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Original Research

Tuling Wendan Decoction combined with flunarizine in the treatment of migraine patients and the effect of intervention on serum cyclooxygenase-2, endothelin-1 and nitric oxide

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Abstract: This experiment aimed to explore the curative effect of Tuling Wendan Decoction combined with flunarizine on migraine patients and the intervention effect on serum cyclooxygenase-2 (COX-2), endothelin-1 (ET-1), nitric oxide(NO) levels. For this purpose, from January 2019 to January 2020, 96 patients with migraine in our hospital were selected as the research object. Using a simple randomization method, patients who meet the criteria were assigned 1:1, and each patient was assigned a random number, of which the number 1 to 48 were the observation group, and the number 49 to 96 were the control group. The control group was treated with flunarizine, and the observation group was treated with Tuling Wendan Decoction combined with flunarizine. Comparing the efficacy, incidence of adverse reactions, the incidence of headache, cerebral blood flow rate [basal artery (BA), vertebral artery (VA), middle cerebral artery (MCA)], vascular endothelial function (serum COX-2, ET-1, NO levels), neurological function [5-hydroxytryptamine (5-HT), brain-derived neurotrophic factor (BDNF), calcitonin gene-related peptide (CGRP)] before treatment, 4 weeks and 8 weeks after treatment between the two groups. The results for efficacy showed that after 8 weeks of treatment, the total effective rate of the observation group (93.75%) was higher than that of the control group (77.08%, $P<0.05$). In regards to the situation of headache attack, the number of headache attacks, duration, pain degree and accompanying symptom scores of the observation group after 4 weeks and 8 weeks of treatment were lower than those of the control group ($P<0.05$). Results of cerebral blood flow velocity showed that the blood flow velocity of BA, VA, MCA in the observation group was lower than that in the control group after 4 and 8 weeks of treatment ($P<0.05$). Vascular endothelial function results indicated that the serum COX-2 and ET-1 levels of the observation group were lower than those of the control group after 4 weeks and 8 weeks of treatment, and the serum NO levels were higher than that of the control group ($P<0.05$). The serum BDNF and CGRP levels of the observation group were lower than those of the control group after 4 weeks and 8 weeks of treatment, and the serum 5-HT levels were higher than the control group ($P<0.05$). The incidence of adverse reactions between the two groups was not statistically significant ($P>0.05$). It was concluded that Tuling Wendan Decoction combined with flunarizine is the first treatment for migraine, with definite curative effect and can effectively improve the onset of headache, reduce the speed of cerebral blood flow, regulate vascular endothelial function and nerve function, and ensure safety.

Key words: Tuling Wendan Decoction; Flunarizine; Migraine; Vascular endothelial function; Cerebral blood flow velocity; Brain-derived neurotrophic factor.

Introduction

Migraine is a common neurological disease, which features repeated attacks, long treatment courses and difficult recovery (1). Epidemiological survey shows that the incidence of migraines in adults is 8.0%~18.7% in China, which tends to grow and occur in younger groups with increasing life pressure. The disease is most common among females (2-3). At the same time, related studies have confirmed (4) that migraine attacks have a certain relationship with the abnormal release of vascular endothelial factors such as cyclooxygenase-2 (COX-2), endothelin-1 (ET-1), nitric oxide (NO) which acts on cerebral blood vessels, and induces dysfunction of intracranial vasomotion. At present, most patients with migraines are mainly symptomatically treated with non-steroidal anti-inflammatory drugs, ergotamines and other Western medicine. Although it can temporarily relieve or eliminate headaches, long-term use can produce drug resistance, resulting in repeated attacks. In recent years, Chinese medicine has been used to treat migraine through holistic, comprehensive and dynamic ways, showing characteristics of multiple targets and multiple levels, which helps make up for the insufficiency and limitations of Western medicine treatment, thus achieving the goal of addressing both the symptoms and root causes. Chinese medicine believes that migraine belongs to the scope of "headache", "wind syndrome of the head". Its main pathogenesis is that Qi stagnates and accumulates in phlegm, transmitting heat, developing phlegm-heat syndrome, with pathogen attacking orifices in head and resulting in a headache. The treatment should aim to reduce phlegm and clear dampness, activate meridians to stop pain (5-6). Tuling Wendan Decoction is derived from "Medical Notes in Xianxing Study" by Miao Xiyong in the Ming Dynasty,

which has the effect of dispelling wind and overcoming dampness, invigorating blood circulation and relieving pain. However, the intervention effect of Tuling Wendan Decoction combined with flunarizine on serum COX-2, ET-1 and NO levels in migraine patients have not been fully elucidated. Based on this, this study makes the first attempt to use Tuling Wendan Decoction combined with flunarizine to investigate its effect on migraine and its effect on serum COX-2, ET-1 and NO levels. The specific analysis is as follows.

Materials and Methods

Normal information

96 migraine patients treated in our hospital from January 2019 to January 2020 were selected as the research subjects. According to a simple randomization grouping method, patients meeting the criteria were allocated at a ratio of 1:1. Each patient was given a random number, of which, 1~48 patients were classified in the observation group, and 49~96 patients were classified in the control group. The basic data of the two groups [age, course of the disease, gender, body mass index (BMI), disease subtype, pain level, headache location] are balanced and comparable (P>0.05), as shown in Table 1.

Selection criteria

Inclusion criteria

Western medicine standard: Included (A): all meet the relevant standards for migraine in the "2017 Taiwan Prevention and Treatment Guidelines for Migraine"(7); (B): headache attack duration> 4 h; (C): unilateral, pulsating, moderate pain or above; (D): number of attacks ≥5 times;

TCM standard: With reference to the migraine standard in [Diagnostic and Efficacy Standards for TCM Syndrome] (8), it belongs to the syndrome of upward disturbance of phlegm-turbidity, with the main symptoms of headache and head pain, or dizziness; secondary symptoms of chest tightness, abdominal distension, nausea with reduced appetite, less phlegm, sticky white phlegm; tongue and pulse: white greasy tongue coating, slippery pulse.

This study was approved by the medical ethics committee of our hospital, and patients and their families have signed informed consent.

Exclusion criteria

This section included (A) Those who have a history of allergy to flunarizine; (B) Those who have a history of anti-migraine treatment such as non-steroidal anti-inflammatory drugs and β-blockers within the past 4 weeks; (C) those combined with ocular migraine or other primary headaches; (D) Those with high altitude hypoxia, meningitis, pheochromocytoma or encephalitis; (E) Those with craniocerebral injury, hypertension, epilepsy and cervical spondylosis-induced headaches; (F) Those who are in special periods such as puerperium or lactation; (G) Those with an organic lesion in important organs such as liver and kidney; (H) Those with asthma and allergic rhinitis; (I) Those with abnormal mental behavior.

Method

Treatment method

Both groups avoided inducing factors such as direct strong light stimulation, emotional stress, consumption of irritating food, and received health education. The control group was treated with flunarizine orally [Chifeng Wanze Pharmaceutical Co., Ltd., National Medicine Permission Number H15021331, specification: 5 mg (calculated as C26H26F2N2)], 5 mg/time, once/day. The observation group was treated with Tuling Wendan Decoction on this basis. Prescription composition: rhizoma smilacis glabrae 30 g, Licorice 3 g, Ligusticum wallichii 15 g, Rhizoma Pinellinae Praeparata 10 g, Fructus aurantii 10 g, fresh ginger3 pieces, radix angelicae 10 g, Poria cocos 20 g, tangerine peel 10 g, caulis Bambusa in taeniam 15 g, Fructus Ziziphi Jujubae 5 pieces (smashed). 200 ml juice from the decoction was taken once a day in the morning and evening, 1 dose/d. Both groups received continued treatment for 8 weeks.

Detection method

6 ml venous blood was taken on an empty stomach, centrifuged at 2500 r/min for 10 min with a centrifugal

Table 1. Two sets of general information.

Normal information	(n=48) Observation group (n=48)	(n=48) Control group (n=48)	t/χ^2	*P*
Gender (male/female)	17/31	20/28	0.396	0.529
Age (years)	23~62(38.72±5.98)	22~60(39.31±6.29)	0.471	0.639
BMI(kg/m^2)	17.2~26.3(22.86±1.53)	17.0~26.5(23.05±1.72)	0.572	0.569
Course of disease (year)	1.9~8.3(4.69±1.21)	1.7~8.6(5.02±1.64)	1.122	0.265
Disease classification				
Aura	12(25.00)	15(31.25)	0.464	0.496
Without omen No aura	36(75.00)	33(68.75)		
Pain level				
Moderate	38(79.17)	35(72.92)	0.515	0.473
Severe	10(20.83)	13(27.08)		
Headache area				
Unilateral	41(85.42)	39(81.25)	0.300	0.584
Bilateral	7(14.58)	9(18.75)		

radius of 8 cm to separate and take the serum. The serum was stored in a refrigerator at -70°C until testing: (A) serum ET-1 and calcitonin gene-related peptide (CGRP) level were detected by radioimmunoassay. The kit was purchased from Shanghai Hengyuan Biotechnology Co., Ltd.; (B) Enzyme-linked immunosorbent assay was used to detect serum NO, 5-hydroxytryptamine (5-HT), brain-derived neurotrophic factor (BDNF), COX-2 level. The kit was purchased from Wuhan Xinqidi Biotechnology Co., Ltd. The above operations were performed in strict accordance with the kit instructions.

Criteria for curative effect

After 8 weeks of treatment, pulsating headache or swelling pain, paroxysmal migraine symptoms like photophobia, phonophobia, vomiting, nausea basically disappear, with TCM syndrome score decreased by>95%, then the disease is clinically cured; after 8 weeks of treatment, the above paroxysmal migraine symptoms are obviously improved, with 75% ≤ TCM syndrome score reduction ≤ 95%, the treatment is markedly effective; after 8 weeks of treatment, the above paroxysmal migraine symptoms are controlled, with 30% ≤ TCM syndrome score reduction <75%, the treatment is effective; after 8 weeks of treatment, the above paroxysmal migraine symptoms show no improvement or worsen, with TCM syndrome score reduction<30%, the treatment is invalid. Total effective rate = clinical cure rate + markedly effective rate + effective rate. Where, the TCM syndrome scores are evaluated by a 4-level scoring method, with headache, abdominal distension, nausea with reduced appetite, less phlegm, sticky white phlegm; white greasy tongue coating, slippery pulse divided into 4 levels of none (0 points), mild (1 point), moderate (2 points), severe (3 points).

Observation indicators

(A) Curative effect. (B) The scoring method was taken to compare headache attacks between the two groups before treatment, at 4 weeks and 8 weeks after treatment, including the number of attacks, duration, pain level, and accompanying symptoms. Where, number of attacks: ≥5 times/month is given 6 points, 3~4 times/month is given 4 points, ≤ 2 times is given 2 points; Duration: >48 h is given 6 points, 12~48 h is given 4 points, <12 h is given 2 points; Pain: severe pain requiring bed rest is given 6 points, moderate pain that affects work but with no bed, rest requirement is given 4 points, mild pain, with little impact on work is given 2 points; accompanying symptoms: including photophobia, phonophobia, vomiting, nausea, etc., those with>3 items are given 3 points, 2~3 items are given 2 points, and <2 items are given 1 point. (C) Transcranial Doppler ultrasound system (model: DB-1049, purchased from DWL Germany) was used to compare the cerebral blood flow velocity [basilar artery (BA), vertebral artery(VA), middle cerebral artery (MCA)] between the two groups before treatment, at 4 weeks and 8 weeks after treatment. (D) Vascular endothelial function (serum COX-2, ET-1, NO levels) was compared between the two groups before treatment, at 4 weeks and 8 weeks after treatment. (E) Nerve function (serum 5-HT, BDNF, CGRP levels) was compared between the two groups before treatment, at 4 weeks and 8 weeks after treatment. (F) The incidence of adverse reactions (diarrhea, drowsiness, burnout, dry mouth) was counted in both groups.

Statistical methods

SPSS22.0 statistical software was used to process the data. The measurement data was indicated by ($\bar{x} \pm s$) and tested by the *t-test*, and the count data was indicated by n (%) and tested by χ^2. $P<0.05$ indicates a statistically significant difference.

Results

Curative effect

After 8 weeks of treatment, the total effective rate is higher in the observation group (93.75%) than in the control group (77.08%) ($P<0.05$), as shown in Table 2.

Headache attack

There is no statistically significant difference in scores for the number of headache attacks, duration, pain level and accompanying symptom between the two groups before treatment ($P>0.05$); the scores for the number of headache attacks, duration, pain level and accompanying symptoms are decreased after 4 and 8 weeks of treatment, which is lower in the observation group than in the control group ($P<0.05$), as shown in Table 3.

Cerebral blood flow velocity

There is no significant difference in the blood flow velocity of BA, VA, and MCA between the two groups before treatment ($P>0.05$); the blood flow velocity of BA, VA, and MCA is decreased in both groups after 4 and 8 weeks of treatment, with that lower in observation group than in the control group ($P<0.05$), as shown in Table 4.

Vascular endothelial function

There is no statistically significant difference between the two groups in serum COX-2, ET-1 and NO levels before treatment ($P>0.05$); after 4 and 8 weeks of treatment, serum COX-2 and ET-1 levels are decreased in both groups, which are lower in the observation group than in the control group, while serum NO level is increased after treatment, which is higher in the observation group than in the control group ($P<0.05$), as shown in Table 5.

Table 2. Comparison of efficacy between two groups n (%).

Group	Number of cases	Clinical cure	Marked effect	Effective	Invalid	Total efficiency
Observation	48	21(43.75)	16(33.33)	8(16.67)	3(6.25)	45(93.75)
Control	48	16(33.33)	12(25.00)	9(18.75)	11(22.92)	37(77.08)
χ^2						5.352
P						0.021

Table 3. Comparison of headache attacks between the two groups ($\bar{x}$±s, score).

Time	Group	Number of cases	Number of attacks	Duration	Pain level	Accompanying symptoms
Before treatment	Observation	48	4.48±1.20	4.19±1.32	4.05±1.47	2.28±0.52
	Control	48	4.29±1.08	4.35±1.46	3.86±1.75	2.32±0.49
	t		0.815	0.563	0.576	0.388
	P		0.417	0.575	0.566	0.699
After 4 weeks of treatment	Observation	48	2.75±0.72[a]	2.67±0.53[a]	2.19±0.61[a]	1.57±0.31[a]
	Control	48	3.16±0.58[a]	3.49±0.64[a]	2.66±0.46[a]	1.92±0.26[a]
	t		3.072	6.837	4.262	5.993
	P		0.003	<0.001	<0.001	<0.001
After 8 weeks of treatment	Observation	48	1.70±0.40[ab]	1.49±0.27[ab]	1.15±0.31[ab]	0.76±0.25[ab]
	Control	48	2.19±0.59[ab]	2.08±0.42[ab]	1.90±0.45[ab]	1.50±0.44[ab]
	t		4.763	8.187	9.509	10.131
	P		<0.001	<0.001	<0.001	<0.001

Note: compared with the same group before treatment, [a]*P*<0.05; compared with the same group after 4 weeks of treatment, [b]*P*<0.05.

Table 4. Comparison of cerebral blood flow velocity between the two groups($\bar{x}$±s, cm/s).

Time	Group	Number of cases	BA	VA	MCA
Before treatment	Observation group	48	49.48±5.23	42.70±6.28	81.18±5.73
	Control	48	48.85±5.36	43.21±5.94	80.82±6.25
	t		0.583	0.409	0.294
	P		0.561	0.684	0.769
After 4 weeks of treatment	Observation group	48	42.28±4.68[a]	36.64±4.77[a]	74.69±5.52[a]
	Control	48	45.38±4.55[a]	40.15±4.28[a]	78.13±5.27[a]
	t		3.290	3.795	3.123
	P		0.001	<0.001	0.002
After 8 weeks of treatment	Observation group	48	40.18±3.53[ab]	32.18±3.56[ab]	70.28±4.43[ab]
	Control group	48	43.66±3.91[ab]	37.53±4.75[ab]	75.64±4.76[ab]
	t		4.577	6.244	5.711
	P		<0.001	<0.001	<0.001

Note: compared with the same group before treatment, [a]*P*<0.05; compared with the same group after 4 weeks of treatment, [b]*P*<0.05.

Table 5. Comparison of vascular endothelial function between the two groups($\bar{x}$±s).

Time	Group	Number of cases	COX-2(ng/ml)	ET-1(ng/L)	NO(μmol/L)
Before treatment	Observation	48	3.81±1.67	88.75±10.31	47.46±7.85
	Control	48	4.02±1.85	90.28±12.46	46.94±8.22
	t		0.584	0.655	0.317
	P		0.561	0.514	0.752
After 4 weeks of treatment	Observation	48	2.82±0.71[a]	74.65±9.77[a]	66.29±10.37[a]
	Control	48	3.55±0.58[a]	80.10±10.15[a]	58.35±9.86[a]
	t		5.517	2.680	3.844
	P		<0.001	0.009	<0.001
After 8 weeks of treatment	Observation	48	2.20±0.39[ab]	65.36±7.84[ab]	80.59±12.46[ab]
	Control	48	2.98±0.35[ab]	71.28±8.49[ab]	74.87±11.25[ab]
	t		10.313	3.549	2.361
	P		<0.001	0.001	0.020

Note: compared with the same group before treatment, [a]*P*<0.05; compared with the same group after 4 weeks of treatment, [b]*P*<0.05.

Table 6. Comparison of nerve function between the two groups($\bar{x}$ ±s).

Time	Group	Number of cases	5-HT(ng/L)	BDNF(ng/ml)	CGRP(ng/L)
Before treatment	Observation	48	74.18±13.06	8.41±2.32	18.44±4.21
	Control	48	73.85±14.52	9.33±2.84	19.13±4.48
	t		0.117	1.738	0.778
	P		0.907	0.086	0.439
After 4 weeks of treatment	Observation	48	87.69±15.80	3.55±1.43	14.76±3.58
	Control	48	80.27±15.13	5.29±1.86	17.63±3.74
	t		2.350	5.138	3.841
	P		0.021	<0.001	<0.001
After 8 weeks of treatment	Observation	48	96.88±16.40	1.64±0.97	11.96±2.91
	Control	48	88.39±15.57	2.84±1.50	14.58±3.13
	t		2.601	4.654	4.247
	P		0.011	<0.001	<0.001

Table 7. Comparison of the incidence of adverse reactions between the two groups n (%).

Group	Number of cases	Diarrhea	Drowsiness	Burnout	Dry mouth	Total incidence
Observation	48	1(2.08)	1(2.08)	2(4.17)	1(2.08)	5(10.42)
Control	48	0(0.00)	1(2.08)	1(2.08)	1(2.08)	3(6.25)
χ^2						0.136
P						0.712

Nerve function

There is no statistically significant difference in serum 5-HT, BDNF, and CGRP levels between the two groups before treatment (P>0.05); after 4 and 8 weeks of treatment, serum BDNF and CGRP levels are decreased in both groups, which are lower in the observation group than in the control group, serum 5-HT level is increased after treatment, which is higher in the observation group than in the control group (P<0.05), as shown in Table 6.

Adverse reactions

The incidence of adverse reactions has no statistically significant difference between the two groups (P>0.05), as shown in Table 7.

Discussion

Migraine has complicated pathogenesis, which has not been fully elucidated in clinics so far. Many scholars support the angiogenic theory and neurology theory of vasomotor dysfunction (8, 9), and believe that there is a possible correlation with environmental, diet, genetic factors (10, 11). At present, the key to clinical treatment of migraines is to relieve the headache and reduce the number of headache attacks. "Chinese Prevention and Treatment Guidelines for Migraine" believe that (12), flunarizine for preventive treatment of migraine has sufficient clinical evidence, which can be used as a clinically recommended drug. Flunarizine is a calcium channel antagonist, which can effectively improve the intracellular calcium content, prevent abnormal contraction of vascular smooth muscle, and then prevent migraine attacks. However, single drug use receives an unideal effect, which can easily cause drug-overuse headaches.

First recorded in "Internal Canon of Medicine", headache is referred to as "wind of the head" and "brain wind" in "Plain Questions·Theory of Wind". Migraine with an upward disturbance of phlegm-turbidity is its common syndrome. According to Li Ting's "Introduction to Medicine" in the Ming Dynasty, “The symptom of headwind usually includes phlegm and retained fluid, which may be caused by wash or sleep in wet draught”. Hence, the pathological mechanism for migraine lies in the invasion of wind evil, phlegm turbidity, stasis blocking channels. The wind evil causes qi and blood stasis, resulting in loss of nourishment in the brain. The disease has occasional attacks due to cold, heat, depression, anger, then leading to headaches (11-12). The key to treatment is to dispel the wind, dehumidify, remove blood stasis, eliminate phlegm, and dredge collaterals. In Tiling Wendan Decoction, Rhizoma smilacis glabraecan detoxify, induce diuresis and ease joint movement; Ligusticum wallichii can invigorate blood and qi circulation, dispel wind and relieve pain, relieve depression and eliminate dampness; Rhizoma Pinellinae Praeparata can eliminate dampness and phlegm; Fructus aurantii can promote qi circulation to alleviate middle energizer, help digestion and eliminate phlegm; fresh ginger can promote blood circulation to remove blood stasis, lengthen life, resolve phlegm and relieve cough; radix angelicae can relieve exterior syndrome, dispel cold and stop pain; Poria cocos can induce diuresis to alleviate edema, excrete dampness and tonify spleen; caulis

Bambusa in taeniam can eliminate phlegm by cooling; Tangerine Peel can regulate qi and strengthen spleen, eliminate dampness to reduce phlegm; licorice can tonify spleen and qi, clear heat and detoxify, eliminate phlegm and stop pain; Fructus Ziziphi Jujubae can invigorate spleen-stomach and replenish qi, nourish blood for tranquilization. A combination of the medicines can dispel wind to free the collaterals, reduce phlegm and eliminate dampness. In this study, Tuling Wendan Decoction was used in combination with flunarizine for the treatment of migraine patients for the first time. The results indicate that a combination of the two can effectively alleviate headache attacks, and the total effective rate of clinical treatment can reach 93.75%. Modern pharmacological studies have shown that rhizoma smilacis glabrae is rich in chemical components like alkaloids, oleic acid, sterols, which can help improve oxygen-free radical scavenging enzyme activity, inhibit lipid peroxidation, prevent abnormal activation of platelets, and alleviate hemorheology abnormalities (13); The main components of Ligusticum wallichii are ligustrazine, chuanxingol, and volatile oils, etc., which can significantly increase the content of platelet cyclic adenosine monophosphate, reduce platelet surface activity, inhibit platelet aggregation, promote vasodilation, and improve central blood supply (14); Poria cocos rich in pachymaran has a variety of biological activities, which can effectively eliminate free radicals in the body's cell metabolism, and play a good role in anti-oxidative stress (15). Therefore, the use of flunarizine plus Tuling Wendan Decoction can create a good synergistic effect and improve migraine treatment effects from various aspects and multiple action mechanisms. According to further research, Tuling Wendan Decoction combined with flunarizine helps reduce the cerebral blood flow velocity in migraine patients. The mechanism is that radix angelicae in Tuling Wendan Decoctioncan promote vasodilation, improve blood flow in the brain, and regulate blood circulation in the brain; Ligustrazine dilates intracranial blood vessels through the blood-brain barrier and then relieves vasospasm to achieve the purpose of regulating intracranial blood flow. Combined with flunarizine, it helps to inhibit vascular smooth muscle contraction, block histamine HI receptors, reduce blood viscosity, thereby regulating blood circulation in the brain and guaranteeing blood oxygen supply.

Sun et al. (16) found that peripheral blood vasoactive substances may be involved in migraine attacks. Where, ET-1 level can release vascular endothelial contraction factors and induce vasoconstriction, which is one major factor involved in the vasoconstriction phase of migraine attacks (17). NO cannot only promote cerebral vasodilation but also activate the sensitivity of nociceptive neurons, activate and amplify the body's pain signals, thereby increasing the risk of migraines. COX-2 is highly expressed in neurons and cerebrovascular endothelial cells, which can mediate neurogenic inflammation during migraine attacks and increase pain sensitivity. Wang et al. (18) confirmed that the high expression of COX-2 levels participates in the pathophysiology process of migraine. The data of this study reveals that Tuling Wendan Decoction combined with flunarizine is superior to flunarizine monotherapy in improving vascular endothelial function in migraine patients. It is possibly because Tuling Wendan Decoction has rich Chinese herbal ingredients of Fructus aurantii, which can give play to the role of active ingredients like naringin, hesperidin, naringenin, help reduce oxidative stress and inflammation caused by tumor necrosis factor-α induction, downregulate mononuclear cell adhesion molecules, promote NO production, reduce vasoconstriction and improve vascular endothelial function.

Another study confirmed that abnormal neurotransmitter content may also be major pathogenesis of migraine (19). 5-HT is an inhibitory neurotransmitter. Xu et al. (20) have shown that 5-HT neural pathway plays an important role in the pathophysiology of migraine including descending pain facilitation and pathway imbalance inhibition. BDNF plays an important role in regulating central nervous system pain and development, which may be involved in the occurrence and development of migraines. Wang et al. (21) confirmed that CGRP is a neuroactive substance that can regulate nociceptive information transmission and can play an important role in the pathophysiology of migraine through the trigeminovascular system. This study shows that Tuling Wendan Decoction combined with flunarizine can help improve the nerve function of migraine patients. The possible mechanism is that a combination of the two can inhibit glutamate release and certain calcium channel activities, reduce CGRP and inflammatory peptide release, balance the content of neurotransmitters, reduce neurological dysfunction, thereby improving nerve function. Further research also found that Tuling Wendan Decoction combined with flunarizine has a certain safety in the treatment of migraines.

To sum up, it can be seen that Tuling Wendan Decoction combined with flunarizine as the first treatment for migraine receives definite curative effect, which can effectively alleviate headache attack, reduce cerebral blood flow velocity, regulate vascular endothelial function and nerve function, and ensure safety. However, this study fails to further investigate the effect of Tuling Wendan Decoction combined with flunarizine in the intervening inflammatory reaction of migraine patients. In the case of nitric oxide, oxidized compounds have several reports and their effects have been investigated (22-27). In this study, nitric oxide was investigated.

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These first two authors (XiaYang Xie, Kai Shang) contributed equally to this work.

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