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Review Article

Clinical characteristics of migraines in patients and the efficacy analysis of flunarizine combined with aspirin

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Abstract: To explore the application value of flunarizine combined with aspirin in patients with migraine headaches. A total of 257 migraine patients admitted to our hospital were collected as research subjects. Among them, 132 patients treated with flunarizine combined with aspirin were taken as the observation group (OG), and another 125 patients treated with flunarizine were regarded as the control group (CG). The levels of high sensitivity C-reactive protein (hs-CRP), calcitonin gene related peptide (CGRP), 5-hydroxytryptamine (5-HT) and quality of life were observed and compared. After intervention of different treatments, the pain degree, duration and attack frequency were improved when compared with those before treatment ($P<0.001$). The improvement of clinical symptoms in the OG was more obvious than that in the CG, and the curative effect was higher than that in the CG ($P<0.05$). There was no difference in serum indexes between the two groups before treatment, and the levels of 5-HT, CGRP and hs-CRP changed in both groups when compared with those before treatment, while the levels of hs-CRP in the CG was not significantly different from that before treatment ($P>0.05$). After treatment, the levels of CGRP and hs-CRP in the OG were remarkably lower than those in the CG ($P<0.05$), and the level of 5-HT was notably higher than that in the CG ($P<0.05$). Cerebral blood flow was improved in both groups after treatment, while the OG showed better effects. The MSQ scale evaluated the quality of life of migraine patients, and the score of the OG was remarkably higher than that of the CG ($P<0.05$). Aspirin combined with flunarizine can effectively relieve the clinical symptoms of migraines, and is superior to flunarizine alone in improving the quality of life of patients, reducing inflammation and regulating cerebrovascular function.

Keywords: Migraine, flunarizine, aspirin, clinical characteristics

Introduction

The migraine is a common and recurrent brain dysfunction disease in clinic. It has been listed as the sixth most disabling disorder in the world, with an incidence rate of about 15-18% [1]. Females account for a large proportion of the disease, with a male to female ratio of 1:3 [2]. It is reported that the disability caused by severe a migraine is equivalent to mental diseases and dementia, and is most prevalent in America, Europe and other places [3]. Many researches believe that the cause of migraines is related to nerves and blood vessels, extensive cortical inhibition, 5-hydroxytryptamine (5-HT) consumption and other factors [4]. Some scholars also believe that the occurrence of negative emotions (such as anxiety and depression) is an important reason for inducing migraines [5]. A migraine is complicated and has multiple influencing factors, which may last for several days after the occurrence of the onset, causing serious impact on the life and economy of patients [6].

Migraines are divided into the acute attack period and chronic remission period [3]. Among them, for acute treatment, drugs are currently an effective means in treating a migraine [7]. Drugs that show curative effects in treating acute migraine attacks can be divided into non-specific drugs (analgesics and non-steroidal anti-inflammatory drugs-NSAIDs) and specific drugs (ergot derivatives and triptan) [3, 8]. Aspirin is a non-steroidal anti-inflammatory drug with anti-inflammatory, antipyretic, and analgesic effects [9]. This medicine can relieve headaches by dilating blood vessels in patients,

and has good effect in the treatment of migraines [9, 10]. For preventive treatment, there are commonly used angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), and β receptor blockers, etc. [11]. Flunarizine is currently the only CCB that can penetrate the blood-brain barrier and has the characteristics of being an antihistamine, anti-5-HT and antidopaminergic [12]. Flunarizine has been extensively used in the clinical treatment of migraines. It is a first-line drug for migraine prevention and treatment, and has reliable curative effects and good safety [11]. Therefore, this study uses flunarizine as a control drug to explore the curative effect of flunarizine combined with aspirin in treating migraines.

Methods

General data

A total of 257 migraine patients admitted to Cangzhou Central Hospital were collected as research subjects. The clinical characteristics of patients were observed. Among them, 132 patients treated with flunarizine combined with aspirin were taken as observation group (OG), including 35 males and 97 females. Migraine types: 26 cases of migraine with aura and 106 cases of migraine without aura. Another 125 patients treated with flunarizine were taken as control group (CG), including 34 males and 91 females. Migraine types: 22 cases of migraine with aura and 103 cases of migraine without aura. There was no remarkable difference in general clinical data between the two groups, suggesting comparability. This study was conducted with the approval of the Ethics Committee of Cangzhou Central Hospital.

Inclusion criteria were as follows: Migraines of patients met the diagnostic criteria of the International Headache Society [13]. Patients were older than 18 years old. Patients whose vital signs and nervous system were normal. Patients who knew the contents of the experiment and signed the informed consent form. Patients who were not complicated with other tumor diseases. Patients who were willing to cooperate with the study.

Exclusion criteria were as follows: Patients combined with liver and renal dysfunction. Patients whose compliance was poor. Patients who pregnant or breastfeeding. Patients who were allergic to the drugs in this study. Patients who relied on sedatives or analgesics for a long time.

Therapies

CG: Flunarizine (Xi'an Janssen Pharmaceutical Co., Ltd., SFDA approval number: H10930003) was taken orally, 10 mg once a day at night. If depression occured, external reactions and other serious adverse reactions occurred during treatment, the drug was stopped immediately. If there was no obvious improvement after 2 months of treatment, treatment could be stopped. If the curative effect was great and only maintenance treatment was required, it could be reduced to continuous administration for 5 days per week and withdrawal for 2 days.

OG: Aspirin was used in addition to the treatment of the CG (Bayer health care manufacturing S.r.l, SFDA approval number: J2017021). Once a day, 100 mg at a time, aspirin was taken with the appropriate amount water before meals. Both groups were reexamined one month after treatment, and then the clinical effects of the two groups were observed and compared.

Detection indicators

Four ml fasting venous blood was collected from the two groups before and after treatment, centrifuged at 3000× g for 10 min at 4°C, and the serum was stored for later use. Enzyme linked immunosorbent assay (ELISA) was applied for determination of high sensitivity C-reactive protein (hs-CRP), calcitonin gene related peptide (CGRP) and 5-HT. ELISA kits were all purchased from Shanghai Gefan Biotechnology Co., Ltd., the batch numbers were HC041, HC020 and HS014. HR-801 enzyme label analyzer (Shenzhen Huakerui Technology Co., Ltd., China) was used for determination. Firstly, 10 μl of sample and 40 μl of diluent were added to the sample well to be tested, and 50 μl of standard products of different concentrations were added to the standard well. Except for the blank well (same as the other steps, but without the addition of enzyme-labeled reagents and samples). Fifty μl of enzyme-labeled reagents was added to each well and washed after 1 h of incubation. After that, 50 μl of substrates A and B were added to

Table 1. Statistics on the clinical characteristics of the two groups n [%]

	OG (n=132)	CG (n=125)		
Gender			0.015	0.902
Male	35 (26.52)	34 (27.20)		
Female	97 (73.48)	91 (72.80)		
Age (years)			0.011	0.916
<35 years	79 (59.85)	74 (59.20)		
≥35 years	53 (40.15)	51 (40.80)		
Migraine type			0.186	0.666
Migraine with aura	26 (19.70)	22 (17.60)		
Migraine without aura	106 (80.30)	103 (82.40)		
Pain type			0.041	0.998
Dull/distending pain	27 (20.45)	26 (20.80)		
Pulsating	62 (46.97)	59 (47.20)		
Tight/oppressive feeling	18 (13.64)	16 (12.80)		
Other	25 (18.94)	24 (19.20)		
Accompanying symptoms				
Nausea	80 (60.61)	77 (58.33)	0.027	0.870
Vomiting	30 (22.73)	28 (22.40)	0.004	0.950
Photophobia	71 (53.79)	65 (52.00)	0.082	0.774
Fear of sound	73 (55.30)	66 (52.80)	0.162	0.687
Attack time			1.511	0.680
Night	35 (26.51)	29 (23.20)		
Night and other	5 (3.79)	7 (5.60)		
Other	41 (31.06)	34 (27.20)		
Not specified	51 (38.64)	55 (44.00)		
Pain site			0.167	0.983
One side	55 (41.67)	50 (40.00)		
All the head	20 (15.15)	19 (15.20)		
Tempus	27 (20.45)	25 (20.00)		
Other	30 (22.73)	31 (24.80)		

each well, and the color was developed in the dark at 37° oncentration. Fifty μl of stop solution was put into each well, the blank wells were zeroed to measure the absorbance (OD value) within 25 min at 450 nm. The specific operation steps were strictly carried out according to the ELISA kit instructions.

Cerebral hemodynamics examination

Two groups of patients underwent transcranial Doppler (TCD) examination before treatment and one month after treatment. TC 8080 Doppler ultrasound diagnostic instrument (US Nicolet Vascular) with probe frequency of 2.0 MHz was used to detect bilateral middle cerebral artery (MCA) and basilar artery (BA) flow, the average blood flow velocity was calculated.

Outcome measures

The indexes of the two groups were tested before treatment and one month after treatment: 1) Efficacy evaluation [14]: According to headache degree and clinical symptoms, it could be divided into markedly effective, effective and ineffective. Among them, markedly effective meant that the headache disappeared within 24 hours after the patient took medicine, and the disappearance duration was longer than 48 hours. Effective meant that the symptoms and degree of headache were obviously relieved within 24 hours after the patient took medicine, and the duration was more than 48 hours. Ineffective meant that the headache was not relieved within 72 hours after the patient took the medicine. The effective rate was the sum of the effective rate and the effective rate. 2) The improvement of clinical symptoms and the score of migraine quality of life questionnaire (MSQ) were observed [15]. 3) The levels of serum 5-HT, CGRP and hs-CRP in the two groups were observed and compared.

Statistical treatment

SPSS 19.0 Software System (IBM, SPSS, Chicago, IL, USA) was utilized to carry out statistical analysis on the experimental data, with [n (%)] representing the counting data and Chi-square test for inter-group comparison. The measurement data was represented by ($\bar{x}$ ± sd), the inter-group comparison was conducted using t test, the multi-group comparison was carried out via one-way analysis of variance, and LSD-t was used for post-event examination. When $P<0.05$, there was a statistically significant difference.

Results

Clinical characteristics analysis

According to the statistics of the clinical characteristics of the two groups of patients, as shown in **Table 1**, it could be seen that the

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

	Markedly effective	Effective	Ineffective	Total effective rate
OG (n=132)	61 (46.21)	57 (43.18)	14 (10.61)	89.39%
CG (n=125)	37 (29.60)	55 (44.00)	33 (26.40)	73.60%
X^2				10.720
P				0.001

Table 3. Comparison of clinical improvement between the two groups ($\bar{x} \pm sd$)

	Pain intensity (points)	Duration of pain (h/month)	Attack frequency (times/month)
OG (n=132)			
Before treatment	3.89±1.34	18.77±2.76	3.36±1.32
After treatment	1.76±0.71	8.14±2.01	1.61±0.92
t	15.750	36.030	12.400
P	<0.001	<0.001	<0.001
CG (n=125)			
Before treatment	3.83±1.27	18.91±2.81	3.40±1.21
After treatment	2.14±0.96*	11.79±1.85*	2.54±1.10*
t	12.160	23.480	5.929
P	<0.001	<0.001	<0.001

Note: *indicates comparison with the OG, *P<0.05.

majority of migraine patients had non-aura headaches, the number of male patients was remarkably lower than that of female patients, and unilateral and pulsating headaches accounted for the majority, along with irregular onset. They were generally accompanied by nausea, vomiting, photophobia, fear of sounds and other symptoms. There was no remarkable difference in clinical data between the two groups (P>0.05).

Analysis of curative effect

By comparing the curative effects of the two groups after one month of treatment, as shown in **Table 2**, it could be seen that the total effective rate of the OG was notably higher than that of the CG (89.39% VS 73.60%), with a statistically significant difference (P<0.05). During one month of treatment, no obvious adverse reactions were found in either group.

Improvement of clinical symptoms

We evaluated the degree of headache by using a pain numerical rating scale (NRS) [16], and the frequency and duration of headache were measured in "months". The results were shown in **Table 3**. There was no difference in the indexes of patients before treatment. After intervention of different treatments, the pain degree, duration and attack frequency, after treatment were improved compared with those before treatment (P<0.001). At the same time, it could be seen that the improvement effects of the clinical symptom in the OG were more obvious than that in the CG (P<0.05).

Changes of serum indexes

After detection, the results were shown in **Figure 1**. There were not considerably differences in the levels of in 5-HT, CGRP and hs-CRP between the two groups before treatment (P>0.05). After treatment, however, the levels of the three changed in both groups compared with those before treatment, but the level of hs-CRP in the CG had no considerable difference compared with that before treatment (P>0.05). In addition, CGRP and hs-CRP levels in the OG were notably lower than those in the CG (P<0.05), and 5-HT level was notably higher than that in the CG (P<0.05).

Changes of cerebral hemodynamics

The changes of MCA and BA in cerebral hemodynamics indexes of the two groups were observed, as shown in **Figure 2**. There was no remarkable difference in MCA and BA flow rates between the two groups before treatment. After treatment, their levels decreased in both groups (P<0.05), and the flow rates in the OG were lower than those in the CG (P<0.05).

Quality of life

We used the MSQ scale to assess the quality of life of patients with migraines; including dysfunction, functional limitations and emotional function. As shown in **Figure 3**, it could be seen that before treatment, there was no remarkable difference in the scores between the two groups (P>0.05). One month after treatment,

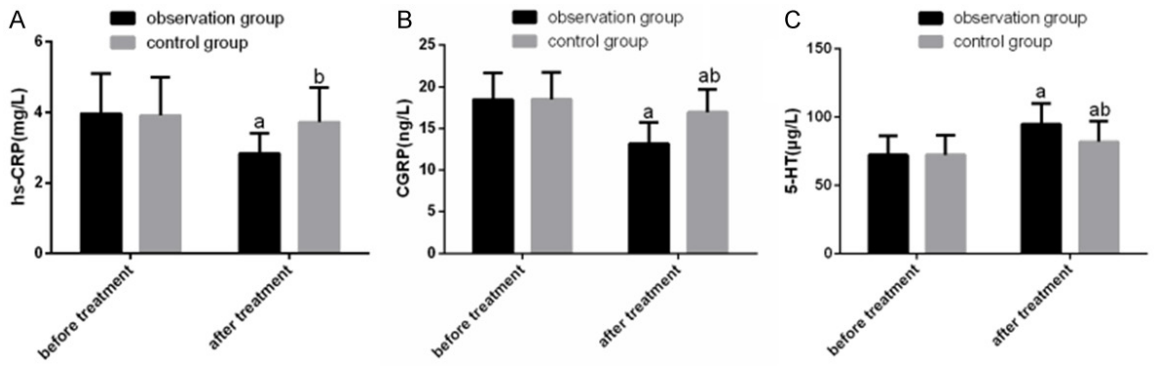

Figure 1. Comparison of serum indexes between the two groups. A. Comparison of inflammatory factors hs-CRP between the two groups. B. Comparison of inflammatory factor CGRP between the two groups. C. Comparison of inflammatory factor 5-HT between the two groups. Notes: a means comparison with before treatment, a = P<0.05. b means comparison with the OG, b = P<0.05.

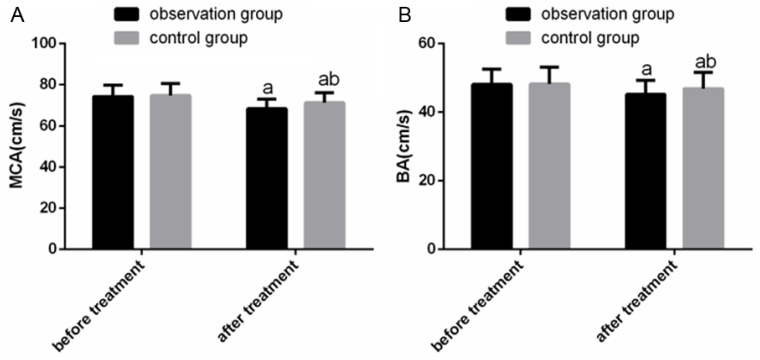

Figure 2. Comparison of cerebral blood flow rate between two groups. A. Comparison of MCA flow rate between two groups. B. Comparison of BA flow rate between the two groups. Notes: a means comparison with before treatment, a = P<0.05. b means comparison with the OG, b = P<0.05.

the quality of life scores of the two groups were both higher than before treatment, and the scores of the OG in dysfunction, functional limitations and emotional function were considerably higher than those of the CG (P<0.05).

Discussion

In this study, the clinical characteristics of patients with migraines treated with aspirin and flunarizine were statistically analyzed, and it was found that the majority of migraine patients presented with unilateral, pulsating headaches, and most of them were headache without aura. Migraines are often irregular, have recurrent attacks, are generally accompanied by nausea, vomiting and other neurological disorders, and are very sensitive to other inputs such as sound and light. This is similar to previously reported symptoms [17, 18]. Moreover, the incidence rate of females in our study is higher than that of males, which is the same as that in other studies. It is speculated that hormonal changes during menstruation and pregnancy, and genetic susceptibility may be responsible for the high incidence [19]. According to relevant reports, it is found that the frequency of headache does not change with age, and the severity of migraine attacks is related to the frequency, duration and disabling symptoms of migraine attacks [20].

Previous studies have investigated 200 adult patients. The results show that flunarizine is effective in the treatment of migraines, with only 24% of patients showing no effect, it is also of high safety, and only a few patients suffer from fatigue, mood changes and weight gain [21]. Luo et al [22] reported in a study that the combined use of flunarizine and topiramate has better curative effects and drug tolerance. Flunarizine combined with transcutaneous supraorbital neurostimulation is more effective than flunarizine alone in the treatment of migraine patients [23]. It is suggested that the combined therapy has made good progress in clinical practice. However, there is little research on aspirin combined with flunarizine. For this reason, we compared the clinical effects of the two dosages after one month of treatment. The results showed that the combined use of flunarizine and aspirin was better than flunarizine alone in preventing migraine.

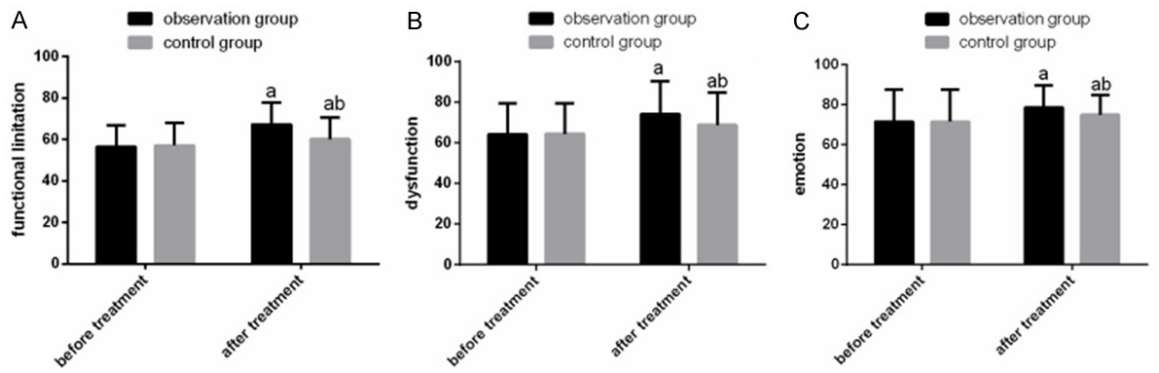

Figure 3. Comparison of quality of life scores between the two groups. A. Comparison of functional limitation scores between the two groups. B. Comparison of dysfunction scores between the two groups. C. Comparison of emotional function scores between the two groups. Notes: a means comparison with before treatment, a = P<0.05. b means comparison with the OG, b = P<0.05.

Literature reports shows that long-term use of flunarizine can easily cause side effects such as drowsiness and general fatigue, and also causes dependence and addiction [24]. However, due to the short follow-up period of this study, which is only one month, there are no intolerable side effects in the two groups, which also reflects that aspirin will not aggravate the side effects of flunarizine. Clinically, it is widely believed that the migraine has a high frequency and long duration, and the prognosis of patients' performance is not good [6]. After comparing the pain degree, duration and attack frequency of the two groups, we found that the improvement effects of clinical symptoms with aspirin combination were more obvious than that of flunarizine alone. This shows that combined use of flunarizine and aspirin can significantly reduce the degree of pain, shorten the duration of headache and reduce the frequency.

At present, the trigeminal neurovascular reflex theory holds that the neurogenic inflammatory reaction is the basis of migraine pathogenesis, while abnormal changes in the levels of vasoactive substances (5-HT, endothelin-1, nitric oxide, etc.) and abnormal secretion of neurotransmitters (CGRP, substance P, etc.) produce a marked effect on the occurrence and progression of neurogenic inflammatory reaction [25]. At present, studies have shown that 5-HT has a certain regulatory effect on blood vessels and can be used as a pain modulation. The serum level of 5-HT changes sharply during headache attacks, which can induce secondary dilation of blood vessels and other clinical symptoms of pain [26]. CGRP is a 37 amino acid neuropeptide. During migraine attack, the content of CGRP will obviously increase, and the pain duration and intensity of patients are positively correlated with the content of CGRP [27]. However, flunarizine has shown regulatory effects on 5-HT and CGRP in previous studies, and can inhibit platelet aggregation and release, reduce the damage of calcium overload to cells, relieve vasospasms, and protect cells [28, 29]. Therefore, we found that both combined use and simple use of flunarizine could improve the levels of 5-HT and CGRP. By comparison, the effect of combined use of flunarizine and aspirin was more significant. The reason is speculated to be the possible mechanism that aspirin can play a role in the metabolism of 5-HT, which can help tryptophan substances to be released from the binding site of serum albumin, increasing the concentration of 5-HT, and form the prevention and control of migraine symptoms to a certain extent. Aspirin, as a non-selective cyclooxygenase-2 (COX-2) inhibitor, has been mentioned in previous studies. Both as a non-selective inhibitor and COX-2 selective inhibitor it can prevent CGRP release in vitro [30]. hs-CRP is a marker of inflammation and vascular diseases [31]. According to Tromsø7 et al [32], migraines are most often associated with elevated hs-CRP. Flunarizine did not show any regulatory effect on hs-CRP in this study, while aspirin could reduce the level of hs-CRP. This may be related to the anti-inflammatory effect of aspirin [33], and the relief of inflammatory reactions also improves the effect of symptomatic treatment.

In previous studies, TCD can objectively reflect the systolic and diastolic functions of cerebral vessels, and is often used to detect the blood flow rate of intracranial arteries in migraine

patients [34]. Mi et al [35] used TCD to study migraine patients, and the results show that the blood flow rate was accelerated, and MCA and BA were decreased in the remission group. Therefore, the changes of MCA and BA in cerebral hemodynamics indexes of the two groups were detected in this research. It was found that the levels of MCA and BA decreased in both groups, and the flow rate of MCA and BA of aspirin combined with flunarizine was lower than that of flunarizine alone after treatment. It is suggested that aspirin combined with flunarizine can better improve cerebral blood flow, regulate cerebral vasomotor function, correct excessive cerebral blood flow rate related to high nerve reactivity and nerve function damage, which is conducive to eliminating the pathogenesis and progression of migraines, and it plays a positive role in improving curative effects and reducing recurrence. At present, the MSQ scale is a universally recognized quality of life assessment tool with great reliability, validity and sensitivity [36]. In this study, by MSQ scale examination, it was found that the quality of life of both groups improved after treatment, while aspirin combined with flunarizine had higher scores in improvement of dysfunction, functional limitation and emotional function than flunarizine alone. The reason may be that aspirin relieves the symptoms and curative effects of migraine patients, and relieves the effect of headaches on quality of life at the same time.

This study explores the application of aspirin combined with flunarizine in migraine patients from multiple directions. The results show that aspirin combined with flunarizine can effectively relieve the clinical symptoms of migraines, and the effect is better than that of flunarizine alone in improving the quality of life of patients and regulating cerebral vasomotor function. However, this study only investigated the clinical indexes of migraine after one month of treatment, and does not explore the long-term effects and complications, so there are certain limitations.

Disclosure of conflict of interest

None.

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