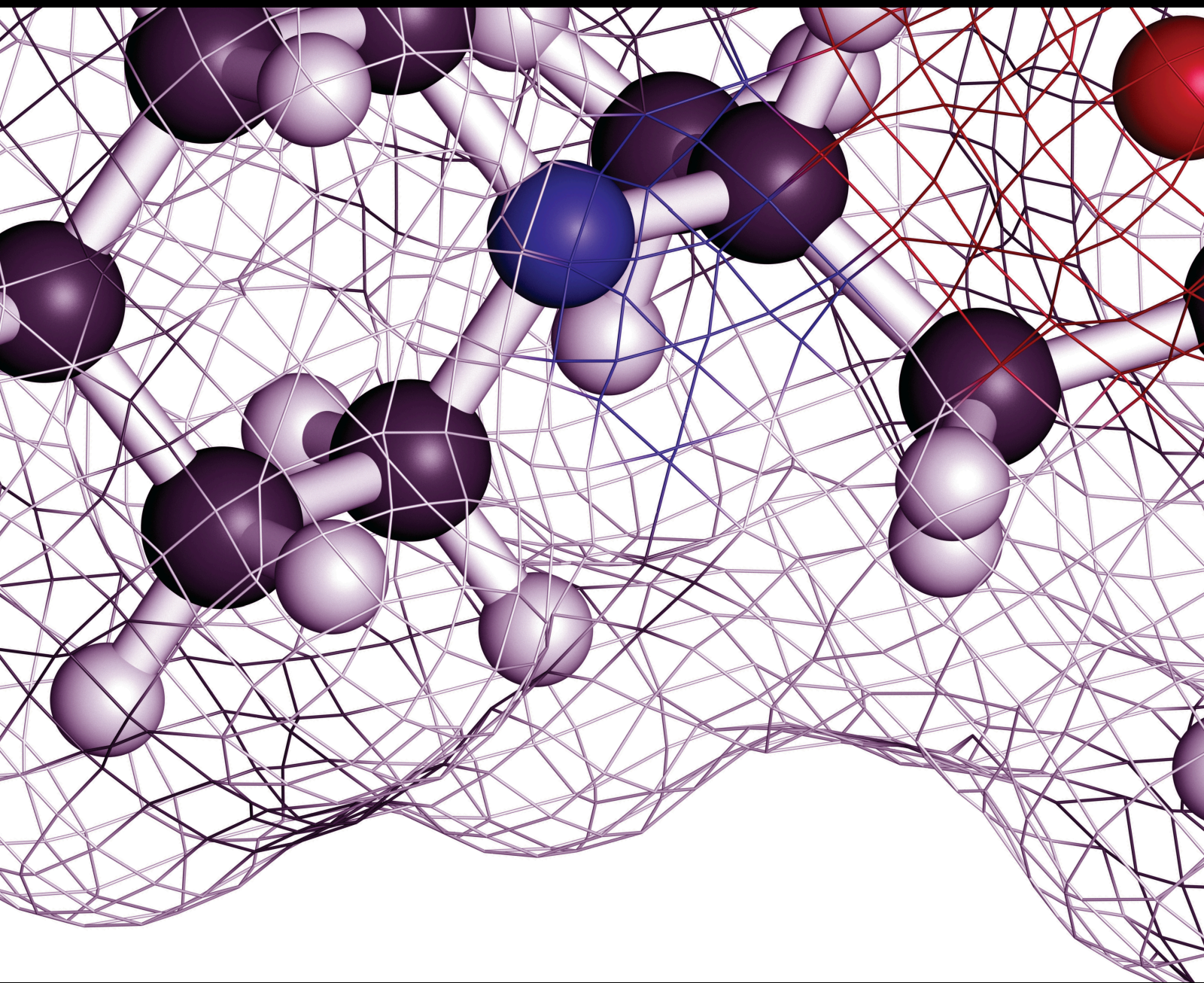
Pain Research and Management

Basic and Clinical Advances in the Diagnosis and Management of Migraine

Lead Guest Editor: Xiaolei Shi
Guest Editors: Wei Di and Aneta Wieczorek



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Editorial

Basic and Clinical Advances in the Diagnosis and Management of Migraine

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Migraine is a common headache disorder and is one of the highest causes of disability among the population in the world [1]. It is estimated that 20.2% of women and 9.4% of men suffer from this disorder [2]. It is typically unilateral and frequently present in the form of throbbing or pulsating sensation and other associated symptoms, including nausea, vomiting, phonophobia, and photophobia [3]. Usually, the symptoms may last several hours to days, severely impairing the quality of life. It is believed that neuroinflammation, dysfunction of the descending pain-modulating network, altered trigeminal and autonomic system function, and other mechanisms may contribute to migraine [4–6]. Moreover, recent studies have provided new findings in the genetic causes, anatomical and functional characteristics, and pathological potentials of migraine. For example, genomic loci associated with migraine were enriched in genes that are expressed in gastrointestinal tissues [7]. This may explain the gastrointestinal symptoms concomitant with pain attacks, like nausea, vomiting, and the like. Studies have suggested that migraine headache is significantly associated with infant colic and inflammatory bowel disease [8, 9].

This special issue aims to cover migraine-related studies and provide a multidisciplinary treatment strategy for it. In this issue, readers will find six papers studying a wide spectrum of aspects of migraine: "Human Urinary Kallidinogenase Reduces Lipopolysaccharide-Induced Neuroinflammation and Oxidative Stress in BV-2 Cells" by Z. Zhao et al., "Curcumin Protects Human Umbilical Vein Endothelial Cells against H_2O_2-Induced Cell Injury" by J. Ouyang, "Cognitive Decline in Chronic Migraine with Nonsteroid Anti-Inflammation Drug Overuse: A Cross-Sectional Study" by X. Cai et al., "Effects of Diet Based on IgG Elimination Combined with Probiotics on Migraine Plus Irritable Bowel Syndrome" by Y. Xie et al., "The Relationship between Infant Colic and Migraine as well as Tension-Type Headache: A Meta-Analysis" by D. Zhang et al., and "Effect of Core Stability Training Monitored by Rehabilitative Ultrasound Image and Surface Electromyogram in Local Core Muscles of Healthy People" by Y. Zheng et al.

The studies included in this issue will help understand and develop new research in a most recent viewpoint.

Conflicts of Interest

The editors declare that there are no conflicts of interest.

Xiaolei Shi
Wei Di
Aneta Wieczorek

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Research Article

Curcumin Protects Human Umbilical Vein Endothelial Cells against H_2O_2-Induced Cell Injury

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Guest Editor: Xiaolei Shi

Migraine is a prevalent neurological disorder which causes a huge economic burden on society. It is thought to be a neurovascular disease with oxidative stress might be involved. Curcumin, one of the major ingredients of turmeric, has potent antioxidative and anti-inflammatory properties, but whether it could be used as a potential treatment for migraine remains to be explored. In the present study, human umbilical vein endothelial cells (HUVECs) were pretreated with various concentrations of curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h, thereby exposed to H_2O_2 (100 μM) for another 12 h. The viability of HUVECs was tested by the CCK-8 assay, and the activities of antioxidant enzymes including superoxide dismutase (SOD) and glutathione (GSH) were also examined. Intracellular reactive oxygen species (ROS) and malondialdehyde (MDA) were assayed to determine H_2O_2-induced oxidative stress. In addition, several cell death-related genes (p53, p21, Bax, and Bcl-2) were detected by PCR, and an apoptosis-related protein (caspase3) was evaluated by western blotting. Our results showed that curcumin improved the H_2O_2-induced decrease of cell viability and antioxidative enzyme activities and decreased the level of oxidative stress. As a conclusion, curcumin could mitigate H_2O_2-induced oxidative stress and cell death in HUVECs and may be a potential therapeutic drug for migraine.

1. Introduction

Migraine is a widespread neurological disorder with the typical clinical symptom being recurrent headache [1]. The global prevalence of migraine was reported to be 15%, and 10% will progress to chronic migraine [2]. Migraine-associated functional disability affects patients' work capacity and productivity, thus leading to a huge economic burden on society [3]. Currently, long-term use of migraine drugs may cause some adverse events, such as abuse, addiction, and dependence [4]. As a result, it is of value to conduct more research to promote the understanding of the molecular mechanism of migraine, thus developing novel approaches with improved efficacy and safety.

Curcumin, one of the major ingredients of turmeric, attracted much attention because of its antioxidative, anticarcinogenic, antitumor, and anti-inflammatory properties [5, 6].

A growing body of evidences reports curcumin may have a beneficial antioxidative and neuroprotective potential for neurological diseases such as Alzheimer's disease and Parkinson's disease [7]. As reviewed by Shameemah, 17 studies have revealed the protective effect of curcumin in different cellular models of neurodegenerative disorders [8]. However, to the best of our knowledge, curcumin's treatment potential in migraine has not yet been evaluated.

It is believed that migraine is a neurovascular disorder caused by chronic sensitization of central pain pathways [9]. However, the mechanism of migraine could not be explained by a single theory.

In recent years, oxidative stress has attracted growing interest in the pathogenesis of this disease [10]. For instance, the research conducted by Geyik et al. revealed that oxidative stress marker 8-OHdG was higher in the plasma of migraine patients than that in the control group [11]. Oxidative stress may be caused by a lower activity of certain antioxidant enzymes and a higher activity of oxidant-generating factors [12]. Angiotensin, endothelin-1, and urotensin-2 have been reported to be implicated in this process [13]. Migraines may also be associated with mitochondrial defects, resulting in a

much higher metabolic rate. Magnesium, Coenzyme Q10 (CoQ10), and vitamins B2 and B12 have been revealed to have the potential for the treatment of migraine because of their antioxidant abilities [14].

In the present study, we investigated curcumin's effect on H_2O_2-induced oxidative stress in HUVECs *in vitro* and aimed to explore the potential use of curcumin in migraine treatment.

2. Materials and Methods

2.1. Cell Culture. HUVECs were obtained from Cell Bank in the Shanghai Institute for Biological Sciences of the Chinese Academy of Sciences and were cultured in Dulbecco's modified Eagle's Medium (DMEM) medium with 10% fetal bovine serum, 1% penicillin/streptomycin in 37°C, and 5% CO_2 [15]. All reagents were purchased from Gibco Thermo Fisher Scientific Inc. (MA, USA). HUVECs were treated with various concentrations of curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) and H_2O_2 (0 μM, 25 μM, 50 μM, 75 μM, and 100 μM, Sigma-Aldrich, St. Louis, MO, USA) 12 h later.

2.2. CCK-8 Assay for Cell Viability. The effects of curcumin and H_2O_2 on HUVECs viability were detected by the CCK-8 assay. In brief, cells were cultured on a 96-well plate at a density of 1×10^4 per well for 24 h and then administrated with curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h or with H_2O_2 (0 μM, 25 μM, 50 μM, 75 μM, 100 μM) for another 12 h. Then, the HUVECs were incubated at 37°C for 2 h. Thereafter, a multifunctional microplate reader (SpectraMax M5, Sunnyvale, CA, USA) was adopted to read the absorbance values at 450 nm [16].

2.3. LDH, GSH, and SOD Assay. In order to estimate the level of oxidative damage, we used a colorimetric assay kit (Beyotime, Nanjing, China) to measure the activity of lactate dehydrogenase (LDH) release [17], superoxide dismutase (SOD), and glutathione (GSH). In brief, HUVECs were seeded in 6-well plates at a density of 1×10^5/well. The HUVECs were then treated for 12 h with various concentrations of curcumin (10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) followed by H_2O_2 (25 μM, 50 μM, 75 μM, and 100 μM) for another 12 h.

2.4. Analysis of Oxidative Stress. The generation of reactive oxygen species (ROS) was measured using the fluorescent probe 2,7-dichlorofluorescein diacetate (DCFH-DA). The level of intracellular ROS was detected using a BD FACSCalibur Flow Cytometer (Becton, Dickinson and Company, USA). Another indicator of oxidative stress malondialdehyde (MDA) was also detected with commercial kits.

2.5. RNA Isolation and Real-Time Quantitative PCR. HUVECs were harvested, and RNA samples were exacted with the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The primer sequences used were as follow: p53: 5′-CTTTGAGGTGCGTGTTTGTGC-3′ (forward), 5′-TGTTGTTGGGCAGTGCTCG-3′ (reverse); p21: 5′-TAGCAGCGGAACAAGGAG-3′ (forward), 5′-AAACGGGAACCAGGACAC-3′ (reverse); Bcl-2: 5′-GTAGTGAATGAACTCTTCCG-3′ (forward), 5′-GTATCCCAGCCGCCGTTCTC-3′ (reverse); Bax: 5′-GACGTGGGCATTTTTCTTAC-3′ (forward), 5′-GTGTCCCGAAGGAGGTTTAT-3′ (reverse); and *ß*-actin: 5′-TGGCACCCAGCACAATGAA-3′ (forward), 5′-CTAAGTCATAGTCCGCCTAG AAGCA-3′ (reverse).

2.6. Western Blot. The protein was extracted using the RIPA buffer and measured using the BCA Protein Assay Kit (Beyotime, P0013B, Shanghai, China) according to the instruction. Equal amounts of proteins were separated and transferred to the PVDF membrane (Merk Millipore, Billerica, MA) and incubated with the primary antibodies at 4°C overnight.

This was followed by incubation with the goat anti-rabbit IgG antibody (1 : 10000, Cell Signaling Technology) at room temperature for 2 h. Membranes were scanned by using a chemiluminescent detective system (Amersham Biosciences UK Ltd., Little Chalfont, UK). The primary antibodies anticleaved caspase3 (1 : 1000, Abcam, MA, USA) and GAPDH (1 : 1000, Cell Signaling Technology) were used in this study.

2.7. Statistical Analysis. SPSS 18.0 for Windows (IBM Corp, Armonk, NY, USA) was used for the statistical analyses. Statistical analyses were performed using one-way analysis of variance (ANOVA) and Student's *t*-test for comparisons between groups. The data were expressed as mean ± SEM, and $p < 0.05$ was regarded as significant differences.

3. Results

3.1. Cell Viability. To examine the cytotoxicity of curcumin and H_2O_2 on HUVECs, cell viability was detected by the CCK-8 assay. As shown in Figure 1, treatment with H_2O_2 (0 μM, 25 μM, 50 μM, and 75 μM) for 12 h had no effect on cell viability of HUVECs. However, cell viability of HUVECs decreased when the concentration of H_2O_2 increased to 100 μM ($p < 0.05$). Meanwhile, curcumin treatment at the concentrations of 0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM showed no cytotoxicity on HUVECs when compared with the control group ($p > 0.05$). Therefore, the concentrations of 0 μM, 10 μM, 20 μM, 30 μM, 40 μM, 50 μM, and 100 μM were chosen for curcumin and H_2O_2, respectively, for the subsequent experiments. Furthermore, the decreased cell viability of HUVECs induced by H_2O_2 was improved with curcumin treatment (40 μM and 50 μM) ($p < 0.05$), suggesting that curcumin rescued H_2O_2-induced cell injury in HUVECs.

3.2. The Effect of Curcumin on the Level of LDH Release and GSH and SOD Activity in H_2O_2-Exposed HUVECs. Superoxide dismutase (SOD), glutathione (GSH), and lactate dehydrogenase (LDH) have been widely used as indicators for oxidative injury. As a result, the production of LDH and activities of SOD and GSH were measured to evaluate the effects of curcumin on H_2O_2-induced injury in HUVECs. Cells were pretreated with curcumin (0 μM,

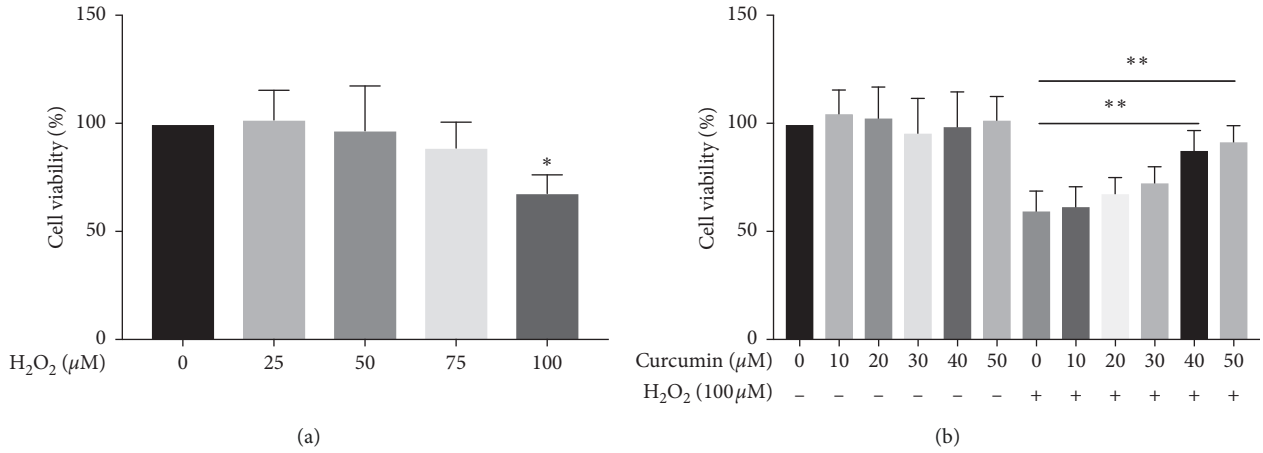

Figure 1: Cell viability of HUVECs treated with curcumin and H_2O_2. (a) Treatment with H_2O_2 (0 μM, 25 μM, 50 μM, and 75 μM) for 12 h had no effect on cell viability of HUVECs, while H_2O_2 (100 μM) decreased cell viability which was tested by the CCK-8 assay. $^*p < 0.05$ versus the control group. (b) HUVECs treated with curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h showed no change of cell vitality. The cell vitality after H_2O_2 (100 μM) treatment increased after curcumin (40 μM and 50 μM) administration compared with curcumin (0 μM). $^{**}p < 0.01$ ($n = 3$).

10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h and with H_2O_2 (100 μM) treatment for another 12 h. As shown in Figure 2, H_2O_2 administration increased the levels of LDH when compared with the control group ($p < 0.05$). However, the productions of LDH decreased significantly upon treatment with curcumin at the concentration of 40 μM ($p < 0.05$) and 50 μM ($p < 0.05$), even though there was no significant change at the concentrations of 10 μM, 20 μM, and 30 μM ($p > 0.05$). Conversely, the activities of GSH and SOD were enhanced by curcumin (40 μM and 50 μM). Taken together, our result indicated that curcumin showed protective capacity in a dose-dependent manner in H_2O_2-induced cell injury in HUVECs.

3.3. Curcumin Inhibited H_2O_2-Induced Oxidative Stress in HUVECs. In order to test whether curcumin could influence oxidative stress in HUVECs, we examined the generation of the intracellular ROS and MDA level. As is shown in Figure 3(a), intracellular ROS was increased in HUVECs under H_2O_2 treatment ($p < 0.05$). In addition, H_2O_2 treatment also caused a significant induction of another oxidative stress marker, malondialdehyde (MDA) (Figure 3(b)) ($p < 0.05$). Notably, a significant reduction of both the intracellular ROS and MDA level was observed with curcumin pretreatment (40 μM and 50 μM) for 12 h. In contrast, the curcumin concentration of 10 μM, 20 μM, and 30 μM had no effect on in H_2O_2-induced HUVECs in terms of either intracellular ROS or MDA level ($p > 0.05$). Our data suggested that the effect of H_2O_2 on the intracellular ROS and MDA levels in HUVECs could be blocked by curcumin at a certain concentration.

3.4. The Effect of Curcumin on Cell Death-Related Genes in H_2O_2-Exposed HUVECs. In order to elucidate the effect of curcumin on cell apoptosis, the expression of cell apoptosis-related genes, including p53, p21, Bax, and Bcl-2, was examined by PCR. The result showed that H_2O_2 induced a significant increase in apoptosis-related genes (p53, p21, and Bax) and a significant decrease of antiapoptotic gene (Bcl-2) (Figure 4) ($p > 0.05$). Notably, after curcumin (40 μM, 50 μM) treatment, these effects were partly reversed. Moreover, the expression of apoptosis-related protein was evaluated by western blot. As shown in Figure 4(e), the caspase3 level was significantly reduced by curcumin treatment (50 μM). Therefore, we suggested that curcumin had a protective effect on HUVECs against oxidative stress.

4. Discussion

In the present research, our results showed that curcumin could mitigate H_2O_2-induced decrease of cell vitalities and antioxidative enzyme activities and decrease the level of oxidative stress in HUVECs. Curcumin, an active compound isolated from turmeric, has been demonstrated to have protective effect on neurological disorders [18]. However, as we know, there is still no published paper reported on the role of curcumin in model of migraine.

The safety of curcumin has been well proved [19]. Our result also showed that curcumin at the concentration of up to 50 μM had no effect on the cell viabilities of HUVECs. Notably, the concentration of 40 μM and 50 μM showed a property to inhibit H_2O_2-induced oxidative stress (Figure 1). Furthermore, our results also showed that curcumin suppressed H_2O_2-induced induction of p53, p21, and Bax while enhanced the expression of antiapoptotic gene Bcl-2 (Figure 4).

The oxidative stress is mostly caused by the imbalance of ROS production and the clearance system [20]. It has been reported that curcumin rescued 6-OHDA-induced reduction of the antioxidant enzymes GSH, GPx, GR, and SOD [21]. Harish et al. exposed curcumin-pretreated N27 cells to buthionine sulfoximine and observed the upregulation of GSH and glutathione S-transferase [22]. The effect on GSH levels was also observed in a lipopolysaccharide-induced mouse model with curcumin

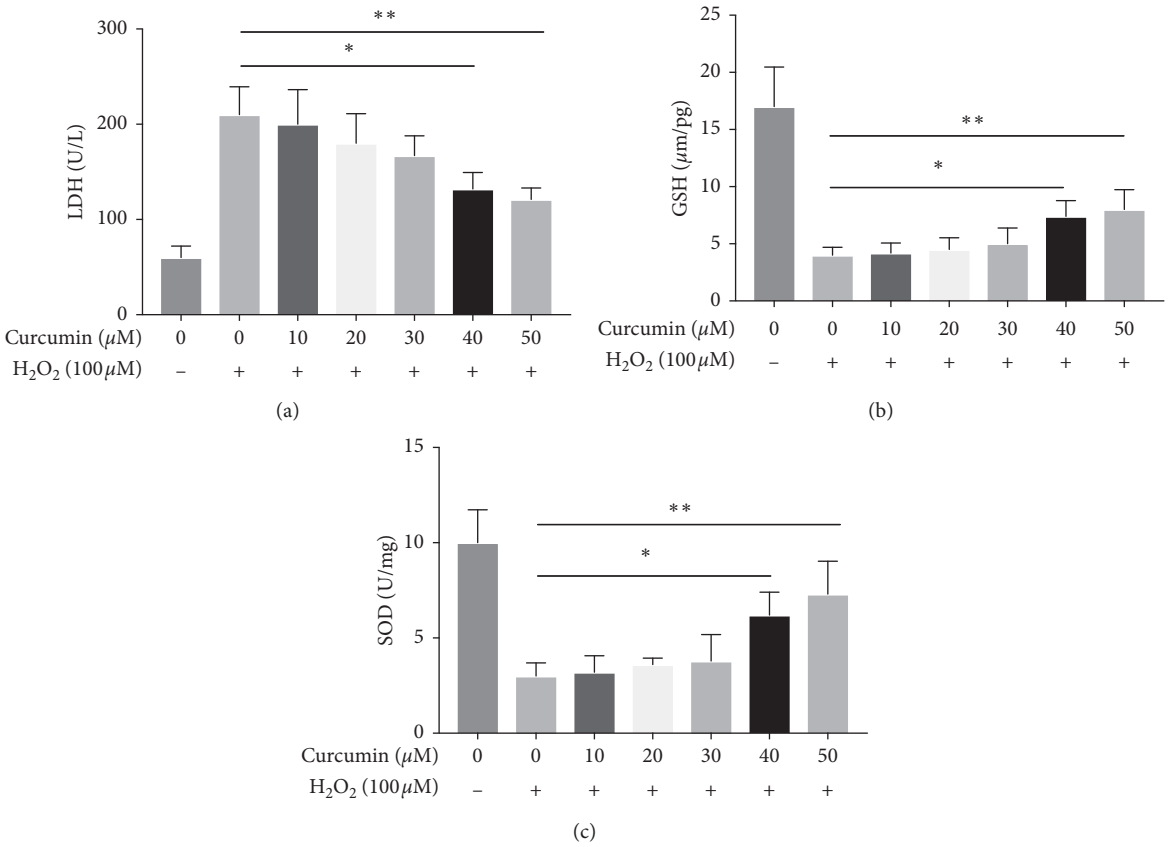

Figure 2: The effect of curcumin on LDH release and GSH and SOD activity in H_2O_2-exposed HUVECs. HUVECs were pretreated with curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h and with H_2O_2 (100 μM) treatment for another 12 h. The LDH release and GSH and SOD activity were measured, respectively. $^{*}p < 0.05$ and $^{**}p < 0.01$, $n = 3$.

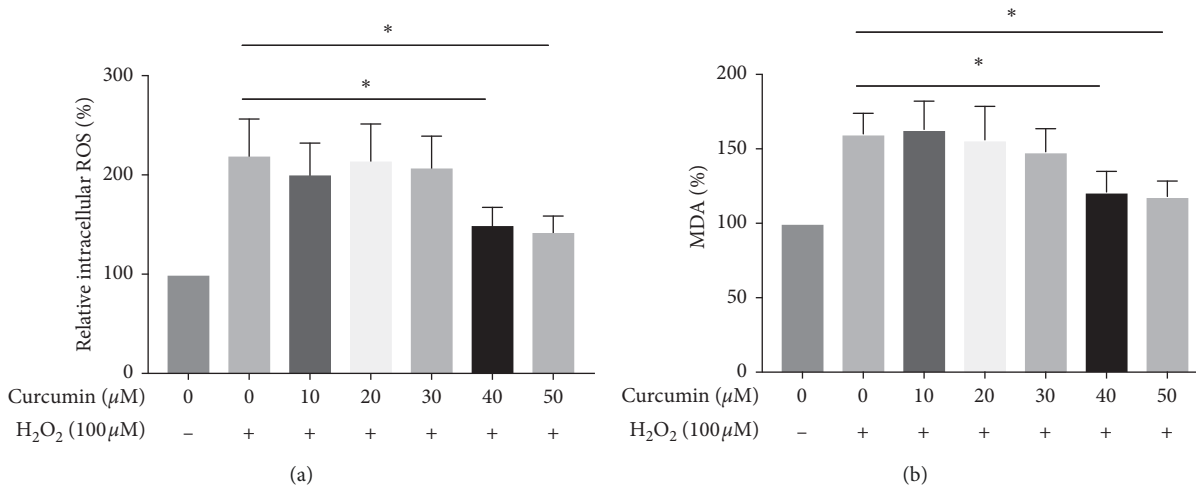

Figure 3: The effect of curcumin on oxidative stress in H_2O_2-exposed HUVECs. HUVECs were pretreated with curcumin (0 μM, 10 μM, 20 μM, 30 μM, 40 μM, and 50 μM) for 12 h and with H_2O_2 (100 μM) treatment for another 12 h. The DCFH-DA assay was adopted to detect endogenous ROS, and the commercial MDA kit was used to examine the MDA level. $^{*}p < 0.05$, $n = 3$.

treatment for seven days [23]. Consistently, we also observed an upregulation of SOD and GSH levels, suggesting that curcumin could regulate oxidative homeostasis in HUVECs by stimulating the activities of antioxidant enzymes.

Increasing evidences have reported the role of oxidative stress in migraine [11]. As shown in Figure 3, curcumin could ameliorate H_2O_2-mediated oxidative stress by reducing ROS and MDA levels. This is similar to the experiment performed by Cui et al. who applied rotenone to

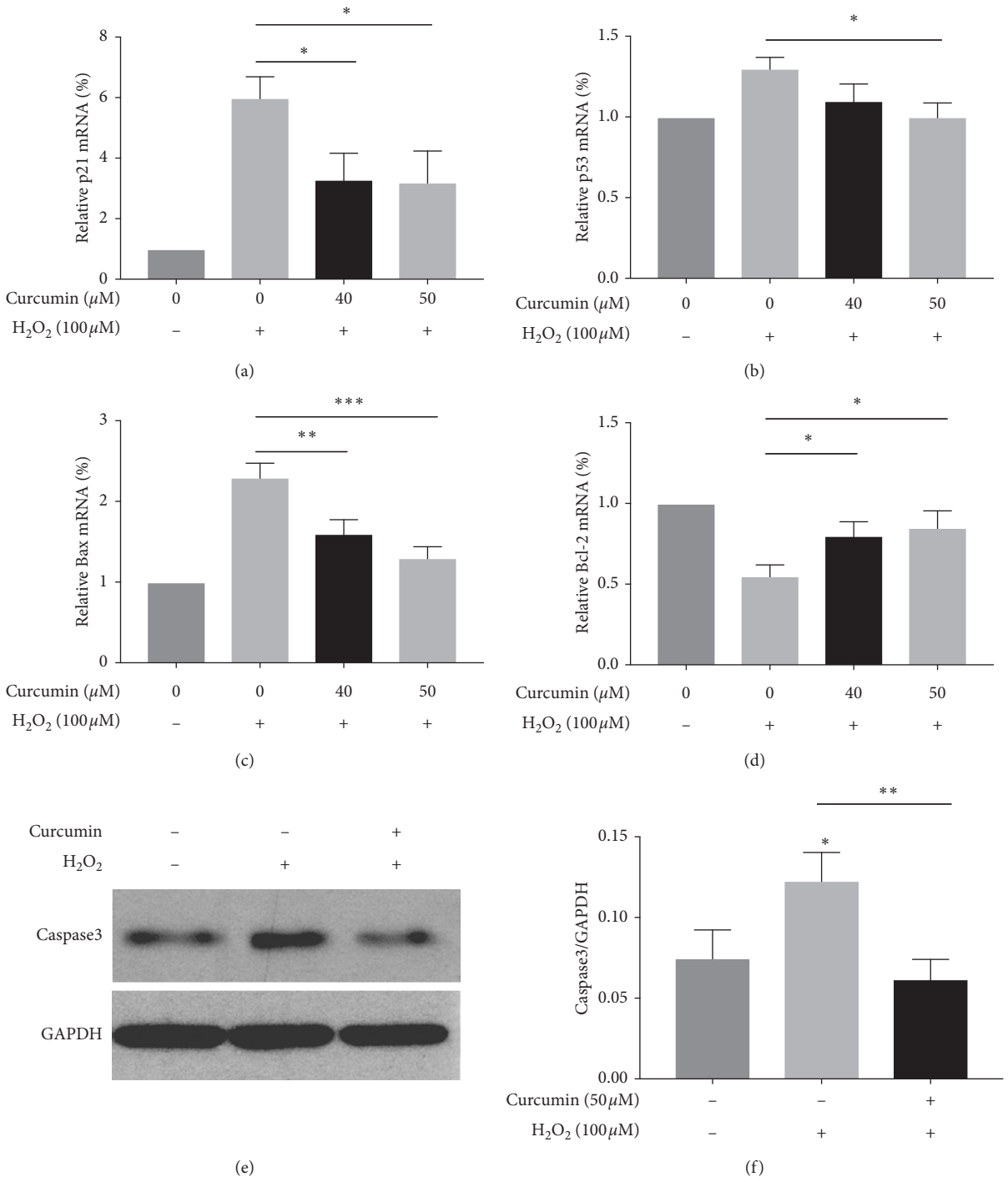

Figure 4: The effect of curcumin on cell death-related genes in H_2O_2-exposed HUVECs. HUVECs were pretreated with curcumin (40 μM and 50 μM) for 12 h and with H_2O_2 (100 μM) treatment for another 12 h. The mRNA level of cell death-related genes including p53, p21, Bax, and Bcl-2 was detected by PCR. The expression of apoptosis protein caspase3 was evaluated by western blot. $^{*}p < 0.05$ and $^{**}p < 0.01$, $n = 3$.

induce oxidative stress in the dopaminergic neuron [24]. In addition, another study investigated the antioxidant properties of curcumin also used H_2O_2 to stimulate oxidative stress. The authors suggested that curcumin was capable of improving both DNA damage and cell apoptosis in PC12, which is an established cell model of PD [25]. However, the effect of curcumin against oxidative damage depends on the cell line. van Meeteren et al. observed poor efficacy of curcumin in H_2O_2-stimulated oligodendrocytes and macrophages cells [26]. In the present study, we firstly showed that curcumin had the protective effect on H_2O_2-induced oxidized proteins and lipid radicals in HUVECs.

The molecular mechanism of the protective effect of curcumin on HUVECs under oxidative stress still remains to

be explored. By exploring the antioxidant effect of curcumin in amyloid-β exposed SH-SY5Y and IMR-32 cells, Sarkar et al. proposed that it might be associated with the activation of antioxidant element and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways [27]. In another study, the reduction of oxidative stress by curcumin only occurred in cells with mutant α-synuclein, suggesting that the oxidative stressor might be essential for the antioxidant effect of curcumin [18]. Another study with a model PC12 cells showed that mitogen-activated protein kinases (MAPKs) and serine/threonine protein kinase (Akt) pathways might play a vital role in the antioxidant effect of curcumin [25]. However, whether the mechanism is implicated in HUVECs is unclear.

In the present experiment, DMSO was adopted as the solvent for curcumin. Previous published papers reported that DMSO might change the conformation of curcumin [28]. However, according to the published paper, the working concentration of DMSO we used in this research (0.1%) is not likely to cause effect on curcumin [29]. With high lipophilicity, curcumin is free to pass through cellular membranes, which might be the basis of the effect in HUVECs [30]. However, the potential application of curcumin in clinical trials is largely hindered by its poor bioavailability [31]. Its low intestinal absorption, poor structural stability, and rapid metabolism, especially the poor permeability across the blood-brain barrier, are major obstacles for the use of curcumin as a therapeutic agent for migraine [19]. As a result, various drug delivery approaches have been used to increase curcumin's bioavailability [8]. It has been demonstrated that structural alteration and bioconjugates enhanced the curcumin's protective property against oxidative stress [23]. In addition, lots of researches showed that nanocarriers including liposomes, isomerization, polymeric nanoparticles, and polymeric micelles rendered a larger effect size for curcumin [32, 33]. For instance, Khalil et al. illustrated that the PLGA-PEG nanoparticles increased the bioavailability of curcumin by up to 55.4-fold by decreasing the degradation [34]. With the improvement of nanotechnology, curcumin would be more likely to be used to treat migraine.

To the best of our knowledge, there is no widely accepted *in vitro* model for migraine. Both C2C12 myoblasts and meningeal mast cells [35] have been used as model for migraine research [36]. Harriott et al. also suggested the spreading depression model to be used as a preclinical model of migraine [37]. Since migraine is a vascular disorder which was thought to be related to the trigeminovascular pathway, we used HUVECs as a model to study the mechanism (oxidative stress) that may be associated with migraine. There are limitations to the approach of using HUVECs as a migraine model. The model we used is just one component part of the complex heterogeneous pathogenesis of migraine; however, we think it could be helpful for the examination of alterations in vascular dysfunction. The effect of curcumin on migraine remained to be confirmed in an *in vivo* experiment and clinical trial.

5. Conclusion

In the present study, we report the effect of curcumin on H_2O_2-induced oxidative stress in HUVECs, which might be a potential therapy for migraine.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Research Article

Effects of Diet Based on IgG Elimination Combined with Probiotics on Migraine Plus Irritable Bowel Syndrome

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Several research studies have revealed that migraine has a solid link with gastrointestinal diseases especially irritable bowel syndrome (IBS). This study was carried out to investigate therapeutic potential of diet based on IgG elimination combined with probiotics on migraine plus irritable bowel syndrome. A total of 60 patients diagnosed with migraine plus IBS were recruited for the study. IgG antibodies against 266 food varieties were detected by ELISA. Then, the subjects were randomized into three groups for treatment of IgG elimination diet or probiotics or diet combined with probiotics. Migraine symptom, gut function score, medication use, and serum serotonin level were measured at baseline, 7 weeks, and 14 weeks. Improvement of migraine and gut symptom was achieved at a certain time point. Reduced use of over-the-counter- (OTC−) analgesics was seen in all groups. However, use of triptans did not show significant difference. An increased serum serotonin level was seen in subjects treated with elimination diet and elimination diet combined with probiotics. IgG elimination diet combined with probiotics may be beneficial to migraine plus IBS. It may provide new insight by understanding the intricate relationship between migraine and gastrointestinal diseases.

1. Introduction

Migraine is described as a debilitated headache with a prevalence of 13–33% over a lifetime. Patients may suffer severely from the symptoms as well as a high economic burden [1]. However, the underlying mechanisms are still not fully understood. There is growing evidence indicating that central nervous system (CNS) manifestations may appear after the gastrointestinal dysfunction [2]. The interactive relationship between the intestine and the brain is termed as the "gut-brain axis" [3]. Gratifying achievements have been made in delineating the bidirectional relationship between the CNS and the intestinal tract. Emerging evidence suggests that migraine patients tend to get gastrointestinal diseases and patients with gastrointestinal (GI) diseases are more liable to catch migraine, as compared to healthy controls [4–6]. Among these patients, migraine concomitant IBS is most commonly seen [7–9]. Growing evidence indicates that the intestinal microbiota and its metabolites may manage GI functions by affecting intestinal sensitivity and motility, intestinal permeability, and mucosal immune function [10, 11]. Undigested food particles and bacterial metabolite may enter the bloodstream and affect intestinal function [12], the leaky gut hypothesis suggests that intestinal disorders may prompt increased intestinal permeability, and then bacterial by-products such as lipopolysaccharides may flow into the bloodstream and ultimately cause a response provoking migraine [13, 14]. Moreover, intestinal microbiotas have been found to have a solid impact on neurotransmitter levels, especially serotonin (5-HT) which plays a significant role in migraine [15, 16]. Thus, amending function of the intestine may ameliorate intensity and duration time of migraine attacks. Probiotics, as living microorganisms, have been verified to stabilize the intestinal epithelial barrier in multiple ways [17]. Reduced pathogenic bacteria have been found when administered in probiotic bacterial strains by

secreting antimicrobial factors. Furthermore, increased mucus output of the goblet cells has been found and they are of great importance for the tight junctions between the intestinal epithelial cells [18]. Several researchers found that diet based on elimination of certain food could reduce the occurrence and severity of migraine attacks [19, 20]. Abundance of food-specific IgGs may indicate food hypersensitivity. Hence, consumption of IgG-free food could ameliorate clinical manifestation of migraine.

Herein, we explored effects of diet based on IgG elimination combined with probiotics on migraine plus IBS, adding to growing evidence that management of intestinal function may be beneficial for migraine patients.

2. Materials and Methods

2.1. Subjects and Ethics. This study was carried out at The First Affiliated Hospital of University of South China. Sixty patients were enrolled in the study from May 2017 through December 2018 in the internal medicine department. International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3-beta), was employed to diagnose migraine; all patients were accompanied with uncomplicated IBS (bowel habit subtypes) according to the Rome III criteria. Five subjects were excluded due to difficulty in keeping the diet.

For meeting the inclusion criteria, the patients should (I) be aged between 18 and 65 years, (II) be diagnosed with migraine for more than 6 months and have at least 4 headache days within the last month, (III) have discomfort in the gut for more than 12 weeks in the past year, and (IV) be treated with preventive medications or acute attack medications unchanged for more than 6 months. Patients who have a definite history of medication overuse, headache, menstrual or other associated headache disorder, and organic abdominal diseases were excluded from the experiment.

Informed consent was obtained from subjects, and all the procedures were approved by the Institutional Review Board of the University of South China.

2.2. IgG Antibody Detection against Food Antigens and Diet Preparation. IgG antibodies against 266 food antigens were measured by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ImuPro 300 test; Evomed/R-Biopharm AG, Darmstadt, Germany). Quantitative measurements were reported in mg/l. Values above 7.5 mg/l were considered as positive reaction to the corresponding food. These samples were graded according to their titres, "low" for titres between 7.5–12.5 mg/l; "moderate" for 12.51–20 mg/l; "high" for 20.1–50 mg/l; and "very high" for 50.1–200 mg/l. According to the IgG antibody results, the elimination diet was composed of IgG negative food and the normal diet was made up with IgG-negative and IgG-positive food. There was no difference in calorie contents between these two diets. Subjects were guided to follow the diet (IgG-negative or IgG-positive) arranged by dietician.

2.3. Experiment Procedures and Measurement. A double-blind, randomized, controlled cross-over clinical trial was performed, and participants were randomly assigned to three groups which include subjects with elimination diet, probiotics, or elimination diet combined with probiotics. The probiotics product contains the following bacterial strains (*Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus*), and the subjects consumed 1.5 grams three times a day for 14 weeks.

During the experiment period, the subjects were requested to fill out a headache questionnaire, the Migraine Disability Assessment Scale (MIDAS), to evaluate severity of the migraine. IB Severity Scale (IBSS) was applied to assess the therapeutic effects of the intestine. A spectrophotofluorimetric method was applied to measure the concentration of serotonin in plasma [21]. Each scale and concentration of 5-HT in serum were assessed every 7 weeks.

2.4. Statistical Analysis. All data are expressed as mean ± S.D. Experiments with three or more groups were compared by ANOVA, followed by the LSD test. $p < 0.05$ was taken significant.

3. Results

3.1. Result of IgG Antibody Tests. Of the total 1506 reactions, 660 (43.8%) were graded as "low," 693 (46%) were "moderate," 105 (7%) were "high," and 48 (3.2%) were "very high". Food types are listed in Table 1.

3.2. Migraine Symptoms. As shown in Figure 1(a), migraine days of subjects with elimination diet in 14 weeks and elimination diet combined with probiotics in 7 and 14 weeks were significantly decreased. However, subjects with probiotics showed no difference. In 7 weeks, the mean MIDAS score decreased significantly only in subjects with elimination diet combined with probiotics. However, all groups exhibited an evident decrease in 14 weeks compared to baseline data (Figure 1(b)).

3.3. IBS Symptoms. As shown in Figure 2, in 14 weeks, a remarkable improvement was observed with all groups in bowel habit, compared to baseline data. No difference was found in 7 weeks. Only subjects with elimination diet combined with probiotics showed improvement in 14 weeks, referring to severity of abdominal distention.

3.4. Use of Medication. As shown in Figure 3, the use of triptans did not alter in all groups. The use of over-the-counter analgesics decreased in all groups in 14 weeks, only subjects with elimination diet combined with probiotics showed improvement in 7 weeks.

3.5. Concentration of 5-HT in Serum. As shown in Figure 4, in 14 weeks, subjects with elimination diet or elimination diet combined with probiotics exhibited a significant increase in concentration of 5-HT in serum compared to

Table 1: Types of food from most to least frequent IgG positivity in patients.

Food types	Number of patients with positive test result ($n = 60$)
Spices	53
Seeds and nuts	50
Grain with gluten	48
Seafood	43
Food additives	26
Eggs	26
Cheese	24
Sugar products	24
Milk product	24
Grain without gluten	19
Vegetable	14
Coffee infusions	10
Salads	5
Yeast	5
Meat	5
Mushrooms	3

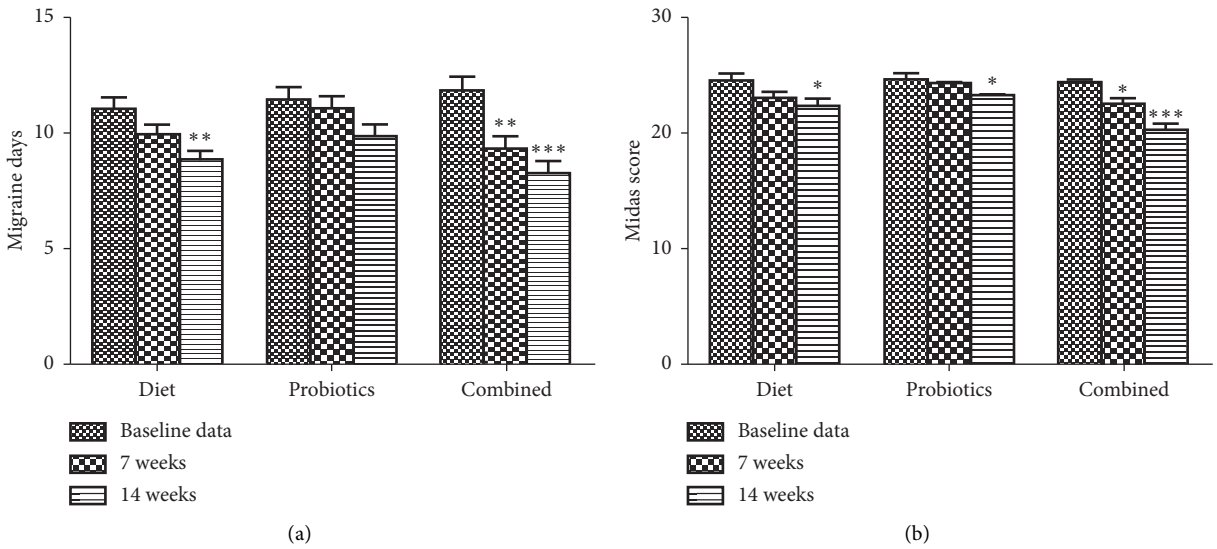

Figure 1: (a) Migraine days per 7 weeks at baseline and after 7 and 14 weeks of IgG elimination diet, oral intake of probiotics, or combined in migraine patients plus IBS. ** $p < 0.01$ and *** $p < 0.001$, compared to baseline data. (b) MIDAS score at baseline and after 7 and 14 weeks of IgG elimination diet, oral intake of probiotics, or combined in migraine patients plus IBS. * $p < 0.05$ and *** $p < 0.001$, compared to baseline data.

baseline data. No difference was found in other groups and time points.

4. Discussion

To our knowledge, it is the first research to prove that IgG elimination diet combined with probiotic may be beneficial to migraine plus IBS. Meanwhile, compliance was high and relevant adverse reactions did not happen. According to our findings, IgG-mediated food allergies have been proved to play an important role in migraine attacks although the mechanism is not fully illuminated. There is emerging proof that inflammation acts as a crucial role in the pathogenesis of migraine [22, 23]. A specific marker is needed if we focus on inflammation response prompted by certain foods. All IgG subclasses except IgG4 cause inflammatory response after contact with specific antigen [24]. Thus, identifying IgG for variety of foods may be applicable to detect allergized food and give guidance for amendment of dietary habits so as to keep away from chronic inflammation and onset of migraine. IBS patients were proved to have a greater gut permeability defect than healthy controls. Thus, increased intake of dietary antigens to lamina propria occurred in individuals with IBS. Decreased lymphocyte proliferation and release of inflammatory cytokines were found when consuming customized elimination diet [25]. Several studies have indicated that probiotics have therapeutic efficacy in gastrointestinal diseases [26, 27]. The potential mechanism of probiotics in treating gut-associated diseases may strengthen intestinal barrier function in several ways. Meanwhile, it may impact pain pathways by influencing brain signaling [28]. Hence, probiotics may relieve migraine

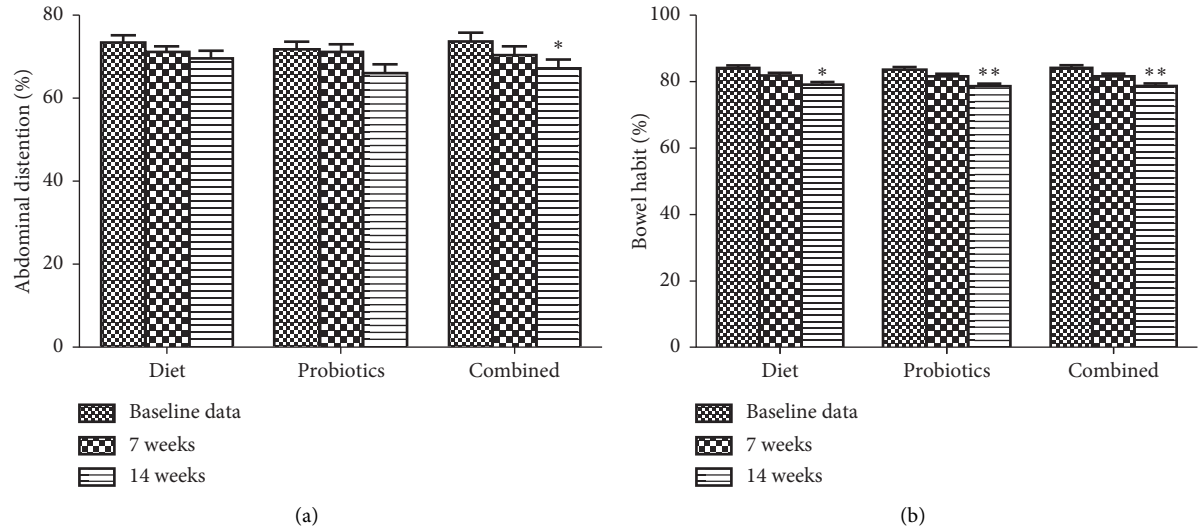

Figure 2: Abdominal distention and bowel habit score at baseline and after 7 and 14 weeks of IgG elimination diet, oral intake of probiotics, or combined in migraine patients plus IBS. $^{*}p < 0.05$ and $^{**}p < 0.01$, compared to baseline data.

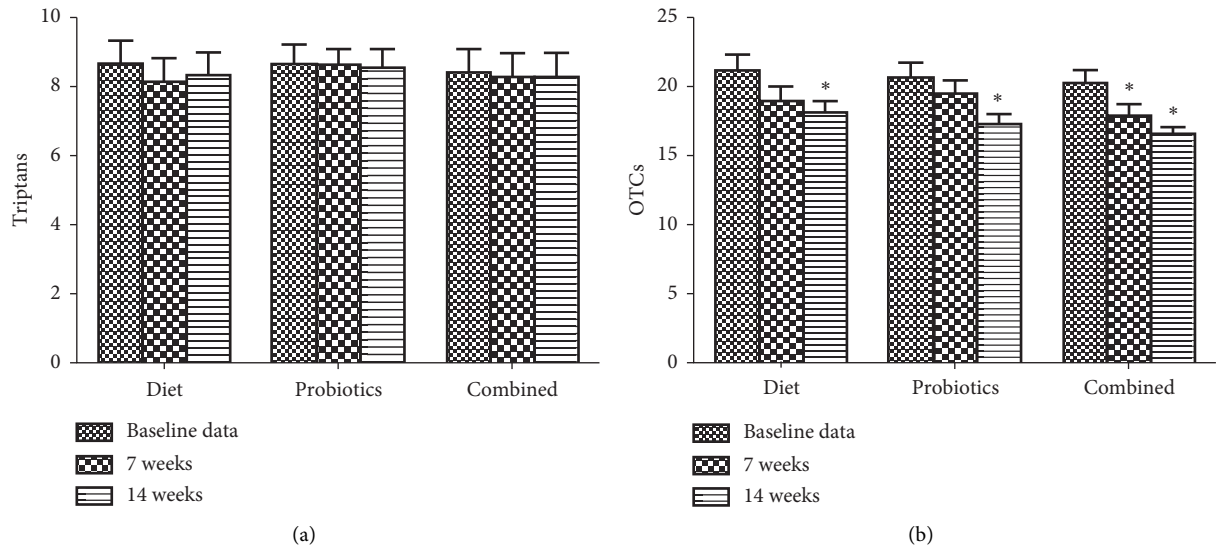

Figure 3: Medication use at baseline and after 7 and 14 weeks of IgG elimination diet, oral intake of probiotics, or combined in migraine patients plus IBS. $^{*}p < 0.05$, compared to baseline data.

headache by amending the intestinal barrier function through the gut-brain axis. Serotonin is neurogenic and serves a pivotal role in cell differentiation, division, and migration [29]. The enteric nervous systems are made up of more than 100 million neurons, and they may communicate with the central nervous system bidirectionally and continuously through several mediators [30]. Of these mediators, serotonin is mostly researched. Several studies suggest that serotonin is an important link in the brain-gut axis. However, only 3% of the whole serotonin of human is located in the central nervous system. The rest is located in the intestine. Enteric bacteria have been elucidated to regulate production of serotonin. Therefore, amending the function of intestine may be a way to cure migraine patients. The migraine days significantly decreased in the diet group in 7 and 14 weeks and got better with time. Also, the diet group exhibited significant change in 14 weeks. Although decrease was seen in the probiotic group, it showed no statistical significance. This may be explained as probiotics may take effect slower than other groups. Improvement was seen in the combined group in 14 weeks, referring to abdominal distention; however, other groups did not show a significant change because the treatment was inadequate. Reduction in triptan use was not seen in all groups, and this may be explained as some subjects were hard to get rid of it due to drug dependence.

Our data are in consistence with other studies which report IgG elimination diet or probiotics are beneficial for migraine plus IBS. Compared to these studies, ours has many superiorities. To begin with, we found that subjects

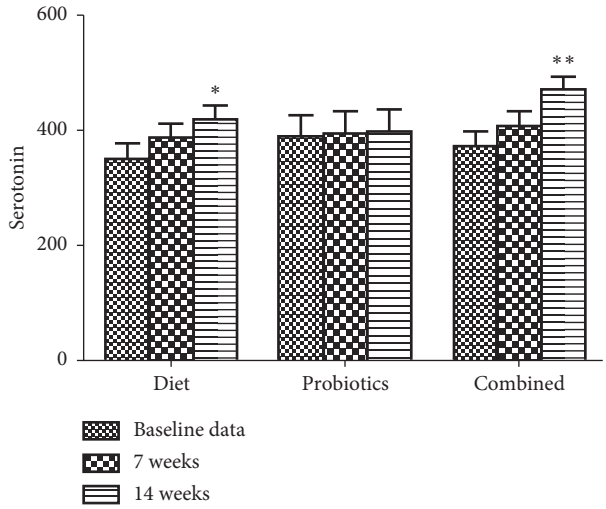

Figure 4: Serum level of serotonin at baseline and after 7 and 14 weeks of IgG elimination diet, oral intake of probiotics, or combined in migraine patients plus IBS. $^{*}p < 0.05$ and $^{**}p < 0.01$, compared to baseline data.

with IgG elimination diet combined with probiotics had effect quicker than other groups when considering migraine symptom (MIDAS score and migraine days). Secondly, although all the groups did not reduce the use of triptans, use of over-the-counter analgesic decreased dramatically in all groups in 14 weeks and only diet combined with probiotics showed effect at 7 weeks, and this indicated it may show effects quicker than other groups in nonacute attack. Moreover, improvement in bowel habit was seen in all groups in 14 weeks, but only subjects with diet combined with probiotics exhibited a relief in severity of abdominal distention. Thus, diet combined with probiotics may be an optimal selection for the management of intestinal function. Finally, titres of serotonin were upregulated in 14 weeks in subjects with diet and diet combined with probiotics, but the latter showed a greater magnitude. However, we must pay attention when translating these results into daily practice due to limited sample size. Further study is required to elucidate the underlying mechanism of IgG-positive, food-induced migraine.

5. Conclusions

In summation, we provide the first clinical evidence that IgG elimination diet combined with probiotics may be beneficial to migraine plus IBS. Future work should uncover the potential mechanism of how it affects pathophysiology of migraine.

Data Availability

The original data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Research Article

Human Urinary Kallidinogenase Reduces Lipopolysaccharide-Induced Neuroinflammation and Oxidative Stress in BV-2 Cells

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Migraine is one of the most common neurological disorders which poses significant socioeconomic burden worldwide. Neuroinflammation and oxidative stress both play important roles in the pathogenesis of migraine. Human urinary kallidinogenase (UK) is a tissue kallikrein derived from human urine. Increasing evidence suggests that UK may protect against ischemic stroke, but UK's treatment potential against migraine remains to be explored. Immortal BV-2 murine microglial cells were treated with UK (125 nM, 250 nM, and 500 nM) and then given lipopolysaccharides (LPS, 1000 ng/mL). Cell viability of BV-2 cells was tested by the CCK-8 assay. Expressions of tumor necrosis factor-α (TNFα), prostaglandin E2 (PGE2), interleukin-6 (IL-6), and interleukin-1β (IL-1β) were examined with the ELISA method and western blot. Intracellular reactive oxygen species (ROS) and malondialdehyde (MDA) were measured to determine oxidative stress. Our results showed that LPS administration increased the levels of proinflammatory cytokines (TNFα, PGE2, IL-6, and IL-1β) and oxidative stress (ROS and MDA) when compared with the control group and decreased significantly upon introduction with UK. Taken together, UK treatment reduced LPS-induced neuroinflammation and oxidative stress in a dose-dependent manner, which might be a potential treatment of migraine.

1. Introduction

Migraine is one of the most common neurologic disorders and is a major cause of disability worldwide [1]. It is a kind of unilateral pulsating headache with clinical symptoms of nausea, vomiting, phonophobia, and photophobia [2]. Antiepileptic drugs (AEDs), beta-blockers, and tricyclic anti-depressants are commonly used agents in the preventive treatment of migraine [3]. Since migraine poses significant socioeconomic burden, looking for new therapies has become an urgent international health priority [4].

The hypothesis that migraine is a neurovascular disorder and the headache is caused by dilation of cerebral and meningeal arteries has been well established [5]. However, the exact mechanism of migraine is still not well understood. Many research studies have proved that neuroinflammation and oxidative stress played important roles in the pathogenesis of this disease [6, 7].

The kallikrein-kinin system (KKS) consists of kinins, kallikreins, kininogens, and kinin receptors. Kinin plays its role by binding to the receptor, resulting in neuroprotective effect [8]. However, kinin could not be used as a drug because of its short half-life [9]. In contrast, kallikrein has much more amount in plasma. Accumulated studies have reported the function of tissue kallikrein on antiapoptotic, antioxidant, and antiexcitotoxic properties, suggesting that tissue kallikrein could be an effective therapy for neurological disorders [10]. Human urinary kallidinogenase (UK) is a tissue kallikrein derived from human urine, cleaving kininogen to release bradykinin [11]. UK has been

considered to be a positive regulatory substance in the kallikrein-kinin system by increasing kallikrein. Recently, UK has been widely used in China to treat ischemic stroke patients [12]. However, UK's treatment potential in migraine has not yet been evaluated.

In the present study, we evaluated a UK's effects on neuroinflammation and oxidative stress in LPS-stimulated BV-2 cells.

2. Materials and Methods

2.1. Cell Culture. Immortal BV-2 murine microglial cells were cultured as described [13, 14]. BV-2 cultures were treated with UK (125 nM, 250 nM, 500 nM, 750 nM, and 1000 nM) for 12 h and then with LPS (125 ng/mL, 250 ng/mL, 500 ng/mL, 750 ng/mL, and 1000 ng/mL, LotL2880, O55:B5, Sigma-Aldrich, St. Louis, MO, USA) for another 12 h. BV-2 cells were cultured at 37°C in Dulbecco's modified Eagle's medium (DMEM) with 1% of 100 U/mL of penicillin/streptomycin and 5% fetal bovine serum. All reagents were purchased from Gibco Thermo Fisher Scientific Inc. (MA, USA). UK was purchased from Techpool Bio-Pharma Co. Ltd., Canton, China.

2.2. CCK-8 Assay for Cell Viability. The effects of UK and LPS on BV-2 cell viability were detected by the CCK-8 assay [15]. In brief, cells were cultured on a 96-well plate at a density of 1×10^4 per well for 24 h and then administrated with UK (125 nM, 250 nM, 500 nM, 750 nM, and 1000 nM) for 12 h, or with LPS (125 ng/mL, 250 ng/mL, 500 ng/mL, 750 ng/mL, and 1000 ng/mL) treatment for another 12 h. Then, the cells were incubated at 37°C for 2 h and the absorbance values of the samples were measured at 450 nm by a multifunctional microplate reader (SpectraMax M5, Sunnyvale, CA, USA).

2.3. Enzyme-Linked Immunosorbent Assay (ELISA). The cells and the samples were stored at −80°C until analysis. We measured the concentration of tumor necrosis factor-α (TNFα), prostaglandin E2 (PGE2), interleukin-6 (IL-6), and interleukin-1β (IL-1β) with the ELISA method, which have been administrated with UK. The assays were performed using commercially available ELISA kits (Thermo Scientific, USA) according to the manufacturer's instructions. The total protein concentration was determined using the BCA Protein Assay kit (Thermo Scientific, USA). The absorbance of the samples was detected with a multifunctional microplate reader (SpectraMax M5, Sunnyvale, CA, USA).

2.4. Measurement of Oxidative Stress. Intracellular reactive oxygen species (ROS) was measured using the fluorescent probe 2,7-dichlorofluorescein diacetate (DCFH-DA) [16]. Another indicator of oxidative stress malondialdehyde (MDA) was detected with commercial kits as described previously [17].

2.5. Western Blot Analysis. BV-2 cells were washed three times with cold PBS, and the proteins were quantified with the BCA assay. Afterward, the PVDF membranes were incubated with primary antibodies at 4°C overnight and incubated with horseradish peroxidase-conjugated secondary antibodies for 1 h (anti-rabbit/anti-mouse IgG). Primary antibodies used were listed as follows: GAPDH as the loading control (1 : 1000, Cell Signaling Technology), TNFα (1 : 1000, Cell Signaling Technology), IL-6 (1 : 4000, Biosource), and IL-1β (1 : 2000, Rockland). The densitometric values of the bands were measured using the ImageJ software (National Institutes of Health, USA). The ratio relative to GAPDH for each band was calculated.

2.6. Statistical Analysis. SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analyses. One-way ANOVA and Student's t-test were used for comparisons between groups. The data were expressed as the mean ± SEM, and differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Cell Viability. To examine the cytotoxicity of UK and LPS on BV-2 cells and select the suitable drug concentrations for the subsequent experiments, the effects of UK and LPS on cell viability were detected by the CCK-8 assay. As shown in Figure 1, cell viabilities after treatment with UK (125 nM, 250 nM, and 500 nM) for 12 h had no effect on cell viability of BV-2 cells. However, cell viability of BV-2 cells decreased when the concentration of UK increased to 750 nM and 1000 nM ($p < 0.05$). Meanwhile, LPS treatment at the concentrations at 125–1000 ng/mL for 12 h showed no cytotoxicity on BV-2 cells when compared with the control group ($p > 0.05$). Therefore, the concentrations of 125 nM, 250 nM, and 500 nM of UK and 1000 ng/mL of LPS were selected as the working concentrations for the following experiments.

3.2. The Effect of UK on the Expressions of Proinflammatory Cytokines in LPS-Stimulated BV-2 Cells. TNFα, PGE2, IL-6, and IL-1β are proinflammatory cytokines which have been demonstrated in the process of migraine. As a result, the productions of TNFα, PGE2, IL-6, and IL-1β were measured by ELISA kits to evaluate the potential anti-inflammatory effects of UK on LPS-stimulated BV-2 microglial cells. Cells were pretreated with UK (125 nM, 250 nM, and 500 nM) for 12 h and with LPS (1000 ng/mL) treatment for another 12 h. As shown in Figure 2, LPS administration increased the levels of TNFα, PGE2, IL-6, and IL-1β when compared with the control group ($p < 0.05$). However, the productions of these cytokines decreased significantly upon introduction with UK at the concentration of 250 nM ($p < 0.05$) and 500 nM ($p < 0.05$), even though there was no significant change at the concentration of 125 nM ($p > 0.05$). In order to confirm the effect of UK on protein expressions of proinflammatory cytokines, the production of TNFα, IL-6, and IL-1β was analyzed by western blot. Cells were pre-treated with UK (500 nM) for 12 h and with LPS (1000 ng/mL) treatment for another 12 h. Consistently, our results showed that LPS increased the protein levels of TNFα, IL-6, and IL-1β

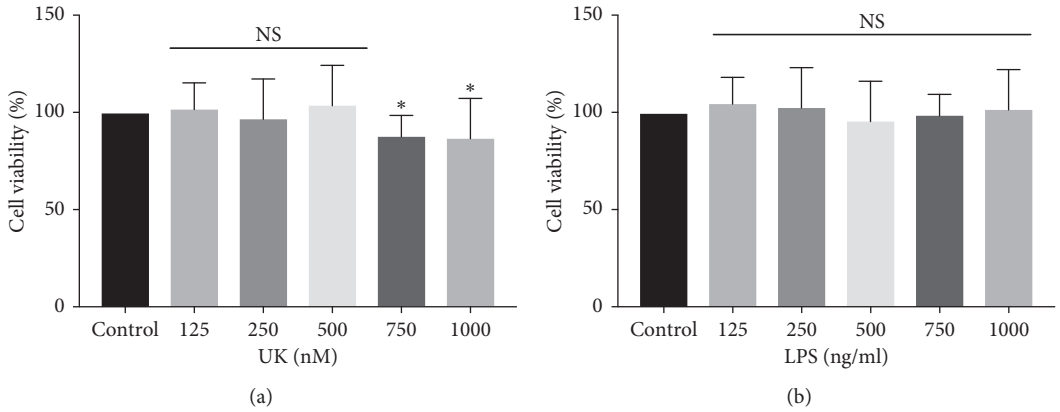

Figure 1: Cell viability of BV-2 microglial cells treated with UK and LPS. Cell viability of BV-2 cells was tested by the CCK-8 assay. Treatment with UK (125 nM–500 nM) for 12 h had no effect on cell viability of BV-2 cells while UK (750 nM–1000 nM) decreased cell viability of BV-2 microglial cells. LPS treatment (125–1000 ng/mL) for 12 h showed no cytotoxicity on BV-2 cells. NS: $p > 0.05$ and $^{*}p < 0.05$ versus the control group.

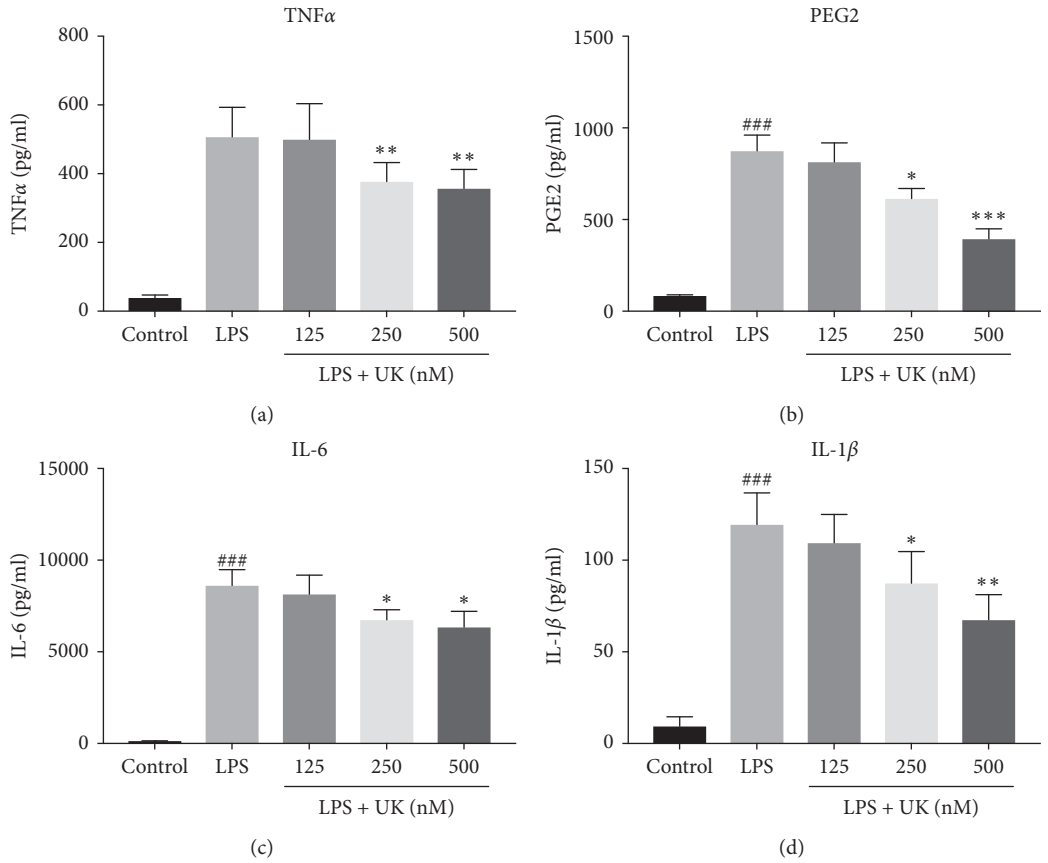

Figure 2: The effect of UK on the expressions of proinflammatory cytokines in LPS- stimulated BV-2 cells. Cells were pretreated with UK (125 nM, 250 nM, and 500 nM) for 12 h and with LPS (1000 ng/mL) treatment for another 12 h. The production of TNFα, PGE2, IL-6, and IL-1β was measured by ELISA kits. $^{###}p < 0.001$ versus the control group, $^{*}p < 0.05$ versus the LPS-stimulated group, $^{**}p < 0.01$ versus the control group, and $^{***}p < 0.001$ versus the LPS-stimulated group, $n = 3$.

($p < 0.05$) and UK treatment decreased the upregulation of protein levels induced by LPS ($p < 0.05$) (Figure 3). Taken together, our results indicated that UK showed anti-inflammatory capacity in a dose-dependent manner in LPS-induced BV-2 cells.

3.3. UK Reduced Oxidative Stress in LPS-Induced BV-2 Cells. Multiple pieces of literature have shown that oxidative stress plays a vital role in migraine. As a result, intracellular ROS level was examined by the DCFH-DA assay and the production of MDA was determined by

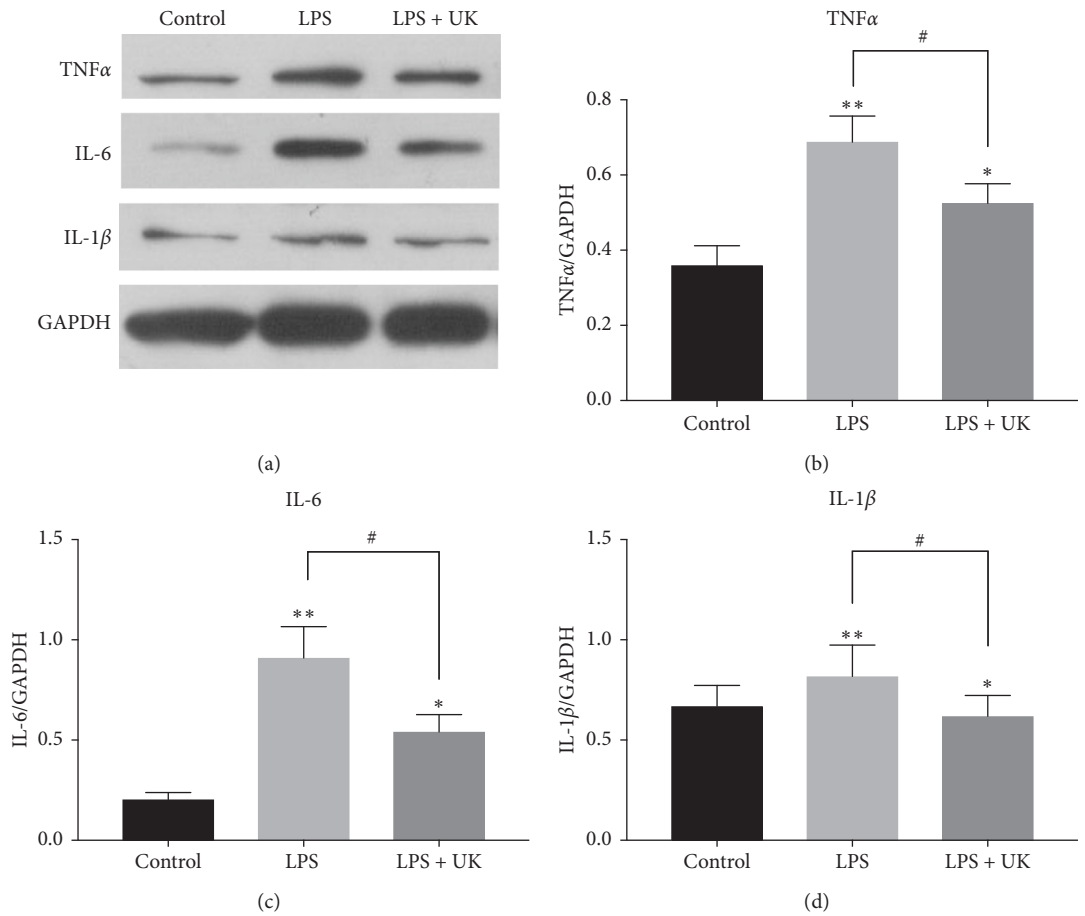

Figure 3: The effect of UK on the protein expressions of proinflammatory cytokines by western blot analysis. Cells were pretreated with UK (500 nM) for 12 h and with LPS (1000 ng/mL) treatment for another 12 h. The production of TNFα, IL-6, and IL-1β was analyzed by western blot. $^{\#}p < 0.05$ versus the LPS-stimulated group, $^{*}p < 0.05$ versus the control group, and $^{**}p < 0.01$ versus the control group, $n = 3$.

MDA kits in the present study. Our results showed that intracellular ROS was increased after LPS treatment in BV-2 cells (Figure 4) ($p < 0.05$). Additionally, lipid peroxidation marker MAD level also increased after LPS stimulation (Figure 4) ($p < 0.05$). Notably, a significant reduction in both intracellular ROS and MAD levels was observed after pretreated with UK (250 nM and 500 nM) for 12 h. The concentration of 125 nM of UK had no effect on LPS-induced BV-2 cells in terms of either intracellular ROS or MAD level ($p > 0.05$). Our data indicate that the effect of LPS on the intracellular ROS and MAD levels in BV-2 cells could be alleviated by UK in a dose-dependent manner.

4. Discussion

UK, a tissue kallikrein isolated from human urine, is a widely used drug for the treatment of ischemic stroke in China [11]. However, there is still no evidence for the role of UK play on inflammation and oxidative stress in model of migraine, which is a multifactorial neurodegenerative disease without satisfactory treatment.

UK is a commercially available KKS-regulating medicine, and the safety of UK has been well demonstrated [12]. Consistently, our results showed that cell viabilities of BV-2 cells after treatment with UK (125 nM, 250 nM, and 500 nM) for 12 h had no change when compared with the control group.

Neuroinflammation has been thought to play an important role in migraine [7]. PGE2 and proinflammation cytokines (IL-6, IL-1β, and TNFα) are crucial indicators of the inflammatory process [18]. In the present study, we observed that UK treatment sufficiently reduced LPS-stimulated neuroinflammation (Figures 2 and 3).

Accumulated evidence has been provided for the role of oxidative stress in migraine [6]. Our study highlighted the inhibition of UK on oxidative stress including intracellular reactive oxygen species and MDA level. Consistently, it has been demonstrated that UK was able to rescue glutamate-induced cell death by attenuating reactive oxygen species production and NOS activity in cultured cortical neurons [19]. The activation of bradykinin B2 receptor (B2R), extracellular signal-regulated kinase 1/2 cascade (ERK1/2), BDNF, and Bcl-2 was thought to be involved in this process. Xia et al. reported that tissue kallikrein gene therapy could protect mouse models from oxidative stress and apoptosis via B2R activation [20]. In addition, B2R-dependent

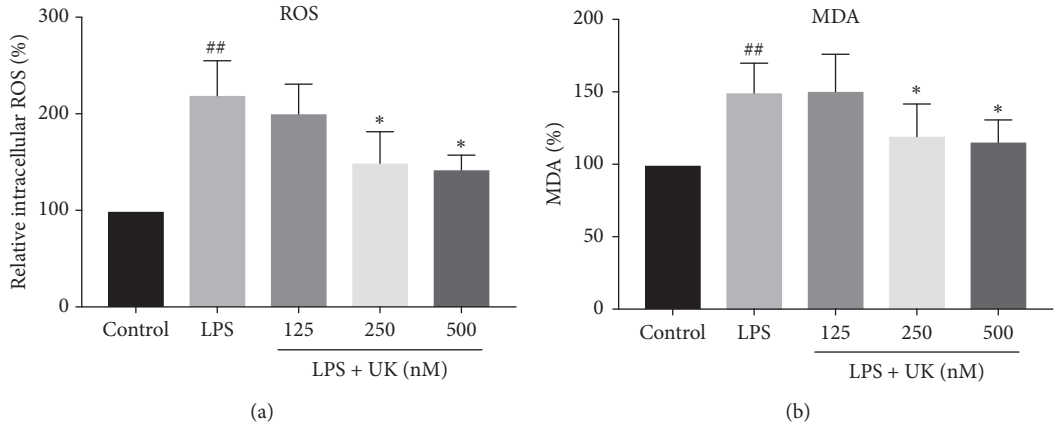

Figure 4: The effect of UK on oxidative stress in LPS-induced BV-2 cells. BV-2 cells were pretreated with UK (125 nM, 250 nM, and 500 nM) for 12 h and with LPS (1000 ng/mL) treatment for another 12 h. ROS level was examined by the DCFH-DA assay, and the production of MDA was determined by MDA kits. $^{\#\#}p < 0.01$ versus the control group and $^{*}p < 0.05$ versus the LPS-stimulated group.

regulation of autophagy is involved in inhibiting oxygen and glucose deprivation-induced neurocytotoxicity [21].

However, the exact mechanism of UK on LPS-induced neuroinflammation in BV-2 cells still remains to be explored. Proinflammatory cytokines are regulated by a transcription factor, NF-κB. It has been proved that UK protected neuron through nuclear factor-kappaB (NF-κB) pathway [9]. Inhibition of NF-κB in the microglia could possibly reduce the expressions of inflammatory cytokines.

The experiment conducted by Yang et al. showed that UK functioned on cerebral ischemia in a rat model by decreasing inflammatory responses [9]. By western blot analysis of the brain tissues, they also found that the levels of TLR4 and NF-κB both significantly reduced after the treatment of UK. They made a conclusion that UK protects ischemic stroke rat model through antioxidation and anti-inflammation by inhibiting NF-κB pathway, which is consistent with our results.

The mechanism of UK on LPS-stimulated BV-2 cells might be related to the transforming growth factor-beta 1 (TGF-β1), which can inhibit neuroinflammation. Previous studies proved that UK could upregulate TGF-β1 and decrease high-sensitivity c-reactive protein, which activates Bcl-2 expression to suppress the apoptosis [22]. Su et al. reported that UK protected neurons against hypoxia-induced cell injury. The process possibly because UK upregulated the phosphorylation of the ERK1/2 cascades by activating Homer1b/c [23].

LPS-stimulated BV-2 cell is a well-established *in vitro* model for inflammation [13]. As a result, we used BV-2 cells in the present research. However, the effect of UK on migraine remains to be examined in animal model.

5. Conclusion

We herein report the effect of UK on inflammatory response and oxidative stress in LPS-induced BV-2 cells, which might be a potential therapy for migraine.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Zhongyan Zhao and Zhiyu Xu contributed equally to this work.

Acknowledgments

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Clinical Study

Effect of Core Stability Training Monitored by Rehabilitative Ultrasound Image and Surface Electromyogram in Local Core Muscles of Healthy People

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Background. The purpose of this study is to investigate the influence of transverses abdominis and lumbar multifidus thickness activation and electromyogram signal characteristics after core stability training monitored by rehabilitative ultrasound imaging and surface electromyogram. *Methods*. 60 healthy volunteers were allocated randomly into two groups, one of which received monitoring training and the other participated identical training without monitoring. Ultrasound image and surface electromyogram signal were collected at 0, 4, and 8 weeks during training. The muscle thickness activation ratio value and integrated electromyogram value were then extracted. During the training, the monitoring group was monitored by real-time rehabilitative ultrasound imaging and surface electromyogram while the control group was not. *Results*. There are no differences in performance of local core muscles between both groups before training ($p > 0.05$). Compared with the control group, the thickness contraction ratio value and integrated electromyogram value of core muscles in the monitoring group were higher after 8 weeks' training ($p < 0.05$). *Conclusion*. Together, the core stability training monitored by rehabilitative ultrasound imaging and surface electromyogram can markedly activate and enhance local core muscles in healthy people, providing a potential strategy to treat low back pain more effectively.

1. Introduction

Low back pain (LBP) is a common disease bothering most populations in both developed and developing countries [1, 2]. Various approaches have been applied to treat LBP, including electrical stimulation [3], message [4], acupuncture [5] and invasive surgery [6]. However, no single modality appears to be superior and the effectiveness of these treatments is still questionable and uncertain. In recent years, core stability was defined as the ability to maintain a stable neutral spine position and core stability training has been proved to be useful in the treatment of LBP through decreasing pain [6–8], reducing disability [9], and preventing relapse [10].

Core muscles are categorized into global muscles (namely, the rectus abdominis, erector spinae, and obliquus externus abdominis) and local muscles (namely, transverse abdominis and lumbar multifidus) by function [11]. The global muscles participate in trunk movements, whereas the local muscles play an important role in core stabilization [12]. As local stabilizers, the transverse abdominis (TrA) and lumbar multifidus (MF) play important roles in the functional activities of spine. Our previous study shows that atrophy of the MF and the TrA could be frequently demonstrated in patients with LBP [13]. However, the application of core stability training targeting TrA and MF needs further optimization and innovation because of uncertainty

about the best way to apply exercise. The key of effective training is to ensure target core muscles contract in correct patterns.

Many studies have been previously reported on the relationship between the surface electromyogram (surface EMG) and muscle force [14]. The reliability and validity of this measurement are well established. Since it was found that recording the muscle activity of the deep fibers of TrA or MF by surface EMG may be inaccurate, another method currently used to examine core muscles function is rehabilitative ultrasound imaging (RUSI), an up-to-date method used to evaluate muscle activation without invasion [15, 16]. RUSI is increasingly adapted in pain therapy to quantify core muscle performance, assess clinical outcomes, and provide biofeedback during functional reeducation [17]. The degree of muscle thickness change that occurs during exercise can be measured by RUSI, whose reliability is well established for younger adults [18].

Above all, the objective of this study is to determine the effect of core stability training monitored by RUSI and surface EMG in local core muscles of healthy people.

2. Methods

2.1. Experimental Approach to the Problem. To investigate the effect of core stability training monitored by RUSI and surface EMG, two methods were used to monitor core stability training in the monitoring group. The monitoring group received specific core stability training monitored by RUSI and surface EMG, while the control group finished the same training plan without monitoring. Muscle thickness activation ratio and EMG characteristic were measured by RUSI and surface EMG and collected at 0, 4, and 8 weeks during long-term training.

2.2. Participants. The participants were recruited in Guangzhou, China, between August and December during 2017. The inclusion criteria were as follows: (1) male; (2) the age of 20–25 years old; (3) the willingness to complete a chosen training plan; and (4) the written informed consent of the participants. Participants were excluded if they have (1) the presence of the herniated lumbar disk or lumbar disk protrusion; (2) the presence of the vertebral fracture(s) or other conditions that needs surgery; (3) cardiovascular or systemic diseases or any condition which contraindicated or made the training impossible; (4) the presence of the psychiatric disorder which might affect the compliance and the evaluation of symptoms; (5) inflammatory, infectious or malignant diseases of the vertebra; and (6) the presence of severe neurological and structural deformity.

To ensure that all criteria were fulfilled, an experienced medical doctor would examine each participant. All participants were informed about the purpose and information of the study, including the randomization process. Before participating in the study, they also received a written informed consent, which was approved by the ethics committee of the authors' hospital. This study was qualified and registered in the Chinese Clinical Trial Registry as ChiCTR1800014609, where our data were collected and recorded. Besides, the study design meets the criteria of the latest version of the Declaration of Helsinki.

2.3. Procedures

2.3.1. Randomization. Using a computer-generated random numbers' table, an independent statistician performed all the random allocation of participants. The statistician was not aware of the eligibility of the participants and performed the randomization procedure following the baseline examination of all participants and then informed the participants via messages about group allocation. The randomization codes were stored in a sealed opaque envelope until the study ended.

2.3.2. Intervention. All participants were allocated randomly into the monitoring group and control group, while the control group received the same training without monitoring. All the intervention took place at our sport center.

The physical therapist demonstrated and explained a modified exercise plan based on a previous study [19] to all participants (Figure 1). The participants carried out the core stability exercise program for 45 min, three times a week for 2 months. At the first 4 weeks, the participants were asked to finish primary training, which is shown in Figures 1(a)–1(c), 1(e), and 1(g), and then, in the next four weeks, they should finish superior training shown in Figures 1(a), 1(b), 1(d), 1(f), and 1(h). All the participants were encouraged to finish training 10 repetitions 2 times a day. The program was divided into three categories: warm up, main part, and cool down. In the beginning of each exercise, the examiner determined the participant's lumbar neutral position and the participants were asked to hold this position during training. During training, several certified strength and conditioning coaches guided the participants of both groups to ensure that the training plan was properly executed considering its technique. The time spent on education was need based and varied within both groups and participants. Questions and discussions were encouraged.

During training, rehabilitative ultrasound image and surface EMG were used to provide real-time biofeedback to control the neuromuscular mechanism in the monitoring group while control group were not. In order to give real-time training feedback to participants and guarantee the correct training, four groups of muscles were monitored, including rectus abdominis, erector spinae, TrA, and MF. Monitoring was maintained throughout the whole training once the participants started exercise. When training, the activities of the rectus abdominis and erector spinae were not allowed to be more intense than those of the TrA and MF.

Through shaving, abrading, and cleansing with alcohol, the skin was carefully prepared to reduce skin impedance below 4 kΩ. Once the skin was dry, bipolar self-adhesive, pregelled Ag/AgCl surface electrodes were positioned at an interelectrode distance of 2 cm to the following locations.

Figure 1: Core stabilization exercise. (a) Train TrA muscle activation in a prone lying position without spinal and pelvic movements for 10 seconds. Keep respiration normal. You gently draw in the lower anterior abdominal wall below the navel level (abdominal drawing-in maneuver) with supplemented contraction of pelvic floor muscles, control your breathing normally, and have no movement of the spine and pelvis while lying prone on a couch with a small pillow placed beneath your ankles. (b) Train MF activation in an upright sitting position. You raise the contralateral arm while performing the abdominal drawing-in maneuver in a sitting position on a yoga ball. (c) Perform cocontraction of the two muscles in a crooked lying position with both hips at 45 degrees and both knees at 90 degrees. Then, you abduct one leg to 45 degrees of hip abduction and hold it for 10 seconds. (d) Train cocontraction of these muscles in a crooked lying position with both hips at 45 degrees and both knees at 90 degrees. Then, you slide a single leg down until the knee is straight, maintain it for 10-second holds, and then slide it back up to the starting position. (e) Perform cocontraction of the two muscles while raising the buttocks off a couch from a crooked lying position until your shoulders, hips, and knees are straight. You sustain this pose for 10 seconds and then lower the buttocks back down to the couch. (f) Train muscle cocontraction while raising the buttocks off a couch from a crooked lying position with one leg crossed over the supporting leg. You raise the buttocks off the couch until the shoulders, hips, and knees are straight. You sustain this pose for 10 seconds and then lower the buttocks back down to the couch. (g) Perform cocontraction while raising a single leg from a four-point kneeling position and keeping your back in a neutral position. You sustain this pose for 10 seconds and then return the leg to the starting position. (h) Train muscle cocontraction while raising an arm and alternate leg from a four-point kneeling position and keeping your back in a neutral position. You sustain this pose for 10 seconds and then return to the starting position. Black arrows show the contraction direction of core muscles.

The electrode placement for rectus abdominis was placed 2 cm lateral to the umbilicus. The TrA electrode was positioned 1.5 cm anterior to the midaxillary line, near the ultrasound site. The erector spinae electrode was set at 5 cm lateral to the L3 spinous process. The MF electrode was positioned 1 cm lateral to the L4 spinous process. All the

reference electrode placements were over the anterior superior iliac spine (ASIS). And, the RUSI monitoring sites of each muscle are as follows. The monitoring site of rectus abdominis was set at 3 cm lateral to the umbilicus. The monitoring site of TrA was positioned 2.5 cm anterior to the midaxillary line, at the midpoint between the inferior rib and the iliac crest. The monitoring site of erector spinae electrode was positioned 7 cm lateral to the L3 spinous process, while the monitoring site of MF electrode was positioned 2 cm lateral to the L4 spinous process.

2.3.3. Outcome Measures. All muscle thicknesses and EMG characteristics were carried out at 0, 4, and 8 weeks during study. The measurement positions of TrA and MF were the same as the monitoring sites.

Using B-mode ultrasound imaging (CHISON Q9, China) with transducers with a range of 5–8 MHz, muscle thickness was measured. Several studies have proved the high reliability of RUSI in measuring the thickness of trunk muscles [20, 21]. As core muscle thickness changes during expiration [22], recordings were made at the end of relaxed expiration during the measurements of TrA and MF thickness. The transducer was held perpendicular to the skin surface with a minimum pressure required to achieve a clear image. To improve acoustic coupling, a water-soluble transmission gel was placed over the scan head. The average thickness of three trials was calculated. Activation ratio = relax thickness/contraction thickness.

The EMG data was collected using the TeleMyo2400T (Noraxon, USA). The raw EMG signals were processed using MyoResearch software (Noraxon, USA) at a sampling frequency of 1500 Hz with band-pass filtering at 15–500 Hz for a noise reduction associated with electrical interference. EMG data were processed in MATLAB (MathWorks, Inc., Natick, MA, USA). Each muscle's EMG data were high-pass filtered (40 Hz, 4th order Butterworth), rectified, and low-pass filtered (40 Hz, 4th order Butterworth) to calculate the linear envelope describing muscle activation. All EMG data were measured for 3 s, discarding the first and last "s." The average IEMG value of the three trials was calculated.

2.4. Statistical Analysis. All data are recorded and displayed as mean ± standard deviation (SD). Statistical analysis was conducted using the SPSS 20.0 software (IBM, USA). All the outcome variables were analyzed on the intention-to-treat principle and examined by the normality test firstly. The demographic data were examined by descriptive statistics. Sphericity assumption was identified by the test, and the differences of all the variables in each group were compared using the ANOVA for repeated measures. If the interactive effect of time and group exists, the independent samples t-test between groups were carried out. We also performed the paired samples t-test to determine the differences in activation ratio and integrated EMG (IEMG) at 0, 4, and 8 weeks. The significance level was set at $p < 0.05$ for all of these tests.

3. Results

3.1. Sample Characteristics. 60 participants were recruited in this study, and each group consists of 30 participants. All participants are male. There is no significant difference between groups in age, height, weight, BMI, culture level, and daily amount of exercise (Table 1). This implies that the groups were similar before treatment and the changes observed following the procedure can be referred to the monitor effect on the muscles. All the data are available.

3.2. RUSI Data on Muscle Thickness Activation Ratio. All variables meet the normal distribution. Sphericity assumptions in both sides were identified by the test ($p = 0.424$ (left) and $p = 0.165$ (right) for TrA; $p = 0.660$ (left) and $p = 0.127$ (right) for MF), and the ANOVA for repeated measures can be used to perform the data analysis. The results show that the interaction between treatment effects and time effects was significant (for TrA, $F = 18.378$, $p \leq 0.001$ in left side and $F = 8.652$, $p \leq 0.001$ in right side; for MF, $F = 6.312$, $p = 0.002$ in left side and $F = 1.975$, $p = 0.143$ in right side). The independent t-test showed that both TrA and MF muscle thickness of the monitoring group is much greater than of the control group in 8 weeks, indicating that monitoring by RUSI and surface EMG was effective in core stability training.

Meanwhile, the paired t-test showed that both TrA and MF muscle thickness after 8 weeks' exercise were significantly greater than baseline ($p < 0.05$), indicating that the core stability training is effective in improving the thickness of the local core muscles (Tables 2 and 3; Figures 2(a) and 2(b)).

3.3. EMG Data on Muscle Activity. All variables meet the normal distribution. Sphericity assumptions in both sides were identified by the test ($p = 0.698$ (left) and $p = 0.942$ (right) for TrA; $p = 0.106$ (left) and $p = 0.516$ (right) for MF), and the ANOVA for repeated measures can be used to perform the data analysis. The results show that the interaction between treatment effects and time effects was significant (for TrA, $F = 10.876$, $p \leq 0.001$ in left side and $F = 3.986$, $p = 0.021$ in right side; for MF, $F = 13.243$, $p = 0.005$ in left side and $F = 9.205$, $p \leq 0.001$ in right side). The independent t-test showed that the change of activation of TrA and MF in the monitoring group is greater than that in the control group.

Meanwhile, the mean EMG amplitudes of the TrA and MF were significantly increased after intervention, which shows that deep core muscle activation was effectively promoted following the core stability training (Tables 4 and 5; Figures 2(c) and 2(d)).

4. Discussion

Nowadays, an increasing number of pain rehabilitation strategy has been demonstrated effective to treat low back pain (LBP), but the results are always barely satisfactory [23, 24]. It was reported that muscle force imbalance may lead to kinetic instability of the spine, while the weakness of MF and TrA contributes notably to the development of LBP.

Table 1: Demographic characteristics data of participants (mean ± SD).

	Monitoring group	Control group	p value
Age (y)	22.33 ± 1.47	22.30 ± 1.56	0.932
Height (m)	1.73 ± 0.08	1.71 ± 0.07	0.595
Weight (kg)	63.87 ± 8.18	62.77 ± 7.78	0.344
BMI (kg/m^2)	21.30 ± 2.17	21.37 ± 1.71	0.901

Table 2: Comparison of the muscle thickness activation ratio of TrA between the monitoring group and control group in 0, 4, and 8 weeks (mean ± SD).

		Monitoring group	Control group	Between-group p value
Left	Baseline	1.44 ± 0.05	1.42 ± 0.05	0.251
	4 weeks	1.60 ± 0.03*	1.50 ± 0.07*	≤0.001
	8 weeks	1.67 ± 0.05*	1.56 ± 0.04*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.970$ ($p = 0.424$)				
Right	Baseline	1.45 ± 0.07	1.44 ± 0.07	0.552
	4 weeks	1.60 ± 0.04*	1.55 ± 0.04*	≤0.001
	8 weeks	1.67 ± 0.06*	1.58 ± 0.06*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.939$ ($p = 0.165$)				

Activation ratio = contraction thickness/relax thickness. *Compared with baseline, $p < 0.05$.

Table 3: Comparison of the muscle thickness activation ratio of MF between the monitoring group and control group in 0, 4, and 8 weeks (mean ± SD).

		Monitoring group	Control group	Between-group p value
Left	Baseline	1.23 ± 0.04	1.25 ± 0.03	0.328
	4 weeks	1.33 ± 0.04*	1.30 ± 0.04*	0.013
	8 weeks	1.41 ± 0.05*	1.37 ± 0.05*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.986$ ($p = 0.660$)				
Right	Baseline	1.25 ± 0.05	1.23 ± 0.05	0.117
	4 weeks	1.33 ± 0.05*	1.32 ± 0.04*	0.645
	8 weeks	1.41 ± 0.05*	1.37 ± 0.05*	0.002
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.930$ ($p = 0.127$)				

Activation ratio = contraction thickness/relax thickness. *Compared with baseline, $p < 0.05$.

Moreover, our previous study has shown that decreased cross-sectional area (CSA) of MF is correlated with chronic LBP. Here, we preliminarily verified the effectiveness of core stability training on the restoration of TrA and MF activation and strength. This training targeting local core muscles might be an alternative strategy for LBP management.

The activation ratio formula, which divides muscle thickness in a contraction state by muscle thickness at rest, has shown to be a more reliable method of using the thickness measures by RUSI [25, 26] as a function of activation for TrA and MF. By normalizing the size during a contracted state to the resting size, clinicians can determine the ability to activate the TrA and MF. However, this formula does not take into account the ability to isolate the TrA or MF without evoking a contraction of the superficial core muscles wall. Fortunately, the use of surface EMG can cover the shortage of RUSI. It was reported that the integrated EMG value determined by surface EMG showed positive correlation with muscle force and muscular tension [14], but the condition of deeper muscles may play roles in evaluating surface EMG signal of superficial core muscles during training, which means it is necessary for RUSI to avoid weakness of surface EMG. To sum up, the chance of error decreases when RUSI and EMG monitoring are applied simultaneously.

Compared with the control group, the monitoring group demonstrated better performance during training as expected. Effective core stability training which targeted specific core muscles can increase the number of contraction units and strengthen muscle force [27, 28], which is shown as the characteristic parameters of muscle thickness by ultrasound imaging and surface electromyography. The key of

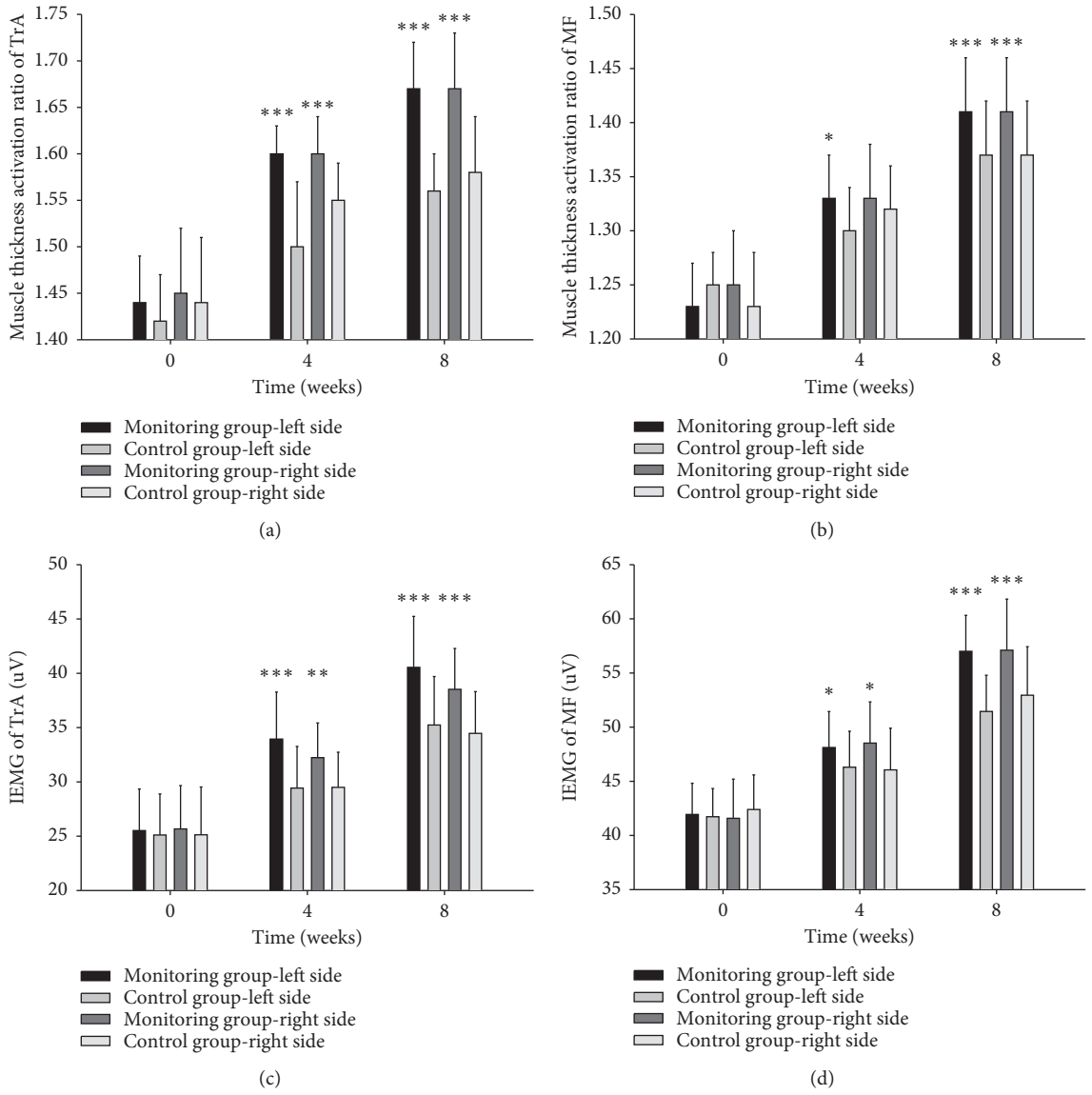

Figure 2: Comparison of the effect on local core muscles between the monitoring group and control group in 0, 4, and 8 weeks. (a) Comparison of the muscle thickness activation ratio of TrA between the monitoring group and control group in 0, 4, and 8 weeks. Activation ratio = contraction thickness/relax thickness. (b) Comparison of the muscle thickness activation ratio of MF between the monitoring group and control group in 0, 4, and 8 weeks. Activation ratio = contraction thickness/relax thickness. (c) Comparison of the IEMG of TrA between the monitoring group and control group in 0, 4, and 8 weeks. (d) Comparison of the IEMG of MF between the monitoring group and control group in 0, 4, and 8 weeks Values are means ± s.e.m. p values were calculated by the two-tailed Student's t-test. $^{***}p$ value < 0.001; $^{**}p$ value < 0.01; $^{*}p$ value < 0.05.

specific training is to ensure the target muscle contracts in normal patterns. The effectiveness of core stability training depends on the contraction sequence and relax patterns [11, 29]. Compensation activity during the process of training will affect the effectiveness of the training. During training targeting local core muscles, the activities of rectus abdominis and erector spinae were not allowed. Thus, the monitoring of these muscles was used to provide real-time training feedback to participants and guarantee the correct training. Based on this research, TrA and MF in both sides showed higher activation ratio and IEMG values than the control group without monitoring during training, while the global core muscles have no change (data not shown). We found that participants benefited greatly from the core stability training monitored by RUSI and surface EMG and reduced compensatory motion. Moreover, our findings taken together with previous studies corroborate the fact that specific monitoring training facilitating selective control of the TrA and MF independently of the other abdominal and back muscles, which can be monitored by RUSI and surface EMG, can be more beneficial for core stability than global, whole-body exercise programs.

In the beginning of this study, obvious compensatory action appears in surface EMG (data not shown) and the thickness of erector spinae or rectus abdominis increased significantly in RUSI. After long-term monitoring training,

Table 4: Comparison of the IEMG of TrA between the monitoring group and control group in 0, 4, and 8 weeks (uV, mean ± SD).

		Monitoring group	Control group	Between-group p value
Left	Baseline	25.52 ± 3.82	25.11 ± 3.78	0.680
	4 weeks	33.94 ± 4.33*	29.43 ± 3.83*	≤0.001
	8 weeks	40.55 ± 4.69*	35.24 ± 4.46*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.987$ ($p = 0.698$)				
Right	Baseline	25.67 ± 3.99	25.13 ± 4.40	0.617
	4 weeks	32.23 ± 3.19*	29.50 ± 3.23*	0.002
	8 weeks	38.52 ± 3.76*	34.47 ± 3.84*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.998$ ($p = 0.942$)				

*Compared with baseline, $p < 0.05$.

Table 5: Comparison of the IEMG of MF between the monitoring group and control group in 0, 4, and 8 weeks (uV, mean ± SD).

		Monitoring group	Control group	Between-group p value
Left	Baseline	41.94 ± 2.88	41.73 ± 2.60	0.769
	4 weeks	48.12 ± 3.32*	46.30 ± 3.32*	0.038
	8 weeks	57.00 ± 3.32*	51.45 ± 3.34*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.924$ ($p = 0.106$)				
Right	Baseline	41.58 ± 3.62	42.40 ± 3.19	0.355
	4 weeks	48.53 ± 3.80*	46.05 ± 3.85*	0.015
	8 weeks	57.10 ± 4.72*	52.95 ± 4.48*	≤0.001
Intragroup p value (baseline vs 8 weeks)		≤0.001	≤0.001	
Mauchly's sphericity test $W = 0.977$ ($p = 0.516$)				

*Compared with baseline, $p < 0.05$.

these activities vanished gradually in the same participant, and this phenomenon matched the improvement of IEMG of target muscles. In brief, through real-time monitoring during training, the generation of compensatory actions can be prevented. Besides, the training intensity and exercise time can be guaranteed to meet the training objectives strictly according to the rehabilitation plan.

This study examined the effect of core stability training on the change in muscle thickness and activation ratio in healthy individuals. Other issues to be considered in future research could be the type and timing of the core stability training on local core muscles of individuals with LBP. Whether the effect on healthy individuals is similar to that in patients is still need to be found out.

Together, this study is an important empirical evidence which investigates the intensive effects of core stability training monitored by RUSI and surface EMG on local core muscles of healthy people. The training monitored by RUSI and surface EMG can markedly enhance TrA and MF thickness activation ratio and IEMG in healthy human, providing an effective method of core stability training for LBP patients.

Data Availability

This study was qualified and registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn) by the authors, and all the data used to support the findings of this study, including RUSI muscle thickness and surface EMG characteristic, have been deposited in the Clinical Trial Management Public Platform (http://www.medresman.org) as ChiCTR1800014609.

Conflicts of Interest

All received funding did not lead to any conflicts of interest regarding the publication of this manuscript.

Authors' Contributions

Yaochao Zheng and Songjian Ke contributed equally to this work.

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Research Article

The Relationship between Infant Colic and Migraine as well as Tension-Type Headache: A Meta-Analysis

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Background. Infant colic is a common benign disease during early infancy. Migraine and tension-type headache (TTH) are the most common primary headache forms among pediatric population. Several studies have investigated the incidence of infant colic in patients with migraine and TTH. The meta-analysis was to assess the relationship between infant colic and migraine as well as TTH. *Methods*. PubMed, Web of Science, and Cochrane Library were searched until August 16, 2018, for potential studies. Data were extracted by two independent authors and analyzed using RevMan 5.2 software. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the association between infant colic and migraine as well as TTH, respectively. *Results*. A total of 148 studies were found, and 7 studies were finally included. A higher incidence of colic during infancy was revealed in migraine patients than controls ($P = 0.05$, OR: 2.51, 95% CI: 1.32–4.77) and TTH subjects ($P = 0.02$, OR: 0.33, 95% CI: 0.13–0.86), respectively. And no significances were found between TTHs with controls ($P = 0.51$, OR: 1.17, 95% CI: 0.73–1.89). *Conclusion*. This meta-analysis indicated that migraine was associated with increased incidence of infantile colic history, but TTH incidence was not relevant with the incidence of infantile colic history.

1. Introduction

Infantile colic is a benign disease during the first months of life and is also one of the most distressing challenges for parents [1]. It is estimated that it affects 10% to 40% of the normal infant population in the world. An infant with this disorder has paroxysms of inconsolable crying for more than 3 hours every day, more than 3 days every week, and longer than 3 weeks [2]. Boys and girls may have equal chances to develop infant colic, and no correlation has been identified with respect to feeding methods, gestational age, and socioeconomic conditions of their families [3]. The pathogenesis of this disease has not been well established [4]. Fecal microflora, gastrointestinal immaturity, and serotonin activity may be responsible for it [2, 5]. It is believed that these infants are sensitive to the environment, and they may present crying to the stimuli.

Headache is a symptom in children and adolescents that usually works as cause for a pediatric clinic consultation [6]. Migraine and tension-type headache (TTH) are the most common primary headache forms among pediatric population, although other primary headache disorders could also be encountered, including cluster headache, paroxysmal hemicranias, and trigeminal autonomic cephalalgia [7]. Migraine is a highly prevalent cause of disability worldwide. It is characterized by recurrent episodes of headache attacks with symptoms, including visual changes and other performances [8]. TTH is also a common disabling condition, with a wide prevalence range from 1.3% to 65% in men and 2.7% to 86% in women [9]. It presents a form of frequent mild to moderate headache, but not associated with migraine symptoms of nausea, vomiting, photophobia, and phonophobia.

A child with headache symptoms also presents a sensitive state to external changes around him or her, like one with infant colic. Then, it is speculated whether the two have some connections. Several studies have investigated the association between infantile colic and migraine as well as TTH [10, 11]. Patients with migraine are likely to have a medical history of infant colic, and an infant with colic tends

to have parents with migraine [12, 13]. And infant colic is considered to be early expression of migraine [14]. TTH and migraine exhibit similar pathogenic mechanisms, resulting from the dysfunction of nociceptive pain processing [15]. Then, TTH may also be associated with infant colic. But few studies could be found assessing that between infant colic and TTH. Here, we aimed to investigate the association between infantile colic and migraine, and the relationship between infantile colic and TTH was also studied.

2. Materials and Methods

2.1. Search Strategy. The meta-analysis was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. As this was a meta-analysis, no patient consent was needed for this study. A systematic literature search was done in PubMed, Web of Science, Cochrane Library, and EMBASE until April 5, 2018, to detect the studies assessing the relationship between infantile colic and migraine as well as TTH. The search terms used to retrieve relevant publications included the following in various combinations: "pediatric OR child OR children OR infant OR infantile" and "migraine OR headache OR tension-type headache." No publication language and study-type restriction were put on this process.

2.2. Inclusion Criteria. Studies fulfilling the following requirements were included: (1) a diagnosis of colic within 3 months old, (2) clinical articles, and (3) full record of the incidence of infant colic in migraine or detailed information could be retrieved through contacting the authors. The diagnosis of migraine and TTH were defined according to the criteria of the International Classification of Headache Disorders III; (ICHD III;) [17]. Wessel criteria [18] were used for infant colic as more than 3 hours per day crying, more than 3 days a week, and more than 3 weeks during infancy. Details of diagnostic characteristics of migraine, TTH, and infant colic could be found in Supplementary Table 1.

2.3. Data Collection. Data were manually extracted from each report by two independent authors, and any disagreement was determined by the senior author (the corresponding author). Data were collected, including authors, publication year, publication type, study period, age, no. of patients and controls, and incidence of infant colic in control, migraine, and TTH.

2.4. Quality Assessment. The quality of included studies was analyzed using the Newcastle–Ottawa quality assessment scale (NOS) [19], including representativeness of cases, selection of the nonexposed cases, ascertainment of exposure, demonstration of not presenting the outcome of interest at the start of the study, comparability of the analysis, assessment of outcomes, duration of follow-up, and lost to follow-up. The item with highest quality in NOS was awarded with a maximum of one star with the exception of the item related to comparability rated with two stars. Then, the total score of each study ranged between 0 and 9 stars. Studies with 6 stars or more were considered with relatively high quality.

2.5. Statistical Analysis. Statistical analysis was done using RevMan 5.3 software package (the Cochrane Collaboration, Copenhagen, Denmark). Dichotomous outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity among studies was analyzed using I^2 test methods, with $I^2 \geq 50\%$ or $P < 0.05$ as an indicator of a high level of heterogeneity. Fixed effects ($I^2 < 50\%$) and random effects ($I^2 \geq 50\%$) models were selected according to the level of heterogeneity among the trials. The significance level was set at $P < 0.05$. Publication bias was detected when there were more than 10 studies in the comparisons, by observing the funnel plots.

3. Results

3.1. Search Results and Study Characteristics. The flow diagram of the study is shown in Figure 1. The initial search retrieved 349 records from PubMed, Web of Science, Cochrane Library, and EMBASE. Then, 114 duplicates were removed. Further assessment of titles and abstracts identified 29 papers. Full-text assessment further excluded 7 articles. The final inclusion then confirmed 7 articles in the study [10–12, 20–23]. The baseline characteristics of them are displayed in Table 1. They were published between 1997 and 2017, involving 7 countries: Italy, Saudi Arabia, USA, France, Spain, Finland, and Iran. One study was an international study based on people in France and Italy [10]. All of them were published in English language. Two studies included adult patients [21, 22], and 5 trials enrolled pediatric population [10–12, 20, 23]. Only one study did not indicate age of the included studies [11]. The diagnosis of infant colic was made based on medical history provided by parents in 4 trials [10, 11, 20, 23], two studies confirmed infant colic through follow-up visiting and diagnosis by physicians [22, 24], and one study got the record from examinee questionnaire [21]. All the studies compared the occurrence of colic in migraine and control groups, and 2 trials of them also recorded that in TTH patients [10, 11]. A total of 3174 subjects were enrolled, of which 606 were migraine sufferers, 239 were TTH patients, and 2329 were controls. The results of quality assessment are also shown in Table 1.

3.2. Outcomes. The outcomes in this study are depicted in Table 2. A higher incidence of colic during infancy was found in migraine patients than controls ($P = 0.005$, OR: 2.51, 95% CI: 1.32–4.77), with high heterogeneity ($I^2 = 86\%$; Figure 2). However, no significance was found when comparing TTH patients with controls ($P = 0.51$, $I^2 = 59\%$, OR: 1.17, 95% CI: 0.73–1.89; Figure 3). We also analyzed the infantile colic incidence between migraine and TTH subjects, and a higher incidence was also seen in migraineurs ($P = 0.02$, $I^2 = 86\%$, OR: 0.33, 95% CI: 0.13–0.86; Figure 4).

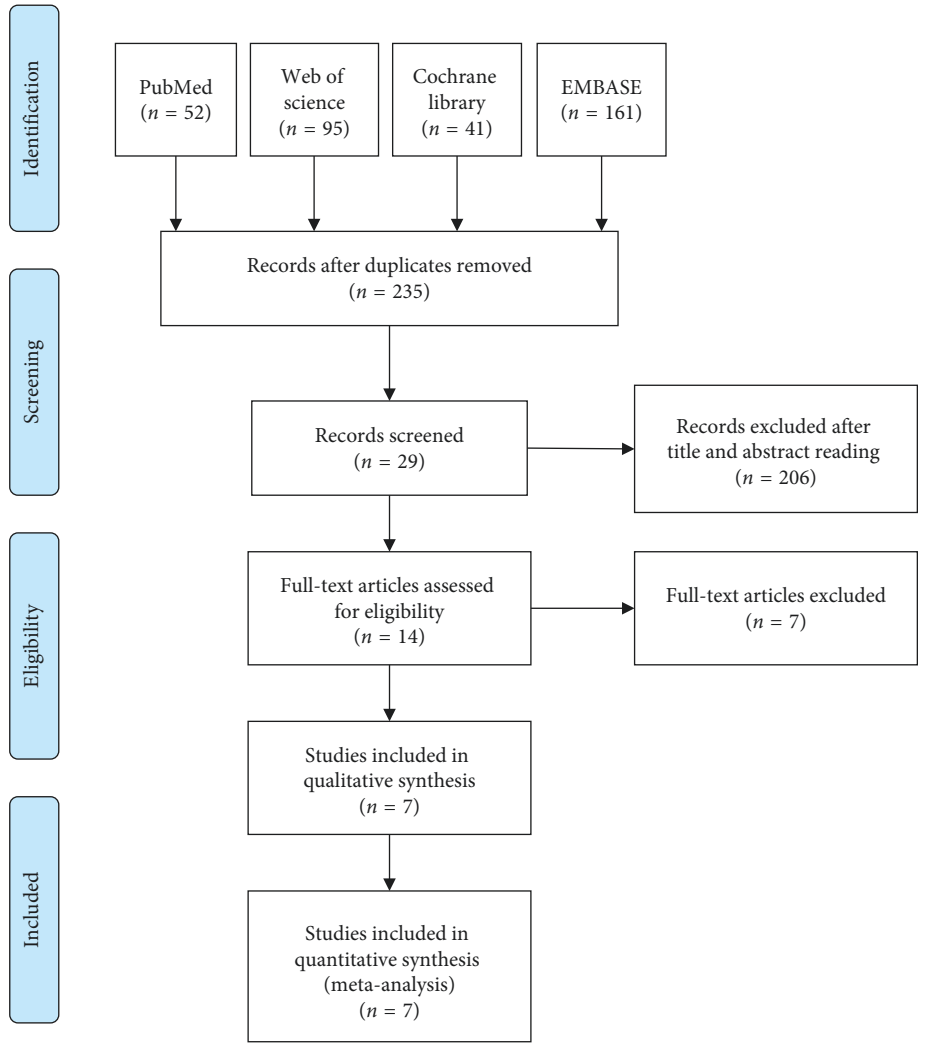

Figure 1: The flow diagram of the meta-analysis.

Table 1: The baseline characteristics of the included studies.

Study	Bruni et al. [11]	Jan and Al-Buhairi [20]	Gelfand et al. [12]	Romanello et al. [10]	Marugán-Miguelsanz et al. [21]	Sillanpaa and Saarinen [22]	Tabrizi et al. [23]
Age	NA	7–12 y	2–12 w	6–18 y	18–45 y	18 y	5–15 y
Type	Prospective	Prospective	Retrospective	Prospective	Retrospective	RCT	Retrospective
Period	1994.09–1995.09	1998.08–1998.12	2010.07–2011.09	2012.04–2012.06	NA	NA	2015–2016
Region	Italy	Saudi Arabia	USA	France and Italy	Spain	Finland	Iran
No.	NA	NA	NA	NA	NA	NA	NA
Con.	893	29	126	471	29	658	123
Migraine	164	29	28	208	7	129	41
TTH	119	NA	NA	120	NA	NA	NA
Colic	NA	NA	NA	NA	NA	NA	NA
Con.	240	6	14	125	9	74	44
Migraine	63	15	8	151	3	22	17
TTH	30	NA	NA	42	NA	NA	NA
Diagnosis of infant colic	Medical history from parents	Medical history from parents	Follow-up visiting	Medical history from parents	Medical history from patients	Follow-up visiting	Medical history from patients
Study quality	6	7	8	7	6	8	6

NA: not applicable, y: year, w: week.

Table 2: Meta-analysis results of the included studies.

Outcome	No. of studies	P	OR [95% CI]	Heterogeneity			
				χ^2	df	I^2 (%)	P-Q test
Colic in migraine	7	0.005	2.51 [1.32, 4.77]	44.14	6	86	<0.00001
Colic in TTH	2	0.51	1.17 [0.73, 1.89]	2.41	1	59	0.12
Migraine vs. TTH	2	0.02	0.33 [0.13, 0.86]	7.29	1	86	0.007

OR: odds ratio.

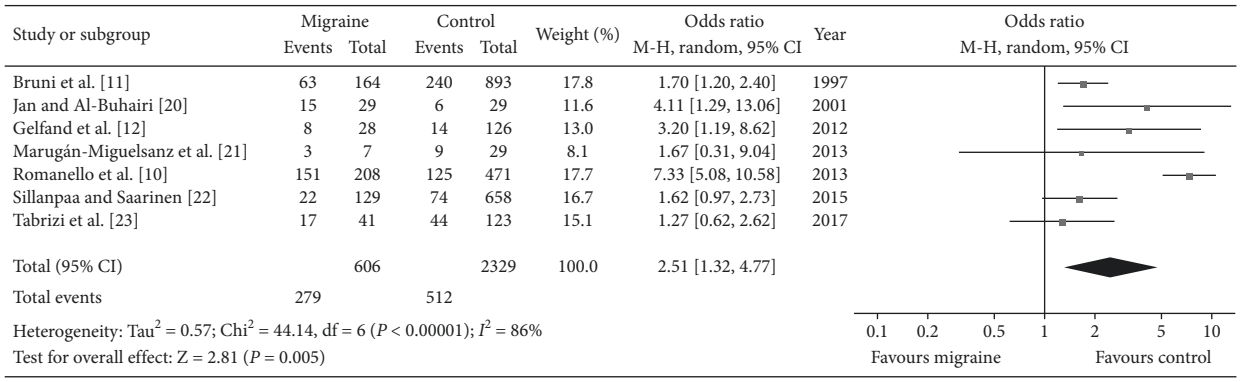

Figure 2: Forest plot of the incidence of infant colic between migraineurs and controls.

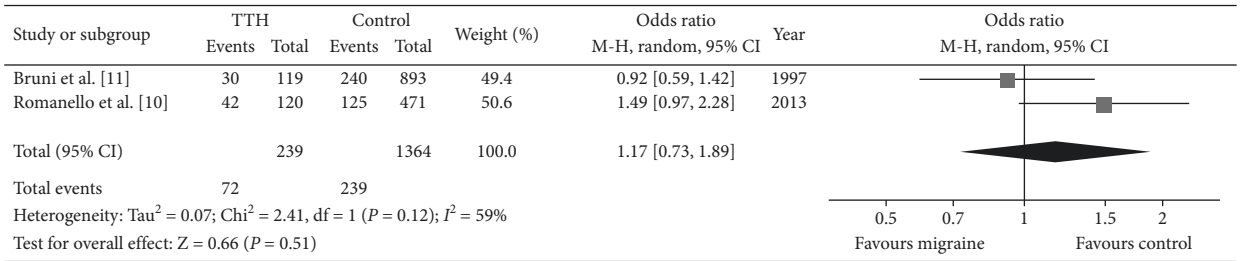

Figure 3: Forest plot of the incidence of infant colic between TTHs and controls. TTH, tension-type headache.

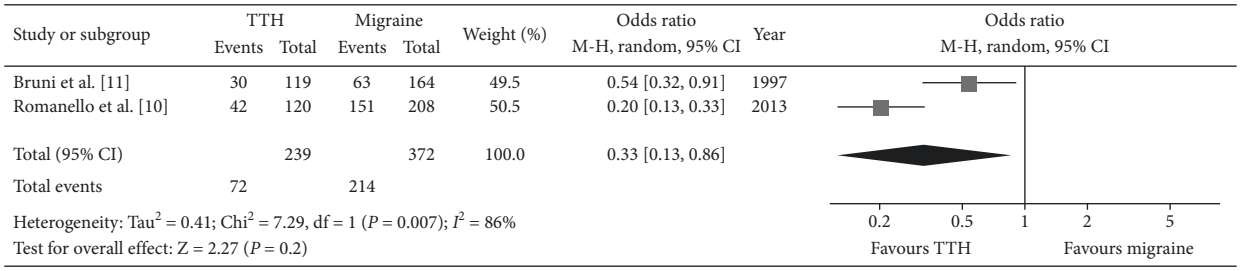

Figure 4: Forest plot of the incidence of infant colic between migraineurs and TTHs. TTH, tension-type headache.

When analyzing data from pediatric population, the results and heterogeneity did not change the trends ($P = 0.01$, $I^2 = 90\%$, OR: 2.89, 95% CI: 1.28–6.50; Table 3). But a mere significance existed in adult population ($P = 0.05$, OR: 1.63, 95% CI: 0.99–2.67), with a marked change of heterogeneity from 86% to 0%. Also, since the diagnosis of infantile colic was quite different among the studies, we assessed the pooling data based on them. Medical history was derived from parents in 4 studies, and the trend of results did not change ($P < 0.0001$, $I^2 = 92\%$; Table 3). Infant colic was defined during follow-up visits in 2 studies, and the pooling data also showed the same trend with the overall outcome with a robust change of heterogeneity ($I^2 = 29\%$). One study with medical history from patients indicated comparable results between migraine and control groups ($P = 0.55$).

3.3. Publication Bias Analysis. Since there were less than 10 studies in the comparisons, an accurate publication bias analysis cannot be performed.

Table 3: Meta-analysis based on age and diagnosis of colic.

Outcome	No. of studies	P	OR [95% CI]	Heterogeneity			
				χ^2	df	I^2 (%)	P-Q test
Age							
Adult	2	0.05	1.63 [0.99, 2.67]	0	1	0	0.98
Children	5	0.01	2.89 [1.28, 6.50]	38.77	4	90	<0.00001
Diagnosis of colic							
Medical history from parents	4	<0.00001	3.15 [2.52, 3.93]	38.77	3	92	<0.00001
Follow-up visting	2	0.03	1.99 [1.08, 3.66]	1.42	1	29	0.23
Medical history from patients	1	0.55	1.67 [0.31, 9.04]	NA	NA	NA	NA

OR: odds ratio and NA: not applicable.

4. Discussion

This meta-analysis evaluated the association between infantile colic and migraine as well as TTH. It indicated that migraine was associated with increased incidence of infantile colic history. But TTH was not relevant to colic incidence during infancy.

Headache is a widely suffering symptom in children and adolescent which leads to pediatric consultations in the hospital [25]. There are many types of headache among the population. Migraine and TTH are more commonly encountered, and other primary headache disorders are quite rare to be seen [7, 26]. Migraine is a common and chronic disorder with multilevel factors in the neurovascular structure accounting for its recurrent headaches. It comes along with TTH, as the most common paroxysmal diseases during childhood. Although the two have similar headache characteristics in some aspects, they have different performances in neuroimaging studies and have various responses to treatment strategies.

Infant colic was first described in 1954. The term "colic" implies an abdominal etiology with little direct localization evidence. An association between infant colic and migraine has been established in several studies [27–29]. Our study assessed the associations between infant colic and migraine as well as TTH. And we did not find any studies collecting information on other forms of headache. All the studies were with quite high quality, ensuring the credibility of the results. Infant colic may have common pathological and physiological changes with these two headache syndromes.

Seven studies indicated a higher incidence of infant colic in migraine patients, which is consistent with the previous trials. Bruni et al. [11] and Jan and Al-Buhairi [20] found a significant higher colic during infancy in migraineurs. But a high heterogeneity was found in the outcome. We tried to find the source of it. It seemed that age may be a source of the heterogeneity. There was a robust change of heterogeneity in the respective analysis of adult and pediatric subjects. Although similarities do exist in the symptoms and treatment for migraine between adults and children, some differences still can be found between them. Psychological treatment is more effective for children than adults, indicating the high proportion of psychological factors in children migraine [30]. Also the different ways to define the diagnosis of infant colic were also responsible for it. Wessel criteria [18] were used to define the disease. However, only subjects in two studies received the diagnosis through periodic follow-up visiting with the doctors. Other studies collected the history of infant colic through questionnaire or medical history from the parents or the patients themselves. Apparently, the process was done based on the memories of the examinees. This might not be so reliable for long-term memory. The respective analysis of groups based on the ways to make the diagnosis indicated the similar results in 4 studies with medical history from parents and 2 studies from follow-up visiting. But the high heterogeneity disappeared in the latter comparison. Also, no significances were found in the comparison based on medical history from patients. A correlation between colic and sleep disorders has been suggested. Infants with colic usually exhibit their crying and other behaviors during sleep. Migraine patients also have a bad sleep status [31]. Children with migraine are more likely to have colic during infancy, and parents with migraine are more likely to have a baby with colic [12, 20]. It is believed that infants with migraine genetics may be more sensitive to environments than healthy ones [32, 33].

TTH is also a common type of headache among children [6]. But the incidences of infant colic were quite comparable between patients and controls, which indicated no link between the two diseases and the different etiology from migraine. But only two studies investigated the records, encouraging further efforts on these subjects.

There is still no consensus concerning the treatment of infant colic. Increasing attention has been paid to the effects of dietary, pharmacological drugs, and behavioral strategies. Breastfeeding and bottle-feeding infants may have distinguished dietary options: (1) a monitored low allergen maternal diet without cow milk, containing vitamins and minerals, may be appropriate for the former ones and (2) a formula based on casein hydrolysate is recommended for the latter infants. Although simethicone is suggested for infants for its effects on reducing gas production, limited evidences can be provided. The application of probiotics is supported by the idea that the medication can alleviate gut dysfunction caused by abnormal intestinal microflora, then reducing gas production and colic symptoms. Many other therapeutic approaches targeting infant colic can be found from literature search. But the lack of high quality and objective outcome assessing method makes it difficult to get a conclusive guideline for this disorder.

4.1. Study Quality. There were also some limitations in this study. First, the number of the included studies was quite limited, limiting the evidence level of this meta-analysis. Second, the definitions of colic in infancy in each study were not so consistent. This might cause the high heterogeneity of the pooling results. Also, no potential mechanisms of infant colic in migraine were assessed in these studies. Further investigation on this field should be done.

5. Conclusion

In conclusion, migraine was associated with increased incidence of infantile colic history. TTH was not relevant to colic incidence during infancy. However, large trials, containing more participants, should be included in the future.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary Table 1: the diagnostic criteria of migraine, tension-type headache, and infant colic. ICHD, the International Classification of Headache Disorders. (*Supplementary Materials*)

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Research Article

Cognitive Decline in Chronic Migraine with Nonsteroid Anti-inflammation Drug Overuse: A Cross-Sectional Study

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Background. Chronic migraine with medication overuse headache (CM-MOH) is the most common type of chronic migraine, and it increases risk of stroke and white matter lesions. These pathologic changes could induce cognitive decline. However, the alteration of cognitive function in CM-MOH patients is not established. Therefore, we took this study to reveal the cognitive performances in CM-MOH. *Methods*. This cross-sectional study was conducted between December 2015 and January 2017. Patients were divided into CM-MOH, CMwoMOH (chronic migraine without medication overuse), and MO (migraine without aura) groups. Cognitive function was assessed in all cases during interictal periods using Addenbrooke's Cognitive Examination Test (ACE-R), Trail Making Test A/B (TMT A/B), and Digit Symbol Test (DST). Detailed headache characteristics and evaluation of anxiety, depression, and living and sleep quality were collected. *Results*. 116 patients were included in this study. There were 21 CM-MOHs, 20 CMwoMOHs, 35 MOs, and 40 controls. Age and education were the independent risk factors of cognitive decline ($P < 0.05$). After adjusting, the risk of cognitive decline was higher in CM compared with control in ACE-R score and language fluency ($P < 0.05$). In addition, CM-MOH sufferers were in higher risk of memory and executive dysfunction ($P < 0.05$). The cognitive function had no difference between CM-MOH and CMwoMOH ($P > 0.05$). Meanwhile, CM-MOH got significantly higher scores than MO in anxiety and depression, with poorer performances in sleep and life quality ($P < 0.05$). *Conclusion*. The risk of cognitive decline increased in chronic migraine patients. Nonsteroid anti-inflammatory drugs overuse had no influence on cognitive performances among chronic migraine sufferers.

1. Introduction

Chronic migraine (CM) is a kind of repeated headache disorder, with a high disability rate among the population [1, 2]. This disorder is manifested as suffering of headache for more than 15 days per month, with no less than 8 days of migraine-like episodes. Also, these symptoms continue for at least 3 months [3]. Taking analgesic or triptans during acute attack of migraine is the most important factor for CM induction [4]. It is believed that chronic migraine with medication overuse headache (CM-MOH) is the most common type of this disease [5, 6]. It is usually accompanied by anxiety, depression, sleep disorder, and so on, leading to serious impact on living quality [7].

Repeated migraine episodes can increase the risk of cerebrovascular diseases, such as stroke and increasing white matter lesion [8–11]. These pathologies were known to be responsible for cognitive decline in migraineurs. So far, it has been demonstrated that these sufferers usually exhibit cognitive decline during acute attacks, including the deficit

of executive function, language, visuospatial ability, and complex tasks [12, 13]. These might be attributed to the reduction of intracranial blood perfusion and the related changes during episodes. However, the cognitive performances recovered in the interictal periods, suggesting the reversibility of cognition among them [14]. In the chronification process, the alteration of cognitive performances is still not demonstrated.

CM-MOH is the most common form of chronic migraine and is usually accompanied with increased clinically silent lesions [15, 16]. Therefore, whether there was irreversible cognitive decline in CM-MOH patients during interictal periods remains to be revealed. This will help evaluate the cerebrovascular risk of CM-MOH patients, as well as provide guidance for clinical prevention and treatment.

2. Methods

2.1. Participants. This cross-sectional study was conducted between December 2015 and January 2017. Patients were recruited from the neurology outpatient clinic, the First Affiliated Hospital of Sun Yat-sen University. They were divided into three groups according to the criteria of the 3rd edition beta version of International Classification of Headache Disorders (ICHD-III beta) [17], including chronic migraine with medication overuse headache (CM-MOH), chronic migraine without medication overuse headache (CMwoMOH), and migraine without aura (MO) groups. A total of 116 cases participated in this study. There were 21 CM-MOHs, 20 CMwoMOHs, 35 MOs, and 40 controls. The included criteria were as follows: (a) diagnosis of episode migraine, CM with and without MOH based on the criteria of ICHD-III beta; (b) headache duration ≥ 1 year; (c) aged between 25 and 65; (d) confirmation of nonstructural lesions according to brain CT/MRI, in the interictal periods of migraine. The excluded criteria were as follows: (a) headache secondary to trauma, intracranial inflammation, brain tumor, and other neurological diseases; (b) existence of cerebrovascular disorders, neoplastic diseases, infectious diseases, rheumatic diseases, or connective tissue diseases; (c) unable to cooperate with the survey because of cognitive impairment or psychiatric disease. 40 controls were from the individuals who attended the hospital to consult for nonspecific complaints. Controls did not suffer from headaches or any other diseases and their neurologic examinations were normal. This study was approved by the Ethics Committee of the First Affiliated Hospital, Sun Yat-Sen University. All the subjects were required to sign informed consents prior to participation.

2.2. Basic Information. We collected demographical data of all participants at the first visit, including age, sex, education, job, weight, height, relevant medical history, and family history. A detailed questionnaire was used to record their headache characteristics, including headache years, location, headache nature, headache duration, comprised symptoms, headache frequency, monthly headache days, and monthly headache attacks. Analgesics used to control headache and their doses were recorded. For CM-MOH patients, monthly analgesic pills doses were calculated.

2.3. Neuropsychology Assessment. Several scales evaluating life quality and psychiatric status were conducted in patients. The Migraine Disability Assessment Test (MIDAS) was used to assess the headache frequency in three months and how often it limited their participation in daily activities. The Hamilton Anxiety Scale and Hamilton Depression Scale were used to display their mood state. The Short Form (36) Health Survey (SF-36) was used to evaluate the participants' health statement. Results of SF-36 were divided into eight sections, including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality of participants.

2.4. Cognitive Evaluation. Addenbrooke's Cognitive Examination (ACE-R) is a set of tests for cognitive dysfunction screening. With a total score of 100 points, it is composed of five elements, including attention/orientation (18 points), memory (26 points), verbal fluency (14 points), language (26 points), and visuospatial abilities (16 points) [18]. It was wildly applied for the cognitive assessment of different diseases, such as Alzheimer's disease, Parkinson's disease, and vascular dementia. Meanwhile, it could detect mild cognitive dysfunction, with high sensitivity and specificity. Trail Making Test A + B (TMT A + B) and Digit Symbol Test (DST) are effective ways to examine the executive function. Therefore, we used a battery of screening test which included these three scales to clarify the cognitive function of CM-MOH sufferers.

To reduce the likelihood of fatigue in participants, after collecting basic information, we performed the cognitive evaluation at the sequence of ACE-R, TMT A + B, and DST, followed by neuropsychology assessment.

2.5. Statistical Analysis. All statistical analysis was performed on IBM SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables such as sex, education, smoking history, and alcohol history were presented with frequency. Continuous variables followed the normal distribution and were presented with mean $\pm$ standard deviation; otherwise, presented with median (interquartile range). One-way analysis of variance (ANOVA), Kruskal–Wallis test, and chi-squared tests were used to evaluate the differences among groups, respectively. For the pairwise comparison between groups, the Tukey–Kramer test after ANOVA and Mann–Whitney test after Kruskal–Wallis test were performed, following with Bonferroni correction of the p values. Binary logistic regression models were used to evaluate the risk factors of cognitive decline after filtering of the independent variable under univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were

calculated. A two-tailed P value < 0.05 was considered as statistically significant.

3. Result

3.1. Baseline Information. In this study, there were 116 participants, including 21 in CM-MOH, 20 in CMwoMOH, 35 in MO, and 40 in control. The baseline characteristics are shown in Table 1. There were no significant differences in age, sex, education, hypertension, diabetes, high low-density lipoproteinemia, smoke history, alcohol history, and family history among groups ($P > 0.05$).

All the cases in our study took NSAIDs, such as aminopyrine, phenacetin, aspirin, ibuprofen, and acetaminophen, to relieve headache. Most of them were compound preparation. The VAS score, drug dosages, and frequency were higher in CM-MOH, compared with CMwoMOH and MO, respectively ($P < 0.05$). The headache duration and family history had no significant difference among groups ($P < 0.05$) (Table 2).

3.2. Neuropsychology Assessment. As shown in Table 3, patients in CM-MOH got significantly higher scores than MO in anxiety and depression ($P < 0.05$). In addition, these scores in CMwoMOH had no statistical differences, compared with CM-MOH and MO groups, respectively ($P > 0.05$). MIDAS assessment had no statistical difference among groups ($P > 0.05$). SF-36 revealed that patients in CM-MOH and CMwoMOH got much lower scores than them in MO, with obvious differences ($P < 0.05$). PSQI showed that the sleep quality in CM-MOH was relatively worse than that in MO ($P < 0.05$).

3.3. Cognitive Function Assessment. The score of memory and TMT B were significantly reduced in CM-MOH, compared with MO and control ($P < 0.05$). However, the assessment of memory and TMT A + B did not reveal any significance in the comparison of CMwoMOH and CM-MOH, MO and control, respectively ($P > 0.05$). Scores of attention, language fluency, language, and visuospace had no statistical differences among groups ($P > 0.05$) (Table 4).

The low 20% performance of each cognitive score was defined as cognitive decline. Due to the narrow score width of MMSE and attention/orientation, they did not implement the partition of cognitive decline. The threshold of cognitive decline in other values was as follows: ACE-R ≤77 points, memory ≤20 points, language fluency ≤7 points, language ≤18 points, visuospace ≤14 points, TMT A ≥35.29 s, TMT B ≥95.86 s, and DST ≤25 points. In cognitive decline, the morbidity rate was higher in CM-MOH and CMwoMOH than in control, especially in ACE-R total score, language fluency, and executive function ($P < 0.05$). In addition, there was no statistical difference between MO and control in the morbidity rate of cognitive dysfunction ($P > 0.05$) (Table 5).

Univariate regression analysis revealed that age and education were the independent risk factors of cognitive decline ($P < 0.05$) (Supplementary table). Hypertension, high low-density lipoproteinemia, smoke history, alcohol history, anxiety, depression, MIDAS, and sleep quality were not the independent risk factors ($P > 0.05$). Therefore, three covariates, including different status of migraine, age, and education, were included in our final multivariate model. After age and education were adjusted, the risk of cognitive decline was higher in CM-MOH than in control for ACE-R score (OR = 8.52, 95% CI: 1.83–39.81, $P = 0.006$), memory (OR = 6.92, 95% CI: 1.86–25.71, $P = 0.004$), language fluency (OR = 7.67, 95% CI: 1.74–33.88, $P = 0.007$), and executive function (TMT B OR = 50.80, 95% CI: 5.35–482.31, $P = 0.001$). The risk of cognitive decline was higher in CMwoMOH than that in controls in ACE-R score (OR = 7.14, 95% CI: 1.50–34.04, $P = 0.014$) and language fluency (OR = 8.24, 95% CI: 1.85–36.67, $P = 0.006$). In order to evaluate the association between chronic migraine and cognitive dysfunction, we compared the cognitive function between CMwoMOH and MO. Results showed that there were not significant differences ($P > 0.017$). Meanwhile, we assessed the impact of analgesic overuse on the cognitive function of chronic migraine patients. In addition, our study found that the cognitive function had no differences between CM-MOH and CMwoMOH ($P > 0.017$) (Table 6).

4. Discussion

Our study indicated that CM patients had increased risk of cognitive decline, especially in language fluency. Besides, CM-MOH sufferers were in higher risk of memory and executive dysfunction. In addition, the cognitive function had no obvious differences between CMwoMOH and CM-MOH.

It has been illustrated that the cognitive function of migraine sufferers declined during acute attacks. This process may be due to the decreased regional blood flow during migraine episodes [19, 20] and the increased brain lesions, such as white matter lesions, and subclinical infarcts [11, 21]. Besides, the grey matter volume (GMV) of several brain areas, including prefrontal, cingulate cortex, right posterior parietal cortex, and orbitofrontal cortex, was decreased in migraine patients [22]. In addition, this change was associated with the increasing headache duration and frequency [23]. As these areas were related to pain conduction, it suggested that repeated acute attack of migraine could induce selective damage of the brain.

There were overlaps between pain conduction pathway and cognitive regions in the brain. For example, the anterior cingulate cortex could regulate selective attention, working memory, and ability of identifying mistakes [24]. The pain-related activation of insular cortex increased when the cognitive function declined. It indicated that the damage of the pain conduction pathway could result in changes of cognition. In addition, previous studies had found that there were structural lesions of pain conduction pathway in CM sufferers. The GMV of cingulate cortex, frontal cortex, and insular lobe was reduced in CM cases compared with episode migraine patients [25, 26]. Therefore, these structural abnormalities could be the reasons of cognitive changes in CM patients.

Table 1: Baseline characteristic of the participants.

		CM		MO	Control
		CM-MOH	CMwoMOH		
No.		21	20	35	40
Age, year, mean ± SD[a]		48.90 ± 13.51	48.40 ± 10.33	45.89 ± 7.10	47.10 ± 7.04
Female, %[b]		80.95	80.00	77.14	77.50
Education, year, %[b]	0–6	19.05	20.00	17.14	17.50
	7–9	52.38	50.00	51.43	52.50
	10–12	14.28	20.00	20.00	17.50
	>12	14.28	10.00	11.43	12.50
Hypertension, %[b]		14.28	10.00	0	0
Diabetes, %[b]		0	0	0	0
High LDL, %[b]		9.52	10.00	11.43	0
Smoke, %[b]		9.52	5.00	11.43	7.50
Alcohol, %[b]		0	0	2.86	2.50
Family history, %[b]		52.38	25.00	28.57	NA

[a]ANOVA, $P > 0.05$; [b]chi-squared tests, $P > 0.05$. CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; SD, standard deviation; LDL, low-density lipoprotein; ANOVA, one-way analysis of variance.

Table 2: Headache characteristic of cases.

	CM		MO
	CM-MOH	CMwoMOH	
Headache years, mean ± SD[a]	22.67 ± 12.27	17.40 ± 10.68	12.54 ± 9.08
VAS, mean ± SD[b]	9.05 ± 1.24	7.30 ± 1.95	7.71 ± 1.51
Duration, day, mean ± SD[c]	1.05 ± 1.15	1.51 ± 0.78	1.63 ± 1.01
Headache frequency, days/month, median (IQR)[d]	30 (20–30)	20 (15–30)	3 (1–4)
Dosage, pills/attack, median (IQR)[e]	3 (2–6)	1 (0–1)	1 (0–1)
Analgesic frequency, days/month, median (IQR)[e]	30 (20–30)	1.5 (0–4.5)	1 (0–3)

[a]ANOVA, CM-MOH vs. MO, $P < 0.05$; CM-MOH vs. CMwoMOH, CMwoMOH vs. MO, $P > 0.05$. [b]ANOVA, CM-MOH vs. CMwoMOH, CM-MOH vs. MO, $P < 0.05$; CMwoMOH vs. MO, $P > 0.05$. [c]ANOVA, $P > 0.05$. [d]Kruskal–Wallis tests, $P < 0.001$; pairwise comparison with adj. sig., CM-MOH vs. MO, CMwoMOH vs. MO, $P < 0.001$; CM-MOH vs. CMwoMOH, $P > 0.05$. [e]Kruskal–Wallis tests, $P < 0.001$; pairwise comparison with adj. sig., CM-MOH vs. CMwoMOH, CM-MOH vs. MO, $P < 0.001$; CMwoMOH vs. MO, $P > 0.05$; CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; SD, standard deviation; IQR: interquartile range; ANOVA, one-way analysis of variance.

Table 3: Neuropsychological assessment of cases[a].

		CM		MO
		CM-MOH	CMwoMOH	
SF-36	Anxiety[b,1,3]	12 (5–16.5)	6 (4.3–8)	4 (3–6)
	Depression[b,1,2]	4 (2.5–13.5)	2 (2–3)	1 (0–2)
	MIDAS	0 (0–180)	12 (0–47.3)	6 (3–18)
	Physical functioning[b]	90 (85–95)	90 (75–93.8)	95 (90–100)
	Physical role	75 (12.5–100)	50 (25–75)	50 (25–100)
	Body pain	40 (22–68)	51 (42–54)	51 (41–74)
	General health[b,1,3]	45 (20–50)	30 (20–48.8)	52 (40–70)
	Vitality[b,1,3]	55 (40–75)	50 (45–60)	80 (60–80)
	Social role[b]	67 (44–89)	72.5 (56–78)	78 (78–89)
	Emotional role[b,1]	33 (16.5–33)	49.5 (33–66)	100 (33–100)
	Mental health[b,3]	60 (48–76)	50 (48–61)	72 (56–80)
PSQI	Overall sleep quality	2 (1–2)	1 (1–1.8)	1 (1–2)
	Sleep latency	2 (1–3)	1 (0–2.8)	1 (0–2)
	Duration of sleep	1 (0–2)	1 (0–1)	0 (0–1)
	Sleep efficiency[b,1,2]	1 (0–1)	0 (0–0)	0 (0–0)
	Sleep disturbance	1 (1–2)	1 (1–1)	1 (1–1)
	Need meds to sleep	0 (0–1.5)	0 (0–0)	0 (0–0)
	Day dysfunction due to sleepiness	1 (0–1)	0 (0–1)	0 (0–1)
	Total[b,1]	7 (5–9.5)	4.5 (3–7)	5 (3–7)

[a]Kruskal–Wallis tests, median (interquartile range); [b]$P < 0.05$. Pairwise comparison with adj. sig.: [1] CM-MOH vs. MO, $P < 0.05$. [2]CM-MOH vs. CMwoMOH, $P < 0.05$. [3]CMwoMOH vs. MO, $P < 0.05$; CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; MIDAS, Migraine Disability Assessment Test; SF-36, Short Form (36) Health Survey; PSQI, Pittsburgh Sleep Quality Index.

Table 4: Scores of cognitive function assessment in different groups[a].

	CM		MO	Control
	CM-MOH	CMwoMOH		
MMSE	29 (27–29.5)	28.5 (28–29)	28 (28–29.5)	29 (28–30)
ACE-R	83 (74.5–88)	83 (76.3–88.5)	86 (78–92)	86 (82.3–89.8)
Attention/orientation	18 (17–18)	17 (17–18)	17 (17–18)	18 (17–18)
Memory[b,1,2]	21 (18–23)	21.5 (19.3–23)	24 (21–25)	23 (22–24)
Language fluency	8 (7–9)	8 (7–9)	9 (7–11)	9 (8–10)
Language	23 (18.5–24.5)	20 (18–22)	20 (18–23)	21 (19–24)
Visuospace	15 (13.5–16)	15.5 (14.3–16)	16 (15–16)	16 (15–16)
TMT A	50.3 (41.2–76.7)	50.3 (35.1–75)	45.1 (34.9–59.4)	48.2 (39.7–59.3)
TMT B[b,1,2]	145.3 (119.2–198.9)	111.2 (87.9–151.7)	116.3 (97.5–129.4)	119.6 (98.5–126.5)
DST	31 (23.5–45.5)	32 (20–41.3)	37 (30–45)	35.5 (30–42.8)

[a]Kruskal–Wallis tests, median (interquartile range); [b]$P < 0.05$. Pairwise comparison with adj. sig.:[1] CM-MOH vs. control, $P < 0.05$. [2] CM-MOH vs. MO, $P < 0.05$. [3]CM-MOH vs. CMwoMOH, $P < 0.05$; CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; MMSE, minimental state examination; ACE-R, Addenbrooke's Cognitive Examination Test; TMT, Trail Making Test; DST, Digit Symbol Test.

Table 5: Morbidity of cognitive decline in different groups[a].

	CM		MO	Control
	CM-MOH	CMwoMOH		
ACE-R[1]	8 (38.1)	7 (35.0)	6 (17.1)	3 (7.5)
Memory[1]	10 (47.6)	6 (30.0)	7 (20.0)	5 (12.5)
Language fluency[1]	8 (38.1)	8 (40.0)	9 (25.7)	3 (7.5)
Language	5 (23.8)	6 (30.0)	14 (40.0)	8 (20.0)
Visuospace	8 (38.1)	5 (25.0)	6 (17.1)	6 (15.0)
TMT A	8 (38.1)	5 (25.0)	6 (17.1)	4 (10.0)
TMT B[1]	11 (52.4)	5 (25.0)	6 (17.1)	1 (2.5)
DST[1]	7 (33.3)	8 (40.0)	3 (8.6)	5 (12.5)

The low 20% performance of each cognitive evaluation was defined as cognitive decline. [a]Chi-squared tests, cases of cognitive decline (%). [1]Chi-squared tests, $P < 0.05$; CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; ACE-R, Addenbrooke's Cognitive Examination Test; TMT, Trail Making Test; DST, Digit Symbol Test.

In our study, we found that the performance of language fluency was poor in CM. Our examination of language fluency consisted of phonemic and semantic elements [27]. In addition, the aim of the TMT B was to test the executive function-related attention, memory, processing speed, and thinking flexibility. The functional magnetic resonance image (fMRI) study has revealed that the neural circuit had some differences between phonemic and semantic fluency. The posterior segment of left inferior frontal gyrus was involved more in the circuit of phonemic fluency, while the anterior frontal lobe and posterior temporal lobe played a much more important role in the regulation of semantic fluency [28]. Moreover, CM-MOH intended to have an impairment of memory and executive function, which was mainly manifested in TMT B. Single-photon emission computerized tomography (SPECT) has found that the TMT B was associated with the function of the anterior cingulate cortex, corpus striatum, and thalamus [29]. These suggested that the dysfunction of language fluency and executive ability may be due to the pathological changes of relevant brain areas. The cognitive function decline caused by CM may be irreversible, and there were more lesions in the CM-MOH brain.

Long-term exposure in inflammation could impair cognitive function. The mechanism of it may be the direct damage from prostaglandin and the prostaglandin-induced suppression of amyloid-β clearage [30]. NSAIDs could break off this toxic effect through inhibition of the production of prostaglandin. However, the role of NSAIDs on cognition is still controversial. Some studies discovered that NSAIDs could improve cognition [31–33], while others found that NSAIDs had no effect [34–37]. Our previous study displayed that the white matter lesions was less and the level of inflammatory factor was lower in CM-MOH patients compared with CMwoMOH, indicating that the anti-inflammation role of NSAIDs could reduce white matter damage [15]. In the present study, we did not find any differences in cognitive performance between CM-MOH and CMwoMOH. This indicated that the brain lesion-related dysfunction of CM patients might be irreversible, and it exceeded the protective effect of NSAIDs. The cases in our study took NSAIDs as analgesic for headache; therefore, our results could not be applied for patients using triptans or ergotamine. It merited further analysis of the cognitive function when triptans or ergotamine was overused.

In addition, our study displayed that the estimation of anxiety and depression was severe in CM-MOH sufferers, as well as worse in life quality and sleep quality, compared with MO. Previous studies had found that constant suffering of anxiety, depression, or lack of sleep could influence cognition [38, 39]. Meanwhile, they could also induce migraine chronification [40]. Although, in our study, they were not the independent risk factors of cognitive decline under Univariate regression analysis, we should still pay attention to them in clinical practice.

Our study had some limitations. Firstly, more objective index of cognitive assessment, such as fMRI, was not obtained. Secondly, the sample size in our study was small. Last, as a cross-sectional design study, we could not evaluate the progress of cognitive decline in these patients. Further study with large sample size to assess the changes of cognitive performance with disease progress, especially after withdrawal of pain killers, is needed.

Table 6: Risk factor analysis of cognitive decline after adjustment.

	N	Cognitive decline	Adjusted OR (95% CI)	*P*
ACE-R				
Control (reference)	40	3	1.00	—
CM-MOH	21	8	8.52 (1.83–39.81)	**0.006**
CMwoMOH	20	7	7.14 (1.50–34.04)	**0.014**
MO	35	6	2.72 (0.60–12.28)	0.194
MO (reference)	35	6	1.00	—
CMwoMOH	20	7	2.63 (0.68–10.14)	0.161
CMwoMOH (reference)	20	7	1.00	—
CM-MOH	21	8	1.19 (0.31–4.67)	0.799
Memory				
Control (reference)	40	5	1.00	—
CM-MOH	21	10	6.92 (1.86–25.71)	**0.004**
CMwoMOH	20	6	3.05 (0.77–12.00)	0.112
MO	35	7	1.80 (0.50–6.41)	0.370
MO (reference)	35	7	1.00	—
CMwoMOH	20	6	1.70 (0.46–6.23)	0.427
CMwoMOH (reference)	20	6	1.00	—
CM-MOH	21	10	2.27 (0.60–8.57)	0.226
Language fluency				
Control (reference)	40	3	1.00	—
CM-MOH	21	8	7.67 (1.74–33.88)	**0.007**
CMwoMOH	20	8	8.24 (1.85–36.67)	**0.006**
MO	35	9	4.39 (1.07–17.96)	0.040
MO (reference)	35	9	1.00	—
CMwoMOH	20	8	1.88 (0.57–6.19)	0.301
CMwoMOH (reference)	20	8	1.00	—
CM-MOH	21	8	0.93 (0.26–3.33)	0.912
Language				
Control (reference)	40	8	1.00	—
CM-MOH	21	5	1.25 (0.34–4.64)	0.742
CMwoMOH	20	6	1.72 (0.48–6.20)	0.405
MO	35	14	2.91 (1.00–8.51)	0.051
MO (reference)	35	14	1.00	—
CMwoMOH	20	6	0.59 (0.17–2.03)	0.592
CMwoMOH (reference)	20	6	1.00	—
CM-MOH	21	5	0.72 (0.17–3.05)	0.660
Visuospace				
Control (reference)	40	6	1.00	—
CM-MOH	21	8	3.94 (1.04–14.99)	0.044
CMwoMOH	20	5	1.86 (0.45–7.75)	0.393
MO	35	6	1.21 (0.33–4.41)	0.776
MO (reference)	35	6	1.00	—
CMwoMOH	20	5	1.54 (0.37–6.49)	0.554
CMwoMOH (reference)	20	5	1.00	—
CM-MOH	21	8	2.12 (0.49–9.10)	0.314
TMT A				
Control (reference)	40	4	1.00	—
CM-MOH	21	8	3.25 (0.64–16.54)	0.156
CMwoMOH	20	5	1.63 (0.31–8.61)	0.564
MO	35	6	2.18 (0.52–9.11)	0.287
MO (reference)	35	6	1.00	—
CMwoMOH	20	5	0.99 (0.22–4.50)	0.987
CMwoMOH (reference)	20	5	1.00	—
CM-MOH	21	8	1.83 (0.36–9.22)	0.466
TMT B				
Control (reference)	40	1	1.00	—
CM-MOH	21	11	50.80 (5.35–482.31)	**0.001**
CMwoMOH	20	5	11.30 (1.14–111.95)	0.038
MO	35	6	8.82 (0.97–79.82)	0.053
MO (reference)	35	6	1.00	—

Table 6: Continued.

	N	Cognitive decline	Adjusted OR (95% CI)	*P*
CMwoMOH	20	5	1.28 (0.30–5.51)	0.739
CMwoMOH (reference)	20	5	1.00	—
CM-MOH	21	11	4.50 (0.98–20.54)	0.052
DST				
Control (reference)	40	5	1.00	—
CM-MOH	21	7	2.83 (0.67–11.91)	0.157
CMwoMOH	20	8	4.25 (1.06–17.09)	0.041
MO	35	3	0.65 (0.14–3.04)	0.580
MO (reference)	35	3	1.00	—
CMwoMOH	20	8	6.59 (1.35–32.08)	0.020
CMwoMOH (reference)	20	8	1.00	—
CM-MOH	21	7	0.67 (0.16–2.84)	0.582

All the data were adjusted by age and education. The low 20% performance of each cognitive evaluation was defined as cognitive decline. $P < 0.017$ (0.05/3) was considered as significant difference; CM, chronic migraine; CM-MOH, chronic migraine with medication overuse headache; CMwoMOH, chronic migraine without medication overuse headache; MO, migraine without aura; *N*, number of cases; OR, odds ratio; CI, confidence interval; ACE-R, Addenbrooke's Cognitive Examination Test; TMT, Trail Making Test; DST, Digit Symbol Test.

5. Conclusion

There was cognitive function decline in CM patients, both in CM-MOH and CMwoMOH. NSAIDs had no influence on the cognition of CM sufferers. Further studies are needed to trace the cognitive function in other types of CM-MOH.

Data Availability

The datasets supporting the conclusions of this article are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary table: risk factor analysis of cognitive decline (univariate regression analysis). (*Supplementary Materials*)

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