

Clinical Study on Traditional Chinese Medicine Syndrome Differentiation-Based Comprehensive Regimen for Migraine Treatment: Observation of Clinical Efficacy and Exploration of 5-HT/CGRP Regulatory Mechanism

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Abstract: This study systematically investigates the clinical efficacy of traditional Chinese medicine (TCM) syndrome differentiation intervention for migraine and its neuroendocrine regulatory mechanism, aiming to provide evidence-based medical support for optimizing clinical diagnosis and treatment strategies for this disease. A total of 120 migraine subjects meeting the inclusion criteria were randomly assigned in a 1:1 ratio to the experimental group and the control group (60 cases each). The experimental group received individualized TCM compound prescription combined with filiform needle acupuncture based on four types identified by four diagnostic methods: hyperactivity of liver Yang, deficiency of both Qi and blood, internal obstruction of phlegm-turbidity, and obstruction of collaterals by blood stasis. The control group was treated with oral flunarizine hydrochloride capsules. The intervention period was 12 weeks, and follow-up observations were extended to the end of the 9th month, with dynamic collection of efficacy endpoints and safety indicators in both groups. Efficacy data showed that the total effective rate of the TCM intervention group was 91.67%, which was significantly higher than 76.67% of the control group, with a statistically significant difference ($p < 0.05$). At 3 and 6 months of treatment, the TCM treatment group exhibited more significant improvements in Numerical Rating Scale (NRS) scores, migraine attack frequency, and single attack duration; the increase in serum 5-hydroxytryptamine (5-HT) level and the decrease in calcitonin gene-related peptide (CGRP) level were also significantly superior to those in the control group ($p < 0.05$). The study concludes that TCM treatment based on syndrome differentiation for migraine has definite and reliable clinical efficacy, which can effectively relieve clinical symptoms and reduce attack frequency. Its mechanism of action may be related to regulating 5-HT/CGRP balance, improving vascular function, and inhibiting neurogenic inflammation. This treatment regimen has good clinical safety with no obvious adverse reactions and possesses practical value for extensive promotion.

Keywords: Migraine; TCM syndrome differentiation; Clinical efficacy; Mechanism of action; Acupuncture therapy

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1. Introduction

Migraine is a common chronic neurovascular disorder in neurology and traditional Chinese medicine (TCM) clinics. It typically presents as recurrent unilateral throbbing headache, often accompanied by nausea, vomiting, photophobia, phonophobia, or visual aura. This disorder severely impairs patients' work, quality of life, and physical and mental health. With a global prevalence of about 14.8%, migraine is the second leading cause of disability worldwide and ranks first among adults under 50 years old. Its high incidence and recurrence also increase the public health burden.

The pathogenesis of migraine remains unclear in modern medicine. Core pathological mechanisms involve overactivation of the trigeminovascular system, neurotransmitter disorders, cortical spreading depression, and neurogenic inflammation. Western medicine focuses on acute analgesia and prophylactic treatment: NSAIDs and triptans for acute attacks, and calcium channel blockers, β -blockers, or CGRP antagonists for prevention. However, long-term use often causes adverse reactions (gastrointestinal discomfort, drowsiness, weight gain) and may lead to medication-overuse headache, with unsatisfactory long-term efficacy and safety.

In TCM, migraine is categorized as “headache”, “migratory wind” or “brain wind”^[1]. Its etiology is linked to dysfunctions of the liver, spleen, and kidney, characterized by Qi-blood disturbance, meridian obstruction, and malnutrition of the brain marrow, manifesting as “pain due to obstruction” or “pain due to insufficiency”. TCM treatment follows the holistic concept and syndrome differentiation, identifies patterns via the four diagnostic methods, and delivers individualized therapy^[2]. Compared with Western medicine, TCM has unique advantages in relieving pain, lowering recurrence, improving accompanying symptoms, and has fewer adverse reactions, making it suitable for long-term management.

With advances in molecular biology, research on TCM for migraine has deepened^[3]. Studies confirm that TCM regulates the neuro-endocrine-immune network through multi-target and multi-pathway effects to treat both symptoms and root causes. Based on clinical experience, we performed a randomized controlled trial to compare the efficacy of TCM syndrome differentiation-based comprehensive therapy with conventional Western medicine for migraine, explore its mechanism in regulating neurotransmitters and vasoactive substances, and provide evidence-based evidence for TCM in migraine management, to promote standardized application and clinical practice^[4].

2. TCM syndrome differentiation types and clinical characteristics

Based on long-term clinical practice, TCM syndrome differentiation for migraine focuses on distinguishing root from manifestation, deficiency from excess, and identifying the core pathologies: pain due to obstruction and pain due to malnutrition. By integrating symptoms, signs, tongue/pulse features, and medical history, four major syndromes are identified: hyperactivity of liver Yang, Qi-blood deficiency, phlegm-turbidity obstruction, and blood stasis blocking collaterals. Some patients present with combined syndromes (e.g., hyperactivity of liver Yang plus phlegm-turbidity obstruction). Flexible adjustments to differentiation and treatment are required to achieve individualized therapy via treating the same disease with different methods.

2.1. Hyperactivity of liver Yang syndrome

This is the most common migraine syndrome, prevalent in middle-aged women and those with frequent emotional swings^[5]. It arises from emotional distress, liver Qi stagnation turning to fire, or liver-kidney Yin

deficiency failing to nourish liver Yang. Typical manifestations: severe distending or throbbing headache at the vertex or temporal sides, worsened by emotion, fatigue, late nights, or alcohol intake; accompanied by dizziness, flushed face, irritability, bitter mouth, dry throat, insomnia, tinnitus, or hypochondriac distension; tongue is red with thin yellow coating, pulse is wiry-rapid or wiry-slippery.

The core pathogenesis is hyperactive liver Yang disturbing the upper orifices and obstructing meridians. It should be distinguished from liver Yin deficiency. Treatment focuses on calming liver Yang, nourishing Yin to calm liver, and unblocking collaterals for pain relief, using modified Tianma Gouteng Decoction combined with liver-soothing herbs to prevent further hyperactivity^[6].

2.2. Deficiency of Qi and blood syndrome

This syndrome is common in weak, chronically ill, middle-aged and elderly patients. It results from spleen injury due to anxiety, insufficient Qi-blood production, or Qi-blood depletion from severe illness or overstrain. Typical manifestations: dull or empty headache, mild but persistent, aggravated by fatigue and relieved by rest; accompanied by dizziness, sallow complexion, lassitude, shortness of breath, poor appetite, palpitations, insomnia, amnesia; female patients may have weakness and scanty pale menstruation. The tongue is pale with white coating, and the pulse is thready and weak.

The core pathogenesis is Qi-blood deficiency failing to nourish the brain and meridians, belonging to “pain due to malnutrition”. It requires differentiation between Qi deficiency and blood deficiency. Treatment focuses on replenishing Qi, nourishing blood, invigorating the spleen, tonifying the kidney, and nourishing the brain. Modified Buzhong YiQi Decoction or Siwu Decoction is applied with flexible dosage adjustment^[7].

2.3. Obstruction by phlegm-turbidity syndrome

This syndrome mainly affects patients with unhealthy diets and obesity, caused by excessive rich, greasy food, alcohol, or cold intake leading to phlegm-dampness formation. Spleen-stomach dysfunction causes water-dampness retention and phlegm-turbidity accumulation, which disturbs the upper orifices and induces headache.

Typical symptoms: heavy, clouding headache with no fixed site, lingering and refractory; accompanied by abdominal distension, nausea, vomiting, poor appetite, heavy limbs, loose stools, sticky mouth, thick greasy tongue coating, and soft-slippery pulse.

The core pathogenesis is phlegm-turbidity obstructing meridians and clouding orifices, belonging to “pain due to obstruction”. It should be differentiated from damp-heat syndrome. Treatment focuses on resolving phlegm, descending rebellion, invigorating the spleen, eliminating dampness, and unblocking collaterals to relieve pain. Modified Banxia Baizhu Tianma Decoction is used to address the root cause^[8].

2.4. Obstruction of collaterals by blood stasis syndrome

This syndrome is common in chronic migraine and head trauma patients, caused by prolonged pain invading collaterals, Qi stagnation and blood stasis, or traumatic blood stasis blocking brain collaterals and impairing Qi-blood flow. Typical manifestations: fixed, stabbing or cutting headache worsening at night; dark complexion, purplish tongue with petechiae, sublingual varices, limb numbness, or amnesia; pulse is hesitant or wiry-tense.

The core pathogenesis is blood stasis blocking brain vessels, belonging to “pain due to obstruction”. Persistent stasis may consume Qi and blood, leading to a mixed deficiency-excess pattern. New vs. old

blood stasis requires differentiation. Treatment focuses on activating blood, resolving stasis, and unblocking collaterals for pain relief, using modified Tongqiao Huoxue Decoction plus blood-nourishing herbs to protect healthy Qi.

3. Observation of clinical efficacy

3.1. Research subjects

A total of 120 migraine patients meeting the relevant diagnostic criteria were selected as research subjects in this study. All enrolled patients met the requirements of the International Classification of Headache Disorders (ICHD) 2018 Diagnostic Criteria for Migraine, and secondary headache caused by organic lesions such as intracranial tumors and cerebrovascular diseases was excluded by cranial CT or MRI examination; at the same time, all the above patients were diagnosed as one of the four syndrome types: hyperactivity of liver Yang syndrome, deficiency of Qi and blood syndrome, obstruction by phlegm-turbidity syndrome, and obstruction of collaterals by blood stasis syndrome through comprehensive four diagnostic methods by the authors and senior TCM physicians in the department.

3.1.1. Inclusion criteria

- (1) Age 18–65 years old, gender unlimited;
- (2) Migraine attack frequency ≥ 2 times/month, each attack duration ≥ 4 hours, disease course ≥ 1 year;
- (3) Poor previous efficacy of Western medicine treatment or unwillingness to take Western medicine for a long time;
- (4) No serious primary pathological changes in heart, liver, kidney and hematopoietic system;
- (5) Patients were informed of the research situation and signed informed consent, able to cooperate with the whole course of treatment and follow-up work, with good compliance.

3.1.2. Exclusion criteria

- (1) Patients with severe heart, liver, renal insufficiency or hematopoietic system diseases, and mental diseases;
- (2) Pregnant or lactating women;
- (3) Those with known allergy to research drugs (flunarizine hydrochloride) or TCM intervention measures (TCM, acupuncture);
- (4) Patients complicated with other severe types of headache (such as cluster headache, tension headache, etc.);
- (5) Those expected to be unable to ensure treatment compliance, difficult to complete the scheduled course of treatment and follow-up observation, or likely to terminate the research in advance;
- (6) Those who have taken relevant drugs affecting efficacy (such as other analgesics, antidepressants) recently.

3.2. Research grouping

A total of 120 eligible patients were randomly divided into TCM treatment group and control group by random number table method, with 60 subjects in each group. Among them, the TCM treatment group included 22 males and 38 females; the age range of patients was 20 to 63 years old, with an average age

of (41.5 ± 8.2) years old. The disease course was 1–12 years, with an average disease course of (5.8 ± 2.3) years; the syndrome type distribution was: 18 cases of hyperactivity of liver yang syndrome, 16 cases of deficiency of Qi and blood syndrome, 14 cases of obstruction by phlegm-turbidity syndrome, and 12 cases of obstruction of collaterals by blood stasis syndrome. The control group included 24 males and 36 females; aged 19–65 years old, with an average age of (42.1 ± 7.9) years old; disease course 1–11 years, average disease course (5.6 ± 2.1) years; syndrome type distribution: 17 cases of hyperactivity of liver Yang syndrome, 15 cases of deficiency of Qi and blood syndrome, 15 cases of obstruction by phlegm-turbidity syndrome, and 13 cases of obstruction of collaterals by blood stasis syndrome.

Statistical analysis of baseline data such as age, gender, disease course, and syndrome type distribution of the two groups showed that there was no statistically significant difference between the groups ($p > 0.05$), indicating that the two groups had good comparability and could ensure the objectivity and reliability of subsequent treatment effect comparison.

3.3. Treatment methods

Both groups took 3 months as a course of treatment, followed up for 6 months after completing the course. During treatment, all patients were informed to avoid migraine inducing factors (such as spicy and stimulating diet, strong light, noise, staying up late, emotional fluctuation, etc.), keep regular work and rest, and exercise appropriately.

3.3.1. Control group

Patients in the control group were treated with oral flunarizine hydrochloride capsules, produced by Xi'an Janssen Pharmaceutical Co., Ltd., with a specification of 5mg per capsule. The administration regimen was set as: take once 30 minutes before going to bed every night, 5 mg each time, for 3 consecutive months. In the follow-up stage, if patients had acute migraine attacks, they could take oral ibuprofen sustained-release capsules (0.3 g each time) temporarily to relieve pain, but the frequency of medication should be strictly controlled, no more than 2 times a week, to prevent interference with the efficacy evaluation of this study.

3.3.2. TCM treatment group

Based on the results of syndrome differentiation, comprehensive treatment of “oral modified TCM compound prescription + acupuncture” was adopted, and the regimen was flexibly adjusted according to patients' constitution and symptoms, as follows:

(1) Oral modified TCM compound prescription

The corresponding basic prescription was selected according to the syndrome differentiation results, and the type and dosage of drugs were adjusted according to patients' specific symptoms, constitution and age. One dose per day, uniformly decocted by the TCM pharmacy of our hospital, 400 mL of water decoction, taken warm three times in the morning, noon and evening (half an hour after meals to avoid gastrointestinal irritation), for 3 consecutive months. ① Hyperactivity of liver Yang syndrome: Modified Tianma Gouteng Decoction, basic drug composition: *Gastrodia elata* 12 g, *Uncaria rhynchophylla* 15 g (decocted later), *Haliotis discus hannai* 30 g (decocted first), *Achyranthes bidentata* 15 g, *Eucommia ulmoides* 12 g, *Angelica sinensis* 12 g, *Paeonia lactiflora* 15 g, *Poria cocos* 15 g, *Leonurus japonicus* 12 g, *Glycyrrhiza uralensis* 6 g; if patients had obvious bitter mouth,

Scutellaria baicalensis 10 g and *Gentiana scabra* 6 g could be added to clear liver fire; if patients had obvious dizziness, *Chrysanthemum morifolium* 10 g and *Cassia obtusifolia* 15 g could be added to calm liver and improve eyesight. ② Deficiency of Qi and blood syndrome: Modified Buzhong Yiqi Decoction for syndrome differentiation treatment, basic drug composition: *Astragalus membranaceus* 20 g, *Codonopsis pilosula* 15 g, *Atractylodes macrocephala* 12 g, *Angelica sinensis* 12 g, *Rehmannia glutinosa* 15 g, *Paeonia lactiflora* 12 g, *Ligusticum chuanxiong* 10 g, *Citrus reticulata* 10 g, *Cimicifuga foetida* 6 g, *Bupleurum chinense* 6 g, *Glycyrrhiza uralensis* 6 g; add *Ziziphus jujuba* 15 g and *Longan arillus* 12 g for those with palpitations and insomnia to nourish blood and soothe nerves; add *Massa Medicata Fermentata* 12 g and *Hordeum vulgare* 15 g for those with poor appetite to promote digestion and accumulation; elderly patients appropriately increase the dosage of *Astragalus membranaceus* and *Codonopsis pilosula* (add 5 g each) to enhance the effect of replenishing Qi. ③ Obstruction by phlegm-turbidity syndrome: Modified Banxia Baizhu Tianma Decoction for treatment, basic drug composition: *Pinellia ternata* 12 g, *Atractylodes macrocephala* 15 g, *Gastrodia elata* 12 g, *Poria cocos* 15 g, *Citrus reticulata* 12 g, *Glycyrrhiza uralensis* 6 g, *Zingiber officinale* 3 slices. Add *Bambusae Caulis* in Taeniam 10 g and *Aurantii Fructus Immaturus* 10 g for those with severe nausea and vomiting to resolve phlegm and descend rebellion; add *Coix lacryma-jobi* 30 g and *Atractylodes lancea* 12 g for those with heavy limbs to invigorate spleen and eliminate dampness; add *Pogostemon cablin* 10 g and *Eupatorium fortunei* 10 g for those with sticky mouth to aromatize turbidity. ④ Obstruction of collaterals by blood stasis syndrome: Modified Tongqiao Huoxue Decoction as the base prescription, basic prescription composition: *Ligusticum chuanxiong* 15 g, Peach Seed 12 g, Safflower 10 g, *Paeonia veitchii* 12 g, *Angelica sinensis* 12 g, *Trichosanthes kirilowii* 12 g, *Gallus gallus domesticus* 10 g, *Allium fistulosum* 3 segments, *Zingiber officinale* 3 slices, Vinegar 10 mL (taken by water); add *Corydalis yanhusuo* 12 g, Frankincense 10 g, Myrrh 10 g for those with severe headache to activate blood circulation and relieve pain; add *Salvia miltiorrhiza* 15 g and *Hirudo* 6 g (taken by water) for those with obvious sublingual varicose veins to promote blood circulation and remove blood stasis; add *Rehmannia glutinosa* 15 g and *Colla Corii Asini* 10 g (melted by decoction) for those with obvious blood deficiency to nourish blood and promote blood circulation^[9].

(2) Acupuncture treatment

Main acupoints selected were Baihui (GV20), Fengchi (GB20), Taiyang (EX-HN5), Hegu (LI4), Zusanli (ST36), and corresponding matching acupoints were selected according to syndrome differentiation results. Operated by senior acupuncturists in our hospital, once a day, 30 minutes of needle retention each time, using 0.30 × 25 mlm filiform needles, routine disinfection before acupuncture, uniform reinforcing and reducing method after obtaining Qi. The treatment was carried out 5 times a week with 2 days of rest, for 3 consecutive months of standardized treatment to ensure the continuity and effectiveness of the intervention regimen. ① Hyperactivity of liver Yang syndrome: add Ganshu (BL18) and Taichong (LR3), reducing method at Taichong (LR3) to enhance the effect of calming liver and subduing Yang; ② Deficiency of Qi and blood syndrome: add Pishu (BL20), Shenshu (BL23), Sanyinjiao (SP6), reinforcing method to replenish Qi and nourish blood, and nourish brain orifices; ③ Obstruction by phlegm-turbidity syndrome: add Zhongwan (CV12) and Fenglong (ST40), reducing method to resolve phlegm and descend rebellion, invigorate spleen and eliminate dampness; ④ Obstruction of collaterals by blood stasis syndrome: add Xuehai (SP10) and Gesu (BL17), reducing

method to promote blood circulation to remove blood stasis and unblock collaterals to relieve pain. During acupuncture, closely observe patients' complexion and chief complaints, adjust stimulation intensity in time to avoid adverse reactions such as fainting, bending, and stagnation of needles. If patients have needle fainting, stop acupuncture immediately, instruct patients to lie flat and rest, drink warm water, and continue treatment after symptoms are relieved.

(3) Auxiliary intervention

Combined with the TCM holistic conditioning concept, targeted emotional regulation and dietary guidance were given according to patients' syndrome types during treatment. Patients with hyperactivity of liver Yang syndrome focused on emotional counseling, instructed to avoid emotional excitement, and regulate emotions by listening to soothing music, meditation, walking, etc.; patients with deficiency of Qi and blood syndrome and obstruction by phlegm-turbidity syndrome focused on dietary conditioning, avoiding rich, greasy, raw and cold food, and eating more food for invigorating spleen and replenishing Qi, light and easy to digest (such as millet porridge, Chinese yam, red dates, etc.); all patients kept regular work and rest, avoided staying up late, and appropriately took mild exercises such as Tai Chi and walking to enhance physical fitness and improve blood circulation.

3.4. Observation indicators

The indicators of the two groups were evaluated before treatment (baseline), at 3 months of treatment (end of course), and at 6 months of treatment (end of follow-up), including the following three categories. All indicators were detected and recorded by special personnel to ensure data accuracy.

3.4.1. Main efficacy indicators

- (1) Headache attack frequency (times/month);
- (2) Single attack duration (h);
- (3) Pain intensity: quantitatively evaluated by NRS (Numerical Rating Scale, 0–10 points), 0 point means no pain, 10 points means extremely severe pain, self-evaluated by patients.

3.4.2. Secondary efficacy indicators

This study evaluated patients' quality of life from 8 dimensions: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The evaluation tool adopted the SF-36 scale, with a total score of 0–100 points. The higher the score, the better the patients' quality of life. The test was carried out in strict accordance with standardized procedures to control measurement bias.

3.4.3. Biomarker indicators

5 mL of fasting venous blood was collected from patients, centrifuged (3000 r/min, 10 minutes) to separate serum. Serum 5-HT and CGRP levels were detected by enzyme-linked immunosorbent assay (ELISA). The detection kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., and operated in strict accordance with the kit instructions. All detections were completed in the Clinical Laboratory of our hospital to ensure reliable detection results.

3.5. Efficacy evaluation criteria

With reference to the Standards for Diagnosis and Efficacy of TCM Diseases and clinical diagnosis and

treatment practice, combined with the improvement degree of migraine attack frequency, attack duration, and NRS score, the efficacy was divided into three grades: markedly effective, effective, and ineffective, as follows:

(1) Markedly effective

Migraine attack frequency reduced by $\geq 75\%$, attack duration shortened by $\geq 75\%$, NRS score decreased by $\geq 75\%$, patients' accompanying symptoms basically disappeared, and quality of life significantly improved;

(2) Effective

Migraine attack frequency reduced by $\geq 50\%$ and $< 75\%$, attack duration shortened by $\geq 50\%$ and $< 75\%$, NRS score decreased by $\geq 50\%$ and $< 75\%$, patients' accompanying symptoms significantly relieved, and quality of life improved;

(3) Ineffective

Improvement of migraine attack frequency, attack duration, and VAS score was $< 50\%$, or even aggravated, patients' accompanying symptoms not improved, and quality of life not improved. Total effective rate = (number of markedly effective cases + number of effective cases)/total number of cases $\times 100\%$ [10,11].

3.6. Statistical analysis

All data in this study were analyzed and processed by SPSS26.0 statistical software package. Continuous variables were statistically described by mean \pm standard deviation, inter-group differences were compared by independent sample *t*-test, and self-before-and-after control was compared by paired sample *t*-test; categorical variables were expressed by constituent ratio or percentage, and inter-group differences were compared by Pearson χ^2 test. $p < 0.05$ was set as the criterion for judging statistically significant data differences in this study.

3.6.1. Comparison of baseline indicators between the two groups

Before treatment, there were no statistically significant differences in migraine attack frequency, attack duration, NRS score, SF-36 score, serum 5-HT and CGRP levels between the two groups ($p > 0.05$), with comparability (Table 1).

Table 1. Comparison of baseline indicators between the two groups

Indicator	TCM treatment group (n = 60)	Control group (n = 60)	<i>t</i> / χ^2	<i>p</i>
Attack frequency (times/month)	5.8 \pm 1.6	5.7 \pm 1.5	0.321	0.749
Attack duration (hours /attack)	8.2 \pm 2.3	8.3 \pm 2.2	0.238	0.812
NRS	7.6 \pm 1.2	7.5 \pm 1.3	0.385	0.701
SF-36	52.3 \pm 8.5	51.8 \pm 8.7	0.302	0.763
5-HT (ng/mL)	89.6 \pm 12.3	90.2 \pm 12.1	0.247	0.805
CGRP (pg/mL)	128.5 \pm 18.6	129.3 \pm 18.2	0.225	0.822

3.6.2. Comparison of changes in main efficacy indicators before and after treatment between the two groups

At 3 and 6 months of treatment, the attack frequency, attack duration, and NRS score of both groups were significantly improved compared with before treatment ($p < 0.05$); and the improvement range of each indicator in the TCM treatment group was significantly better than that in the control group, with statistically significant differences ($p < 0.05$), indicating that TCM syndrome differentiation comprehensive treatment had more significant effects in relieving pain and reducing attacks (Table 2).

Table 2. Comparison of changes in main efficacy indicators before and after treatment between the two groups

Indicator	Group	Before treatment	After 3 months of treatment	After 6 months of treatment
Attack frequency (times/month)	TCM treatment group	5.8 ± 1.6	2.2 ± 0.7Δ#	1.5 ± 0.5Δ#
	Control group	5.7 ± 1.5	3.5 ± 0.9Δ	2.8 ± 0.8Δ
Attack duration (hours / attack)	TCM treatment group	8.2 ± 2.3	3.1 ± 1.0Δ#	2.3 ± 0.8Δ#
	Control group	8.3 ± 2.2	4.8 ± 1.2Δ	3.9 ± 1.1Δ
NRS	TCM treatment group	7.6 ± 1.2	2.5 ± 0.6Δ#	1.8 ± 0.5Δ#
	Control group	7.5 ± 1.3	4.2 ± 0.8Δ	3.3 ± 0.7Δ

Note: Compared with before treatment in the same group, Δ $p < 0.05$; compared with the control group at the same time point, # $p < 0.05$.

3.6.3. Comparison of changes in sf-36 scores before and after treatment between the two groups

At 3 months of treatment and 6 months of follow-up, the SF-36 Health Survey Scale scores of both groups were significantly increased compared with before treatment, with statistically significant differences ($p < 0.05$); further comparison showed that the SF-36 scores of the TCM syndrome differentiation comprehensive treatment group at the same time points were significantly better than those of the control group, with statistically significant inter-group differences ($p < 0.05$). This result suggests that the comprehensive treatment regimen guided by TCM syndrome differentiation has more advantages in improving the quality of life of migraine patients (Table 3 for specific data).

Table 3. Comparison of changes in SF-36 scores before and after treatment between the two groups

Group	Before treatment	After 3 months of treatment	After 6 months of treatment
TCM treatment group (n = 60)	52.3 ± 8.5	72.5 ± 7.8Δ#	78.6 ± 7.2Δ#
Control group (n = 60)	51.8 ± 8.7	63.2 ± 8.1Δ	68.9 ± 7.5Δ

Note: Compared with before treatment in the same group, Δ $p < 0.05$; compared with the control group at the same time point, # $p < 0.05$.

3.6.4. Comparison of changes in serum 5-HT and CGRP levels before and after treatment between the two groups

At 3 and 6 months of treatment, serum 5-HT level in the TCM treatment group was significantly increased and CGRP level was significantly decreased compared with before treatment ($p < 0.05$); serum 5-HT level in the control group was slightly increased and CGRP level had no significant change ($p > 0.05$); and the

improvement range of serum 5-HT and CGRP levels in the TCM treatment group was significantly better than that in the control group, with statistically significant differences ($p < 0.05$), indicating that TCM syndrome differentiation comprehensive treatment could effectively regulate the balance of neurotransmitters and vasoactive substances (Table 4).

Table 4. Comparison of changes in serum 5-HT and CGRP levels before and after treatment between the two groups

Indicator	Group	Before treatment	After 3 months of treatment	After 6 months of treatment
5-HT (ng/mL)	TCM treatment group	89.6 ± 12.3	128.5 ± 13.6 Δ #	139.2 ± 14.1 Δ #
	Control group	90.2 ± 12.1	102.3 ± 12.8 Δ	108.6 ± 13.2 Δ
CGRP (pg/mL)	TCM treatment group	128.5 ± 18.6	89.6 ± 14.2 Δ #	78.3 ± 13.5 Δ #
	Control group	129.3 ± 18.2	118.5 ± 16.7	112.8 ± 15.9

Note: Compared with before treatment in the same group, $\Delta p < 0.05$; compared with the control group at the same time point, # $p < 0.05$.

3.6.5. Comparison of clinical efficacy between the two groups

After 3 months of standardized treatment, among 60 patients in the TCM treatment group, 32 cases reached the markedly effective standard, 23 cases were effective, 5 cases were ineffective, with a total effective rate of 91.67%; among 60 cases in the control group, 14 cases were ineffective, 21 cases were markedly effective and 25 cases were effective, with a total effective rate of 76.67%. Statistical analysis results showed that the total effective rate of the TCM treatment group was significantly higher than that of the control group, and the efficacy difference between the two groups was statistically significant ($p < 0.05$) (Table 5).

Table 5. Comparison of clinical efficacy between the two groups

Group	Markedly effective (cases)	Effective (cases)	Ineffective (cases)	Total effective rate (%)
TCM treatment group (n = 60)	32	23	5	91.67
Control group (n = 60)	21	25	14	76.67

4. Discussion on mechanism of action

Since the pathogenesis of migraine involves multiple interrelated pathological links such as neurotransmitter imbalance, vascular dysfunction, and neurogenic inflammation, the treatment mode targeting only a single target is often difficult to achieve the ideal therapeutic effect of comprehensively improving the condition and controlling recurrence. The core advantage of TCM syndrome differentiation treatment for migraine lies in “multi-target, multi-channel” comprehensive intervention, based on the “holistic concept”, regulating Zang-fu function, balancing Qi and blood, and unblocking meridians to improve the pathological state from the root. Its mechanism of action is mainly closely related to the following aspects.

4.1. Regulating neurotransmitter metabolic balance

5-HT is one of the most key neurotransmitters in the pathogenesis of migraine, and its level fluctuation directly affects the law of headache attack, which has been widely recognized clinically. Combined with clinical observation, during migraine attack, platelets of patients release a large amount of 5-HT, leading to

intracranial vasoconstriction, followed by rapid depletion of 5-HT, abnormal vasodilation, triggering a pain chain reaction; in the remission stage, patients' serum 5-HT level remains at a low level, difficult to maintain intracranial vascular homeostasis, and easy to cause headache recurrence. As specific drugs for acute migraine, triptans solely act by activating 5-HT_{1B/1D} receptors, constricting intracranial blood vessels, and inhibiting neurogenic inflammation, thereby quickly relieving pain symptoms.

The results of this study showed that serum 5-HT level in the TCM treatment group was significantly increased after treatment, and the improvement range was better than that in the control group, suggesting that TCM could restore its normal serum level by regulating 5-HT metabolism, thus exerting an analgesic effect. Combined with TCM syndrome differentiation theory, the liver governs coursing and discharge, closely related to human emotional regulation. Clinically, patients with liver Yang hyperactivity migraine mostly show irritability, which is closely related to 5-HT hypofunction; patients with Qi and blood deficiency syndrome are often accompanied by low mood and listlessness, which may be related to insufficient 5-HT synthesis.

From clinical medication practice, in the prescriptions used for TCM syndrome differentiation, blood-activating and stasis-removing drugs such as *Angelica sinensis* and *Ligusticum chuanxiong* can promote 5-HT synthesis and release, improve neurotransmitter metabolism; Qi-replenishing drugs such as *Glycyrrhiza uralensis* and *Astragalus membranaceus* can inhibit 5-HT degradation and prolong its action time; liver-calming and wind-extinguishing drugs such as *Gastrodia elata* and *Uncaria rhynchophylla* can regulate central 5-HT receptor activity and enhance its analgesic effect. The synergistic effect of multiple drugs achieves balanced regulation of neurotransmitters and reduces headache attacks from the root.

4.2. Improving intracranial vascular dysfunction

As a potent vasodilator peptide, CGRP is a core vasoactive substance in the pathogenesis of migraine, mainly released by trigeminal ganglion neurons. Its excessive release can induce meningeal vasodilation, activate trigeminal nerve endings, release inflammatory mediators, aggravate neurogenic inflammatory reaction, form a vicious cycle of "vasodilation-inflammation activation-pain aggravation", and further aggravate headache symptoms. At present, drugs targeting CGRP and its receptors have become a new direction for migraine preventive treatment, but long-term clinical application has found that such drugs still have certain adverse reactions and high prices, with limited clinical popularity.

In this study, serum CGRP level in the TCM treatment group was significantly decreased after treatment, suggesting that TCM could relieve intracranial vasodilation and neurogenic inflammatory reaction and improve vascular dysfunction by inhibiting CGRP release and blocking its biological effect. Combined with clinical diagnosis and treatment experience, *Gastrodia elata* and *Uncaria rhynchophylla* in TCM syndrome differentiation treatment have clear analgesic and anti-inflammatory effects, which can down-regulate CGRP mRNA expression in trigeminal ganglion and reduce CGRP release; blood-activating and stasis-removing drugs such as *Ligusticum chuanxiong*, Peach Seed, and Safflower can improve intracranial blood circulation, regulate vascular systolic and diastolic function, reduce pain caused by abnormal vascular dilation; phlegm-resolving drugs such as *Pinellia ternata* and *Atractylodes macrocephala* can clear phlegm-turbidity, reduce its compression on blood vessels, improve vascular blood supply, indirectly regulate CGRP level, and break the pain vicious cycle.

4.3. Inhibiting neurogenic inflammatory reaction

Neurogenic inflammation is an important pathological link of migraine attack. Combined with clinical research, when the trigeminovascular system is activated, pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α can be released. On the one hand, these inflammatory mediators lower the pain threshold and prolong the pain course by sensitizing primary afferent neurons; on the other hand, mediate vasodilation, form a positive feedback loop of “pain-vasodilation”, and finally aggravate the degree of headache. TCM has multi-target anti-inflammatory advantages. A variety of drugs in its compound prescription can reduce the expression of inflammatory factors, alleviate neurogenic inflammatory reaction, and relieve pain symptoms.

In this study, heat-clearing drugs such as *Scutellaria baicalensis* and *Gentiana scabra* in TCM syndrome differentiation prescriptions can inhibit the expression of inflammatory factors such as IL-6 and TNF- α , reduce the intensity of inflammatory reaction; blood-activating and stasis-removing drugs such as *Salvia miltiorrhiza* and *Angelica sinensis* can improve local blood circulation, promote the metabolism of inflammatory mediators, relieve nerve ending edema, and reduce its sensitivity; drugs such as *Gastrodia elata* and *Atractylodes macrocephala* can regulate the body’s immune function, inhibit inflammatory cell infiltration, thereby reducing neurogenic inflammation and blocking pain transmission. In addition, acupuncture treatment can regulate central nervous system function by stimulating acupoints such as Baihui, Fengchi, and Hegu, inhibit overactivation of the trigeminovascular system, reduce the release of inflammatory factors, synergize with TCM to exert anti-inflammatory and analgesic effects, and improve therapeutic effect.

4.4. Regulating the function of related signaling pathways

(1) CGRP signaling pathway

As mentioned above, CGRP signaling pathway is the core pathway of migraine pathogenesis, and its abnormal activation is the key to vasodilation and aggravated inflammatory reaction. TCM can block downstream signal transduction by down-regulating CGRP level and inhibiting its binding to receptors, thereby relieving vasodilation and neurogenic inflammation, which is also one of the core mechanisms of action confirmed by this study, consistent with clinical diagnosis and treatment practice.

(2) TRPV1 signaling pathway

Transient receptor potential vanilloid 1 (TRPV1) channel is a key channel for pain signal transmission. During migraine attack, this channel is abnormally activated, leading to the release of inflammatory mediators and increased nerve ending sensitivity, aggravating pain symptoms. During migraine attack, this channel undergoes conformational change and opens abnormally, Ca²⁺ influx triggers the cascade release of neuropeptides (CGRP, SP) and pro-inflammatory factors, inducing peripheral sensitization and neurogenic inflammation, finally forming a positive feedback loop of “channel activation-inflammation amplification-pain aggravation”. Combined with pharmacological research, effective components such as capsaicin and gastrodin in TCM can regulate TRPV1 channel activity. Long-term intervention can achieve channel desensitization, inhibit pain signal transmission, and exert long-term analgesic effect, which is also an important way of TCM in treating migraine.

5. Clinical treatment strategies and experience of traditional Chinese medicine

Combined with long-term clinical diagnosis and treatment practice, the core of TCM treatment for migraine

is “treatment based on syndrome differentiation”, emphasizing “treating both symptoms and root causes”. It is necessary to quickly relieve pain symptoms (treating symptoms) and regulate Zang-fu function, balance Qi and blood, and unblock meridians (treating root causes). An individualized comprehensive treatment plan should be formulated according to patients’ syndrome type, constitution, and age to achieve the best therapeutic effect and reduce recurrence. Combined with the clinical experience of our hospital, the clinical strategies and experience of TCM in treating migraine are summarized as follows.

5.1. TCM medication strategy

- (1) Syndrome differentiation and compatibility, treating both symptoms and root causes: TCM prescriptions emphasize the compatibility principle of “monarch, minister, assistant, and guide”. For different syndrome types of migraine, core monarch drugs are selected, combined with minister, assistant, and guide drugs, to achieve the therapeutic goal of “treating symptoms and caring for root causes”. For example, hyperactivity of liver Yang syndrome takes *Gastrodia elata* and *Uncaria rhynchophylla* as monarch drugs to calm liver and subdue Yang, unblock collaterals and relieve pain (treating symptoms), combined with *Eucommia ulmoides* and *Angelica sinensis* to nourish liver and kidney, nourish blood and soothe nerves (treating root causes), avoiding further hyperactivity of liver Yang; obstruction of collaterals by blood stasis syndrome takes *Ligusticum chuanxiong* and Peach Seed as monarch drugs to promote blood circulation to remove blood stasis, unblock collaterals and relieve pain (treating symptoms), combined with *Angelica sinensis* and *Paeonia lactiflora* to nourish blood and promote blood circulation (treating root causes), avoiding damaging healthy Qi due to blood activation, ensuring safe and effective treatment^[12].
- (2) Individualized adjustment, flexible modification
In clinical diagnosis and treatment, even for the same syndrome type, the dosage and type of drugs should be flexibly adjusted according to patients’ age, constitution, and concurrent symptoms, avoiding “one-size-fits-all” treatment. For example, elderly patients with deficiency of Qi and blood syndrome have weak spleen and stomach function, so it is necessary to appropriately increase the dosage of *Astragalus membranaceus* and *Codonopsis pilosula* to enhance the effect of replenishing Qi, and reduce the dosage of *Ligusticum chuanxiong* to avoid excessive blood activation; patients with severe phlegm-dampness in obstruction by phlegm-turbidity syndrome are added with *Coix lacryma-jobi* and *Atractylodes lancea* to strengthen the effect of invigorating spleen and eliminating dampness; those with severe pain are added with *Corydalis yanhusuo* and Frankincense to enhance the analgesic effect and improve patients’ treatment compliance.
- (3) Pay attention to the course of treatment, consolidate the curative effect
Migraine has a prolonged course and is easy to recur. TCM treatment needs to adhere to a sufficient course of treatment and should not be eager for success. Combined with clinical experience, generally continuous treatment for more than 3 months, after symptoms are relieved, the prescription can be appropriately adjusted to pills or powders for consolidation treatment for 1–2 months to reduce recurrence. At the same time, patients should be informed to take medicine according to the doctor’s advice during treatment, and should not stop or reduce medicine without permission to avoid affecting the therapeutic effect.

5.2. Key points of acupuncture treatment

Acupuncture treatment for migraine follows the principles of “unblocking meridians, harmonizing Qi and blood, relieving pain and calming nerves”. It combines empirical key acupoints with syndrome differentiation matching acupoints, pays attention to standardized operation, and avoids adverse reactions. Main acupoints Baihui and Fengchi can elevate Yang and lift collapse, dispel wind and unblock collaterals, and improve intracranial blood circulation; Taiyang is an extra-meridian acupoint, which can soothe head meridian Qi and unblock collaterals to relieve pain, a key local acupoint; Hegu (source point of Hand Yangming Meridian), taken distally along the meridian, “Hegu governs face and mouth”, with significant analgesic effect; Zusanli (he-sea point of Foot Yangming Meridian, lower he-sea point) is a key health-care acupoint, acupuncture can replenish Qi and blood, regulate the middle energizer, indirectly nourish brain marrow through “invigorating earth to generate metal”. The combination of three acupoints, combining distant and local, local analgesia and overall tonification, synergistically exerts the effect of relieving headache; matching acupoints are selected according to syndrome types to achieve acupuncture based on syndrome differentiation and improve treatment pertinence.

Disposable sterile filiform needles (0.25 mm × 40 mm) were selected. After routine iodophor disinfection of acupoint skin, vertical insertion was performed to obtain Qi (degree of acid, numbness, distension, and heaviness), uniform reinforcing and reducing method was applied, needles were retained for 30 min, and needling was performed once during retention to maintain needle sensation. Treatment frequency: Qd (once a day) × 5 d/week. The stimulation amount was dynamically adjusted according to patients' tolerance during the course of treatment to strictly prevent adverse acupuncture events such as needle fainting and hematoma. For patients with needle fainting constitution, the needle retention time can be shortened (20–25 minutes) and stimulation intensity reduced; patients were instructed to lie flat and rest before acupuncture, avoiding acupuncture on an empty stomach; for elderly patients and those with weak constitution, the acupuncture depth was appropriately reduced to ensure treatment safety.

5.3. Comprehensive intervention measures

TCM treatment emphasizes “holistic conditioning”. In addition to TCM and acupuncture treatment, it is necessary to combine emotional regulation and lifestyle guidance to improve efficacy and reduce recurrence, which is also an important link that cannot be ignored in clinical diagnosis and treatment.

(1) Emotional regulation

Patients with hyperactivity of liver Yang syndrome need to avoid emotional fluctuations, and can regulate emotions by listening to soothing music, meditation, growing flowers and plants, etc., to keep a comfortable mood;

(2) Dietary conditioning

Patients with obstruction by phlegm-turbidity syndrome avoid rich, greasy, raw and cold food, and eat more food for invigorating spleen and eliminating dampness (such as Chinese yam, coix seed, wax gourd, etc.); patients with deficiency of Qi and blood syndrome should choose food with Qi-replenishing and blood-nourishing effects (such as red dates, longan flesh, lean meat, etc.), avoid pungent, fragrant and dry food;

(3) Lifestyle intervention

Establish a regular sleep-wake cycle, fixed bedtime at 22:00–23:00, ensure 7–8 h of sleep, eliminate staying up late and overwork;

(4) Exercise conditioning

Low-to-moderate intensity aerobic exercise such as Baduanjin and brisk walking is recommended (target heart rate controlled at 50–60% of maximum heart rate), 30 min each time, ≥ 3 times a week to improve microcirculation and enhance body tolerance, competitive strenuous exercise is prohibited;

(5) Avoid inducing factors

Establish a headache diary to identify and avoid individual triggering factors (such as specific food, strong light, emotional fluctuation, etc.).

6. Discussion

Combined with the results of clinical randomized controlled trial in our hospital, the clinical efficacy of TCM syndrome differentiation comprehensive treatment for migraine is significantly better than conventional Western medicine treatment. The total effective rate of the TCM treatment group reaches 91.67%, which is significantly higher than 76.67% of the control group. It can effectively reduce migraine attack frequency, shorten attack duration, relieve pain degree, improve patients' quality of life, and significantly increase serum 5-HT level and decrease CGRP level, regulate the balance of neurotransmitters and vasoactive substances, with clear mechanism of action, consistent with clinical diagnosis and treatment practice.

Compared with simple Western medicine symptomatic treatment, the TCM syndrome differentiation and treatment system shows unique advantages in migraine management:

(1) Its intervention mechanism presents multi-target and multi-channel network regulation characteristics

The pathogenesis of migraine is complex, single Western medicine mostly targets a certain target with limited therapeutic effect, while TCM can simultaneously regulate neurotransmitters, improve vascular function, inhibit inflammatory reaction through compound compatibility and acupuncture synergy, achieve multi-dimensional intervention with more comprehensive and durable efficacy.

(2) Durable efficacy and low recurrence rate

TCM treatment focuses on “treating both symptoms and root causes”, not only relieving pain symptoms, but also regulating Zang-fu function and improving constitution, solving the problems of Qi and blood disorder and meridian obstruction from the root. In terms of clinical outcome, TCM intervention can prolong the remission period and reduce the annual recurrence rate.

(3) Better safety, the incidence of adverse events is significantly lower than that of the conventional drug group

In this study, no obvious adverse reactions occurred in the TCM treatment group, while 8 patients in the control group had mild drowsiness and dizziness, indicating that TCM treatment has higher safety and is more suitable for long-term intervention.

(4) Individualized diagnosis and treatment, strong adaptability

TCM syndrome differentiation and treatment can flexibly adjust the plan according to patients syndrome type, constitution, and age, avoiding “one-size-fits-all” treatment, and more in line with clinical actual needs.

This study also has certain limitations: small sample size and single-center study, which may lead to bias in the research results; only 5-HT and CGRP were selected as observation indicators, and inflammatory factors such as IL-6 and TNF- α and related signaling pathway indicators were not detected, and the mechanism of action was not deeply explored; the follow-up time was only 6 months, and the long-term

efficacy and recurrence rate still need further observation.

7. Conclusion

TCM syndrome differentiation treatment for migraine has definite efficacy, which can effectively reduce migraine attack frequency, shorten attack duration, relieve pain degree, and improve patients' quality of life. Its mechanism of action may be related to regulating 5-HT/CGRP neurotransmitter balance, improving trigeminovascular system dysfunction, inhibiting neurogenic inflammation and related signaling pathways. TCM has the advantages of multi-target, durable efficacy, high safety, and strong individualized adaptability, which is an effective choice for clinical treatment of migraine and worthy of clinical promotion and application.

Disclosure statement

The authors declare no conflict of interest.

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