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Original Article

Safety and efficacy of nimodipine combined with flunarizine in patients with angioneurotic headache

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Abstract: Objective: To observe the role of nimodipine combined with flunarizine on angioneurotic headache. Methods: Altogether 101 patients with angioneurotic headache were divided into the control group (CG, n=51) and the therapy group (TG, n=50). Patients in the CG were given nimodipine, while patients in the TG were given flunarizine on the basis of nimodipine. The clinical efficacy and adverse reactions of patients were observed. Results: After treatment, the Visual analog scale (VAS) scores of the TG were markedly lower than those in the CG, and the number of attacks and headache duration of patients in the TG were also markedly reduced. Observation of the clinical efficacy showed that the effective rate of the TG was markedly higher than that of the CG, but no additional adverse reactions were found. In addition, after treatment, the cerebral hemodynamics and quality of life of patients were improved. Conclusion: Nimodipine combined with flunarizine can better promote the recovery of patients with angioneurotic headache and improve their quality of life.

Keywords: Angioneurotic headache, nimodipine, flunarizine

Introduction

Headache is a very common disease and symptom, and it can be grouped into secondary headache and primary headache according to the etiology [1]. Angioneurotic headache, also known as a migraine, is a common intractable disease seen in internal medicine, caused by dysfunction of the intracranial and extracranial vessels in the cerebral cortex [2]. The disease has a long course, repeated attacks or left and right simplified attacks [3]. In recent years, due to the enhanced pressures of modern life and the accelerated pace of life, the incidence of the disease has been rising, especially for young adults and women [4]. Patients will have symptoms such as blurred vision, irritability, or insomnia. In case of nervous tension and emotional excitement, the symptoms can get worse, which may lead to nausea and vomiting, and thus seriously affect the quality of life of patients [5]. Therefore, finding a safe and effective treatment is of great significance.

For the treatment of vascular headaches, drugs are often applied to improve the symptoms of patients [6]. Nimodipine is a dihydropyridine calcium antagonist drug with strong fat solubility, which can quickly pass through the blood-brain barrier and block the calcium channels on the cell membrane after entering the body [7]. It can also effectively reduce calcium overload of vascular smooth muscle cells, relax vascular smooth muscle, relieve spasms of the smooth muscle, relieve calcium overload to brain cells, and accelerate the recovery of Cerebral vasoconstriction [8, 9]. Flunarizine is a dialkyl amine compound, and it is a selective calcium antagonist and acts selectively on the arteries [10]. It can prevent calcium overload of vascular smooth muscle cells and relieve vasospasms, and can effectively inhibit platelet aggregation, reduce platelet activity and reduce the release of 5-hydroxytryptamine, thus alleviating the headache of patients [11]. At the same time, it can dilate blood vessels and protect the function of vascular endothelial cells [12].

There are only a few studies on nimodipine combined with flunarizine in the treatment of angioneurotic headache. In this research, we have applied these two drugs to treat angioneurotic headache, and observed their clinical effects, adverse reactions and effects on patients' lives.

Materials and methods

General information

This study was approved by the ethics committee of Chongqing Qijiang District Peoples Hospital. All patients were aware of the content of the experiment and have signed the informed consent form. Altogether 101 angioneurotic headache patients from January 2018 to June 2019 were selected as the research participants. The research was in line with the diagnostic criteria for angioneurotic headache formulated by IHS [13]. Patients had good compliance and had no contraindications to the use of drugs in the research. Patients who received antidepressants and antipsychotics within one month, patients with craniocerebral trauma, intracranial space-occupying lesions, cerebral infarction or cerebral hemorrhage, rhinogenic or drug-induced trigeminal headache, mental disorders, severe heart, liver and kidney dysfunction, pregnant or lactating women, as well as people with hypertension and diabetes were excluded.

Therapeutic method

The control group (n=51) was given nimodipine tablets (specification: 20 mg*50 tablets, batch number: H14022821, Shanxi Yabao Pharmaceutical Group Co., Ltd., China), 40 mg/time, 3 times/d. The treatment group (n=50) was given flunarizine capsules (specification: 5 mg*20 capsules, batch number: H10930003, Xian Janssen Pharmaceutical Ltd., China) on the basis of the control group, one capsule/time and once a day. A continuation of 7 days is a course of treatment, and the two groups of patients were treated continuously for four courses.

Evaluation of therapeutic effect

The treatment effect of patients was evaluated. Cured: the headache symptoms disappeared, the Color transcranial Doppler examination result returned to normal, there was no recurrence within six months, and the improvement was more than 90% before treatment. Effective: the headache symptoms were alleviated, the number of attacks was reduced, the duration was shortened, and the improvement was more than 40-90% compared with before treatment. Ineffective: compared with before treatment, the improvement was less than 40%.

Outcome measures

The number, degree and duration of headache before treatment were recorded, and the adverse reactions including blurred vision, nausea and vomiting, decreased appetite were recorded.

The Visual analog scale (VAS) [14] was applied to evaluate the pain degree of patients. The VAS score ranged from 0 (no pain) to 10 points (unbearable pain). A higher score indicates a more severe pain degree.

Cerebral hemodynamics was examined by transcranial Doppler, and Vivid7 color Doppler ultrasound diagnostic instrument made by CE Company of America was applied. The recorded parameters include anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), vertebral artery (VA) and basilar artery (BA).

Quality of life scale (SF-36) [15] was applied to evaluate the patients' quality of life before treatment and one month after treatment. The scale included general health, body pain, physiological function, mental health and emotional function, with a total score of 100 points for each item. A higher score indicates a better quality of life.

Statistical methods

IBM SPSS 25.0 was applied for statistical analysis, and $P<0.05$ indicates that there are significant differences between groups. Graphpad Prism 6.0 (Cabit Information Technology Co., Ltd., Shanghai, China) was applied to illustrate figures. Counting data were analyzed using χ^2 and were expressed by percentage (%). Measurement data were represented as Mean ± SD and compared by independent sample t test, and the comparison before and after treatment was conducted by paired t test.

Table 1. General information

Clinical data	CG (n=51)	TG (n=50)	t/χ^2 value	*P* value
Age (years)	47.6±5.7	48.2±5.3	0.548	0.585
Gender			0.047	0.828
Man	28 (54.90)	24 (48.00)		
Woman	23 (45.10)	26 (52.00)		
Course of disease (years)	3.11±0.67	3.02±0.83	0.600	0.550
Residence			0.256	0.613
Urban	38 (74.51)	35 (70.00)		
Rural	13 (25.49)	15 (30.00)		
Drinking history			0.239	0.625
Yes	30 (58.82)	27 (54.00)		
No	21 (41.18)	23 (46.00)		
History of smoking			0.498	0.480
Yes	36 (70.59)	32 (64.00)		
No	15 (29.41)	18 (36.00)		
Occupation			1.713	0.425
worker	12 (23.53)	10 (20.00)		
service sector	17 (33.33)	23 (46.00)		
Others	22 (43.14)	17 (34.00)		
Headache location			0.325	0.850
Left	18 (35.29)	15 (30.00)		
Right	31 (60.78)	33 (66.00)		
Bilateral	2 (3.92)	2 (4.00)		

Results

Clinical data of two groups

There was no remarkable difference between the TG and the CG in terms of age, sex, course of disease, residence, smoking history and drinking history (P>0.05) (**Table 1**).

VAS score, headache frequency and duration in the two groups of patients

The degree of headache attack in two groups, and the times and duration of headache attack were evaluated. Before treatment, there was no significant difference in VAS score, headache frequency and duration between the two groups (P>0.05). After treatment, the VAS scores of patients in the control group and treatment group decreased significantly (P< 0.05), and the frequency and duration of headache were shortened significantly (P<0.05). The VAS scores of patients in the treatment group were significantly lower than those in the control group (P<0.05), and the frequency and duration of headache attacks were significantly shorter than those in the control group (P<0.05) (**Figure 1**).

Comparison of therapeutic effects

The therapeutic effects of the two groups were observed. After treatment, 22 patients (43.14%) in the CG were cured, 17 (33.33%) were effective and 12 (23.53%) were ineffective, with a total effective rate of 76.47%. In the TG, 27 cases (54.00%) were cured, 19 cases (38.00%) were effective and 4 cases (8.00%) were ineffective, with a total effective rate of 92.00%. The effective rate of the TG was markedly higher than that of the CG (P<0.05) (**Table 2**).

Clinical adverse reactions

The adverse reactions of the two groups during treatment were observed. The results showed that the patients in the CG had 1 case of blurred vision (1.96%), decreased appetite (1.96%), and stomachache (1.96%), 2 cases of nausea and vomiting (3.92%) and 2 cases of rash (3.92%), and the incidence of adverse reactions was 13.73%. In the TG, nausea and vomiting occurred in 2 cases (4.00%), loss of appetite occurred in 1 case (4.00%), rash occurred in 1 case (4.00%), and stomachache occurred in 1 case (2.00%), and the incidence of adverse reactions was 12.00%. There was no remarkable difference in the incidence of adverse reactions between the two groups (P>0.05) (**Table 3**).

Arterial blood flow velocity before and after treatment

We evaluated the arterial blood flow velocity before and after treatment, including ACA, MCA, PCA, VA and BA. Before treatment, there was no remarkable difference in ACA, MCA, PCA, VA and BA between the CG and the TG (P>0.05). After treatment, those in the CG and the TG decreased markedly (P<0.05), and those in the TG decreased most markedly and was markedly lower than that in the CG (P< 0.05) (**Figure 2**).

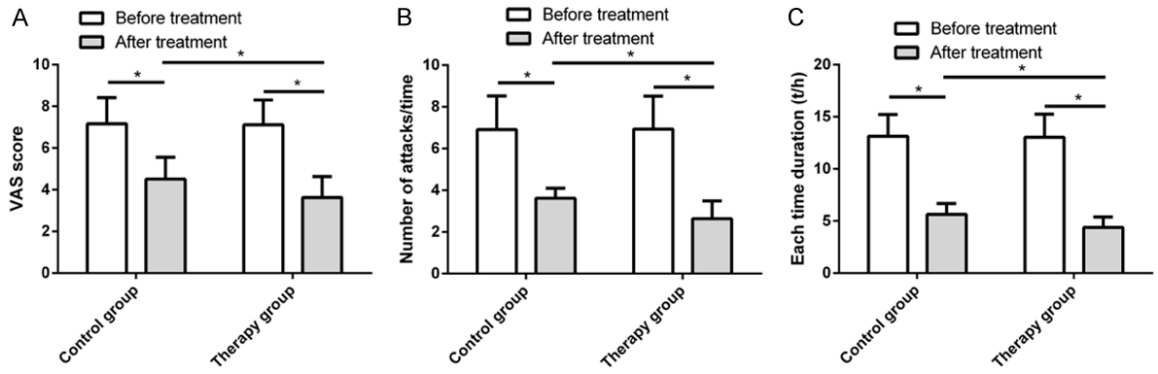

Figure 1. Comparison of VAS scores between two groups. After treatment, the VAS score (A) of patients in the control group and treatment group decreased significantly, and the frequency (B) and duration (C) of headache were shortened significantly. The VAS scores of patients in the treatment group were significantly lower than those in the control group, and the frequency and duration of headache attacks were significantly shorter than those in the control group. Note: *indicates P<0.05.

Table 2. Comparison of therapeutic effects

Group	n	Cured	Effective	Ineffective	Effective rate
CG	51	22 (43.14)	17 (33.33)	12 (23.53)	76.47
TG	50	27 (54.00)	19 (38.00)	4 (8.00)	92.00
χ^2 value	-	-	-	-	4.944
P value	-	-	-	-	0.026

Table 3. Adverse reactions

Adverse reaction	CG (n=51)	TG (n=50)	χ^2 value	*P* value
Blurred vision	1 (1.96)	0 (0.00)	0.990	0.320
Nausea and vomiting	2 (3.92)	2 (4.00)	0.001	0.984
Loss of appetite	1 (1.96)	2 (4.00)	0.364	0.546
Rash	2 (3.92)	1 (2.00)	0.324	0.570
Stomachache	1 (1.96)	1 (2.00)	0.001	0.989
Total incidence rate	13.73	12.00	0.067	0.795

Quality of life

We observed the quality of life of patients before and after treatment. Before treatment, there was no remarkable difference in the scores of general health, body pain, physiological function, mental health and emotional function (P>0.05), but after treatment, these scores of patients in the two groups were markedly improved (P<0.05), especially in the TG (**Figure 3**).

Discussion

Angioneurotic headache, also known as neurofunctional headache, is caused by long-term mental stress and physical fatigue, and can also be induced by brain dysfunction caused by emotional excitement [16]. The disease greatly affects patients' daily life and work. Even though there are many kinds of drugs for treating vascular nerve headaches, the therapeutic effect and drug safety have always been the focus of clinical research [17, 18].

Nimodipine is a commonly applied clinical drug for headaches, which belongs to dihydropyridine calcium antagonist family and it can improve the clinical symptoms and signs of angioneurotic headaches [19]. Studies have shown that due to individual differences, there may be different therapeutic effects, and the curative effect of nimodipine alone cannot be fully reflected, and thus a satisfactory therapeutic effect cannot be achieved [20]. Flunarizine is a dialkyl amine compound and a piperazine calcium antagonist, which can protect vascular endothelial tissue and dilate blood vessels [21]. Cho et al. revealed that nimodipine can obviously relieve the symptoms of light headache, and it is an independent influencing factor for early relief of the disease [22]. Studberud's meta-analysis showed that compared with placebo, flunarizine can reduce the frequency of headaches every 4 weeks, which is effective and well tolerated [23]. This indicated that nimodipine and flunarizine have remarkable benefits in the treatment of headaches. In our research, nimodipine combined

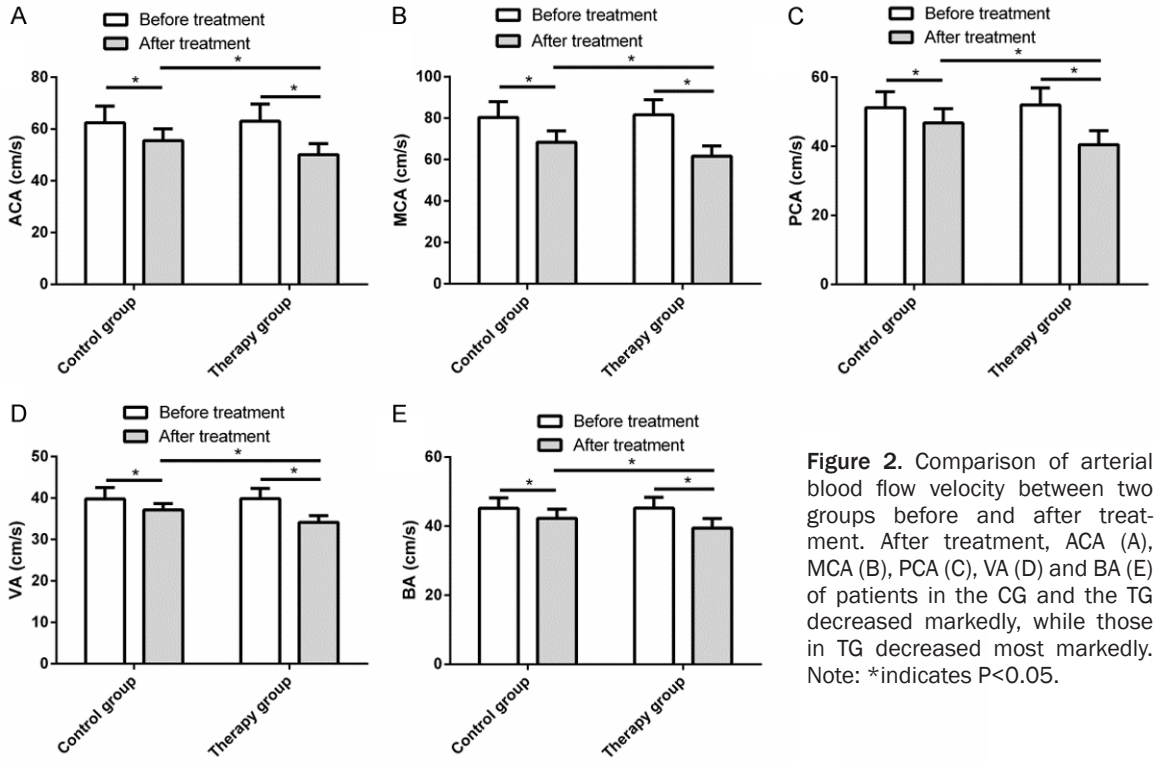

Figure 2. Comparison of arterial blood flow velocity between two groups before and after treatment. After treatment, ACA (A), MCA (B), PCA (C), VA (D) and BA (E) of patients in the CG and the TG decreased markedly, while those in TG decreased most markedly. Note: *indicates P<0.05.

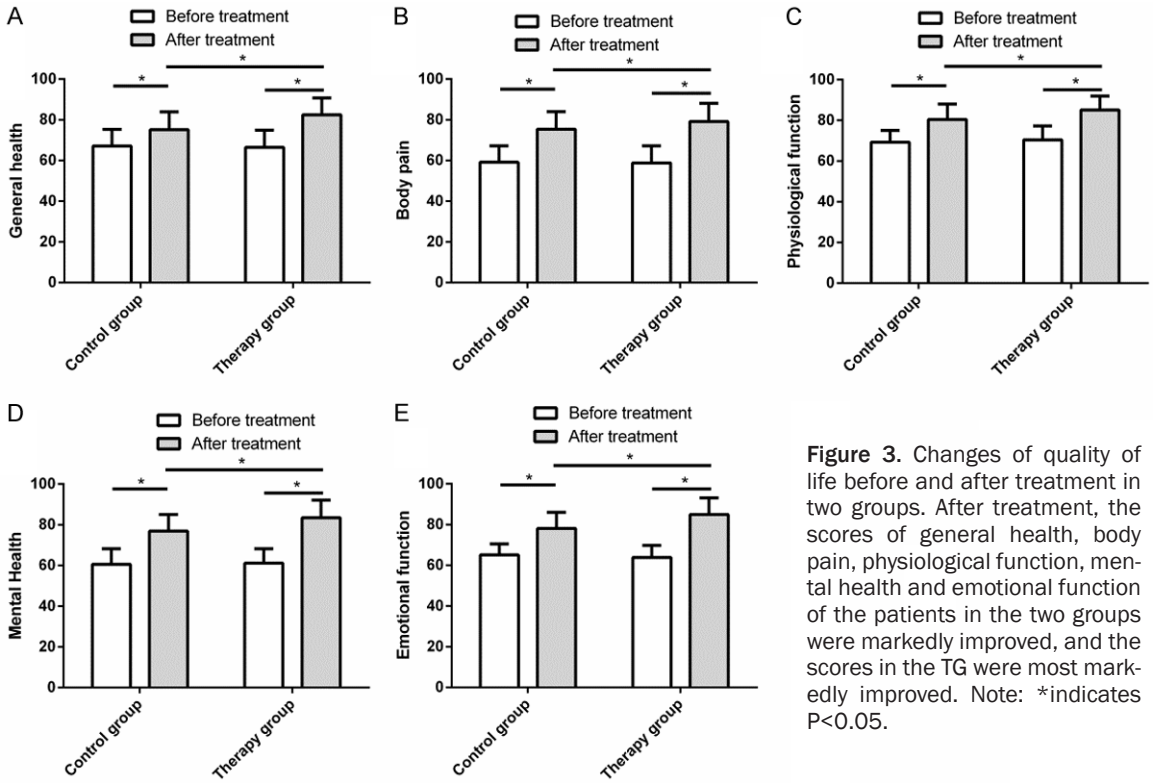

Figure 3. Changes of quality of life before and after treatment in two groups. After treatment, the scores of general health, body pain, physiological function, mental health and emotional function of the patients in the two groups were markedly improved, and the scores in the TG were most markedly improved. Note: *indicates P<0.05.

with flunarizine can markedly improve the pain of patients with angioneurotic headaches, and also markedly reduce the numbers and duration of headache attacks, indicating that the

combination has a good clinical effect. Similarly, Liu reported that flunarizine is effective and safe in preventing vestibular migraines and can reduce the severity of vertigo [24]. In addition, Liu LL et al. revealed that the combination of sibelium and dibazole can markedly improve the hemodynamic indexes and cerebral blood flow velocity, and has a remarkable effect on the treatment of angioneurotic headaches, and will only cause a few toxic side effects, adverse reactions or complications [25]. Our research also showed that nimodipine combined with flunarizine can improve cerebral hemodynamics in the treatment of angioneurotic headaches, and it will not increase the adverse reactions of patients. It may be that nimodipine can act on nerve cells and cerebral vessels through blood-brain barrier, antagonize cerebral vasospasms caused by potassium ions, arachidonic acid or hydrogen peroxide, and improve cerebral blood flow disturbances [26]. Flunarizine mainly acts on arteries, which can relieve vasospasms and dilate blood vessels of patients [27]. The two drugs can effectively relieve vasospasms and improve cerebral ischemia and hypoxia disorders, and tey play a synergistic role.

Finally, by investigating the patients' quality of life, we found that the patients' quality of life has been markedly improved after treatment, which plays an important role in promoting patients' early recovery. Our research showed that the combination of the two drugs has better curative effect on patients. However, the research still has some limitations. First of all, we did not evaluate the pain of patients at different time points after treatment. Secondly, there is no basic experiment to explore the mechanism. These shortcomings need to be further improved in the future.

In conclusion, nimodipine combined with flunarizine can better promote the recovery of patients with angioneurotic headache, they have a high level of safety, and can improve the quality of life of patients.

Disclosure of conflict of interest

None.

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