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Original Research Article

Efficacy and prognosis following combined cinepazaide maleate/nimodipine therapy in cerebral vasospasm patients after hemorrhage

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Abstract

Purpose: *To investigate the efficacy and prognosis following treatment of cerebral vasospasm (CVS) patients with a combination of cinnarizide maleate and nimodipine after subarachnoid hemorrhage (SAH).*
Methods: *Eighty-eight patients with CVS after SAH were selected and divided into control group (CG) and study group (EG), each with 44 patients (n = 44). Patients in CG were treated with intravenous infusion of cinnarizide maleate, while those in EG received intravenous infusion of cinnarizide maleate together, and their clinical efficacy and prognosis were compared.*
Results: *Compared with CG, total treatment effectiveness (response) in EG was significantly higher, while levels of inflammatory factors were lower ($p < 0.05$). Serum protein levels of S100 β and ET-1, and MCA blood flow velocity in EG were notably lower ($p < 0.05$), but GCS scores were higher compared with CG ($p < 0.05$). The NIHSS scores were lower and BI indices were higher in EG than in CG ($p < 0.05$).*
Conclusion: *Treatment of CVS patients after SAH using a combination of cinnarizide maleate and nimodipine effectively reduces the levels of inflammatory factors, improves quality of prognosis, and relieves symptoms of CVS, when compared with administration of cinnarizide maleate only. Therefore, the combination treatment is recommended for the management of CVS after SAH.*

Keywords: *Cinnarizide maleate, Nimodipine, Cerebral vasospasm (CVS), Subarachnoid hemorrhage (SAH)*

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INTRODUCTION

Subarachnoid hemorrhage (SAH) results from cerebral stroke in which blood from ruptured cerebral blood vessels flows into subarachnoid space, resulting in cerebral vasospasm (CVS). The disease affects mostly middle-aged and elderly populations within the age range of 40 to 60 years old, and it accounts for 10 % of all strokes in China. Cerebral vasospasm (CVS) is a common complication of SAH, and its incidence in patients with SAH may reach up to

90 % [1-3]. Failure to intensify therapeutic intervention at the onset of the disease may predispose the patients to severe cerebral ischemia or ischemic brain injury, thereby aggravating their conditions or even endangering their lives.

Nimodipine, a calcium ion antagonist, effectively improves blood circulation in the recovery phase of acute cerebrovascular diseases. Studies have shown that nimodipine produces significant clinical efficacy in the treatment of CVS after SAH caused by various factors; a finding which has been widely applied in clinical practice [4-6]. Cinnarizide maleate is a calcium channel blocker that relaxes vascular smooth muscles and dilates cerebral, peripheral as well as coronary vessels by preventing transmembrane entry of calcium ions into the vascular smooth muscle cells. This relieves vasospasm, reduces vascular resistance and increases blood flow [7,8]. Nimodipine and cinnarizide are clinically used for the treatment of cerebrovascular diseases. However, in clinical practice, not much is known about the effect of combination of these two drugs on outcomes in the treatment of CVS after SAH. The present study was carried out to investigate the clinical efficacy and prognosis associated with application of cinnarizide maleate in combination with nimodipine for treatment of CVS after SAH.

METHODS

Profile of patients

Eighty-eight patients with CVS after SAH, who were admitted to our hospital from January 2017 to December 2018, were selected as study subjects. They were randomized into control group (CG) and study group (EG) based on tossing of a coin, each with 44 patients. CG had 26 males and 18 females, aged from 33 to 72 years (mean age = 53.3 ± 4.5 years), while EG had 28 males and 16 females aged 30 to 73 years, with mean age of 52.1 ± 4.6 years. No statistical differences in the profiles of the patients were observed between EG and CG ($p > 0.05$).

Inclusion criteria

Patients in the following categories were included in the study: those who met the clinical diagnostic criteria for CVS after SAH according to the *Chinese guidelines for diagnosis and treatment of SAH* (2015) after diagnosis using CT and ultrasonic testing, patients aged 18 years and above, and patients who had complete clinical medical records.

Exclusion criteria

Patients who had other organ and tissue lesions e.g., lesions in brain, heart, kidneys, and liver; those with history of cerebral infarction or intracranial tumors, patients with metabolic diseases, and those who had mental and cognitive disorders were excluded from the study. In addition, patients who refused to cooperate with the investigators were excluded.

This study was approved by the Ethics Committee of Linyi Central Hospital (approval no. 20161184). The patients and their family members were duly informed about the purpose of the study and the protocols involved, and they signed informed consent. The study followed international guidelines for human studies.

Treatments

Following doctors' advice, all the patients were subjected to several examinations after admission, and were positively coordinated with the treatment. After surgery, patients in CG were treated with intravenous infusion of 500 mL of 0.9 % sodium chloride containing 320 mg of cinnarizide maleate (Beijing Sihuan Pharmaceutical Co. Ltd; specification: 2 mL, 80 mg/bottle; National Medical Products Administration (approval no. H20020125) [9,10].

In EG, the patients were treated with intravenous administration of nimodipine, in addition to intravenous infusion of cinnarizide as CG. The intravenous pumping of nimodipine (Shandong Fangming Pharmaceutical Group Co. Ltd; specification: 20 mL, 4 mg/vial; National Medical Products Administration (approval no. H20033549) was carried out via a microinjection pump at a flow rate of 2.5 - 5 ml/h. After the medication regimen was adjusted according to conditions of the patients, nimodipine tablets (Chiatai Qingchunbao Pharmaceutical Co. Ltd; specification: 20 mg x 20 tablets; National Medical Products Administration approval no.: H33022285) were administered orally at 1 - 2 weeks after treatment, at a dose of 60 mg, three times daily for 3 weeks.

Treatment indices

The prognosis of patients in both treatment groups was determined in terms treatment efficacy which was categorized into three levels: *ineffective, effective* and *markedly effective*. Treatment was deemed *markedly effective* if clinical adverse symptoms disappeared, and results of CT examination showed no abnormality. If clinical conditions were improved,

the treatment effect was classified as *effective.* However, the treatment effect was classified as *ineffective* if there were no improvements in the conditions of the patients, or if the conditions became aggravated. Total treatment effectiveness was calculated as indicated below:

$$TTE\ (\%) = \frac{(ME + E)}{T} \times 100 \quad \text{..... (1)}$$

where *TTE* = total treatment effectiveness; *ME* = markedly effective cases; *E* = effective cases, and *T* = Total number of patients

The levels of inflammatory factors, serum protein levels of S100 β and ET-1, and velocity of MCA blood flow, were measured before and after treatment.

Glasgow coma scale (GCS) was used to evaluate the physical status before and after treatment in three aspects of eye-opening response, verbal response and motor response. Higher scores indicated better physical status. The National Institute of Health stroke scale (NIHSS) was applied to evaluate the neurologic function before and after treatment. In this scale, lower scores indicated better neural functional recovery. In addition, the Barthel index (BI) was adopted to evaluate capacity of patients for self-care before and after treatment. Higher scores indicated better self-care ability.

Statistical analysis

The SPSS 20.0 software was used for data processing, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for graphics. Measurement data were compared between the two groups using *t*-test, while enumeration data were compared using Chi square test and normality test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Therapeutic effect

Total treatment effectiveness was markedly higher in EG than in CG ($p < 0.05$), see Table 1.

Levels of inflammatory factors

After treatment, the levels of inflammatory factors in both groups obviously decreased, but the levels of inflammatory factors in EG were markedly lower compared with CG ($p < 0.05$), see Table 2.

Serum levels of S100 β protein and ET-1, MCA blood flow velocity

After treatment, serum levels of S100 β protein and ET-1 as well as MCA blood flow velocity in both groups notably decreased, with lower levels and blood flow velocity in EG than CG after treatment ($p < 0.05$).

Table 1: Therapeutic effect of the two groups [n (%)]

Group	Ineffective	Effective	Markedly effective	Total effectiveness
CG (n=44)	11 (25.00)	15 (34.09)	18 (40.91)	33 (75.00)
EG (n=44)	2 (4.55)	12 (27.27)	30 (68.18)	42 (95.45)
χ^2				7.3108
P-value				0.007

Table 2: Comparison of levels of inflammatory factors before and after treatment

Group		IL-6 (ng/L)	TNF-α (ng/L)	CPA (mg/L)
CG (n=44)	Before treatment	12.87±2. 88	47.36±8.25	53.01±5.87
	After treatment	9.85±2.3 9	40.73±7.51	40.70±5.47
χ^2		5.3526	3.9420	10.1769
P		0.000	0.0002	0.000
EG (n=44)	Before treatment	12.75±2. 91	47.21±8.23	52.95±5.89
	After treatment	8.06±2.2 6*	35.64±6.43*	23.88±4.37*
χ^2		8.4434	7.3484	26.2921
P-value		0.000	0.000	0.000

*$P < 0.05$, levels of inflammatory factors after treatment vs CG values

Table 3: Comparison of levels of serum S100 β protein and ET-1 as well as MCA blood flow velocity before and after treatment

Group		S100 β protein (μg/L)	ET-1 (pg/mL)	MCA (cm/sec)
CG (n=44)	Before treatment	0.27±0.06	88.16±12.31	104.23±25.29
	After treatment	0.20±0.05	74.84±8.27	90.42±20.89
χ^2		5.9451	5.9578	2.7927
P		0.000	0.000	0.0064
EG (n=44)	Before treatment	0.26±0.08	87.65±12.24	103.65±26.23
	After treatment	0.15±0.04*	70.22±8.45*	78.58±18.33*
χ^2		8.1578	9.7786	5.1967
P-value		0.000	0.000	0.000

*$P < 0.05$, levels of inflammatory factors after treatment vs CG values

Comparison of GCS scores between the two groups

As shown in Figure 1, GCS scores in both after treatment were markedly higher than the corresponding values before treatment. However, the post-treatment GCS scores in EG exceeded those in CG ($p < 0.05$).

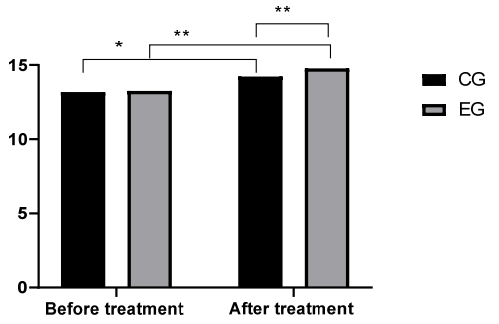

Figure 1: Comparison of GCS scores. Values are expressed as mean ± SD. *$P = 0.0005$, GCS scores in CG before treatment vs score after treatment ($t = 3.6454$); **$p < 0.001$, GCS score in EG before treatment vs score after treatment ($t = 5.1493$); ***$p = 0.0077$, comparison of GCS scores between EG and CG after treatment ($t = 2.7280$)

NIHSS scores

The NIHSS scores in both groups after treatment notably decreased, but the NIHSS score in EG after treatment was markedly lower than that in CG. See Figure 2.

BI index

The values of BI indexes in both groups after treatment increased, but the values of BI indices after treatment in EG were markedly higher than those in CG, which were presented in Figure 3.

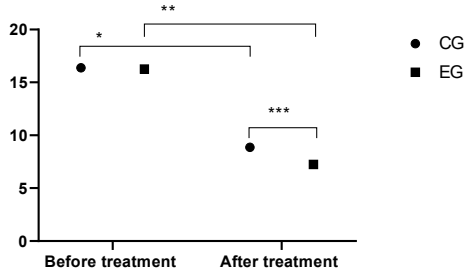

Figure 2: Comparison of NIHSS scores. Values are presented as mean ± SD. *$P < 0.001$, NIHSS score in CG before treatment vs score after treatment ($t = 12.5333$); **$P < 0.001$, NIHSS score in EG before treatment vs score after treatment ($t = 13.7997$); ***$p = 0.0028$, NIHSS scores of the two groups after treatment ($t = 3.0812$)

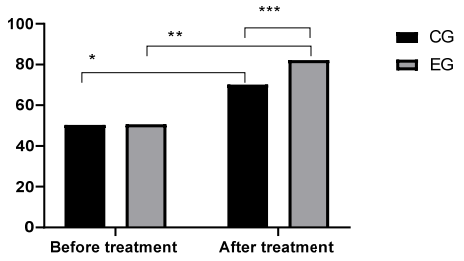

Figure 3: BI index values of the two groups. Values are expressed as mean ± SD). *$P < 0.001$, BI index values in CG before treatment vs values after treatment ($t = 10.7649$); **$P < 0.001$, values of BI indices in EG before treatment vs corresponding values after treatment ($t = 16.3346$); ***$P < 0.001$, values of BI indices of the two groups after treatment ($t = 5.7949$)

DISCUSSION

Cerebral vasospasm (CVS) after subarachnoid hemorrhage (SAH) manifests as smooth muscle contraction due to massive release of calcium

ions from the cellular calcium stores and influx of calcium ions from vascular smooth muscle cells. The affected patients present with cerebral ischemia as a result of cerebral hemorrhage which may lead to increased intracranial pressure. If the patient does not receive timely treatment, the situation may lead to aggravated brain tissue damage. Generally, before clinical treatment, proper blood supply is required so as to avoid irreversible damage due to cerebral ischemia [11-13].

Nimodipine is a calcium antagonist with strong lipo-solubility [14]. Thus, it can cross the blood-brain barrier and act selectively on cerebral blood vessels, leading to reduction of concentration of calcium ions, thereby ensuring proper development of nerve cells. Moreover, nimodipine selectively inhibits smooth muscle contraction in cerebral blood vessels and effectively relieves CVS. Cinnarizide maleate is a novel calcium channel antagonist which blocks the entry of calcium ions into smooth muscle cells, dilates blood vessels at the lesion sites, increases blood flow volume, and improves cerebral metabolism. In addition, cinnarizide reduces the levels of inflammatory factors by inhibiting platelet aggregation [15-17].

The results of this study showed that compared with CG, total treatment effectiveness (response) in EG was markedly higher, while levels of inflammatory factors were markedly lower (p < 0.05). Serum protein levels of S100 β and ET-1, and MCA blood flow velocity in EG were notably lower (p < 0.05). The S100 β protein is a brain injury-specific protein in the nervous system. It enhances the development of nervous system and accelerates the proliferation and differentiation of nerve cells. Besides, when intracranial hemorrhage occurs, the expression of S100 β protein is abnormally elevated. This spills over large number of damaged cells, inducing inflammatory factors and accelerating neural cells apoptosis. Compared with CG, EG achieved markedly higher GCS scores (p < 0.05), notably lower NIHSS scores (p < 0.05) and obviously higher BI indexes (p < 0.05).

These results indicate that combined treatment with cinnarizide maleate and nimodipine produces marked neuroprotective effect on patients. This finding is consistent with those reported earlier, in which the application of nimodipine for treatment of CVS after SAH effectively improved blood flow velocity of the cerebral artery in patients and reduced the incidence of complications [18]. Moreover, nimodipine had positive effect on prognosis, indicating that the application of cinnarizide maleate and nimodipine results in significant therapeutic effect.

CONCLUSION

The application of cinnarizide maleate in combination with nimodipine for the treatment of CVS after SAH effectively reduced the levels of inflammatory factors, improved prognosis, and relieved the symptoms of cerebral vasospasm in patients. The combination treatment produced significant clinical efficacy. Therefore, it merits clinical popularization in the treatment of CVS after SAH.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. TW conceived and designed the study, and drafted the manuscript. FC and HX collected, analyzed and interpreted the experimental data. TX revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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