RESEARCH ARTICLE

Application of nimodipine combined with statins in the treatment of subarachnoid haemorrhage

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Abstract

Objective: To explore the clinical effect of nimodipine combined with statins in the treatment of subarachnoid haemorrhage.

Method: The retrospective study was conducted at the Baoding No.1Central Hospital, China, and comprised data of subarachnoid haemorrhage patients who were treated from March 2019 to March 2022. The patients were divided into two groups on the basis of the treatment method. Control group A was treated with nimodipine, while observation group B was treated with nimodipine combined with statins. Clinical efficacy of the groups were assessed and compared along with endothelin 1, calcitonin gene-related peptide, vascular endothelial growth factor and peroxiredoxin 2 levels at baseline and 7 days after the treatment. Also noted were mean blood flow velocity of cerebral artery and adverse reactions. Data was analysed using SPSS 22.

Results: Of the 100 patients, 50(50%) were in group A; 35(70%) females and 15(30%) males with mean age 66.00±8.26 years. There were 50(50%) patients in group B; 32(64%) females and 18(36%) males with mean age 63.58±7.89 years. The overall response rate was 34(68%) in group A compared to 45(90%) in group B ($p<0.05$). Post-treatment, group B had lower levels of endothelin 1 and vascular endothelial growth factor, and higher levels of calcitonin gene-related peptide ($p<0.05$). The mean blood flow velocity of the cerebral arteries significantly decreased in both the groups, but it was slower in group B than group A ($p<0.05$). The expression levels of peroxiredoxin 2 increased in both the groups, with higher levels observed in group B ($p<0.05$). The incidence of adverse reactions in group B was 3(6%) compared to 10(20%) in group A ($p<0.05$).

Conclusion: Nimodipine combined with statins was found to have good efficacy and higher safety profile in the treatment of subarachnoid haemorrhage.

Keywords: Nimodipine, Statins, Subarachnoid haemorrhage, ET-1, PRX2. (JPMA 75: 767; 2025)

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Introduction

Subarachnoid haemorrhage (SAH) refers to a severe stroke that may induce corresponding clinical symptoms when an intracranial artery ruptures and a large amount of blood enters the subarachnoid space. Accounting for approximately 10% of acute stroke cases, SAH can be caused by intracranial aneurysm, which is the most common factor, as well as cerebral arteriovenous malformation, etc.[1] SAH progresses rapidly, and the affected patients are generally accompanied by obvious symptoms, such as headache, nausea and vomiting,[2,3] which seriously affects people's quality of life. SAH mortality is still high despite significant progress in treatment n recent years. Cerebral vasospasm is one of the major complications of SAH, which primarily contributes to the development and even death of SAH patients.[4-6] Furthermore, nimodipine is a dihydropyridine calcium antagonist with the best liposolubility,[7] which exhibits a strong ability to penetrate the blood-brain barrier. Simultaneously, statins have neuroprotective effects, because of lipid-lowering, anti-inflammatory and antioxidant properties, but the effect of statins in improving cerebral blood flow and alleviating hypertension in patients with SAH is yet to be identified.[8] The current study was planned to explore the clinical effect of nimodipine combined with statins in SAH treatment.

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Materials and Methods

The retrospective study was conducted at the Baoding No.1Central Hospital, China, and comprised data of SAH patients who were treated from March 2019 to March 2022. After approval from the institutional ethics review committee, data was retrieved from patient files on March 31, 2022. The patients were divided into two groups on the basis of the treatment method. Control group A was treated with nimodipine, while observation group B was treated with nimodipine combined with statins. SAH was graded using Hunt-Hess classification.[9]

Those included were patients aged >18 years who met the SAH diagnostic criteria[10] had been diagnosed through computed tomography (CT) scans, and were admitted within 24h of the first onset. Patients or their close relatives had furnished written informed consent.

Those excluded were patients with heart failure, severe liver and kidney dysfunction, patients with coagulation disorders, pregnant or lactating women, patients with allergies to drugs of interest, patients with poor compliance and incomplete treatment record, patients whose therapeutic effect was affected by the use of other drugs, and patients who experienced severe conditions during the treatment that required plan adjustment.

After hospitalisation, all the patients were provided with conventional treatment, such as fluid replacement, haemostasis, dehydration, gastric protection, blood pressure control, neurotrophic treatment, etc. In group A, the patients were given intravenous (IV) infusion of nimodipine injection (H20181106, Bayer AG, Germany) on the basis of conventional treatment, and oral nimodipine tablets 60mg 3 times per day in the later stage of treatment.

In group B, the patients additionally received oral atorvastatin calcium tablets (Jialin Pharmaceutical Co. Ltd., Beijing, China) 20mg once daily.

Among outcome measures, clinical effect total response rate was taken as: (significant effective+effective)/total number of patients, where 'significant effective' was descried as the disappearance of clinical symptoms in patients without neurological damage, while 'effective' was described as significant improvement of clinical symptoms in patients with improved self-care ability. 'Ineffective' meant no obvious improvement and even aggravation of clinical symptoms in patients.[11]

Before and after treatment, 3mL of fasting venous blood was collected from each patient in the morning, followed by the collection of serum after centrifugation. The levels of endothelin 1 (ET-1) and calcitonin gene-related peptide (CGRP) were detected by immunoradiometric assay, while the level of vascular endothelial growth factor (VEGF) was detected using enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturers' (Shanghai Zeye Biotechnology Co., Ltd, Shanghai, China) instructions.

The blood flow velocity of the anterior, middle and posterior cerebral arteries of the patients was detected by transcranial colour Doppler ultrasound (Model: LOGIQ-E9, GE, USA).

The expression level of peroxiredoxin 2 (PRX2) protein was detected by immunoblotting for further comparison between the groups.

Adverse reactions during the treatment were noted, and the rate of incidence was calculated in terms of percentage.

Data was analysed using SPSS 22. Data was subjected to Shapiro-Wilk test, and it followed a normal distribution. Data was expressed as mean±standard deviation and it was compared using independent-samples t-test. Categorical data was expressed as frequencies and percentages, and was subjected to chi-square test. Ranked data was analysed using the rank-sum test. Comparison at different time points was done using repeated measures analysis of variance (ANOVA). P<0.05 was considered statistically significant difference.

Results

Of the 100 patients, 50(50%) were in group A; 35(70%) females and 15(30%) males with mean age 66.00±8.26 years (range: 39-84 years). There were 50(50%) patients in group B; 32(64%) females and 18(36%) males with mean age 63.58±7.89 years (range: 37-74 years). The mean course of disease in group A was 27.64±20.36 days (range: 4-96 days), with mean time from onset to admission being 13.64±4.27 hours (range: 0-24 hours). In group B, the mean course of disease was 22.40±9.12 days (range: 5-34 days), with mean time from onset to admission being 13.64±4.27 hours (range: 0~24 hours). There were 16(32%) cases of grade I, 20(40%) cases of grade II and 14(28%) cases of grade III in group A. The corresponding values in group B were 18(36%), 20(40%) and 12(24%). The intergroup difference across all parameters was not statistically significant (*p*>0.05).

The overall response rate was 34(68%) in group A compared to 45(90%) in group B (*p*<0.05) (Table 1).

There was no significant difference in the comparison of ET-1, CGRP and VEGF levels between the groups at baseline (*p*>0.05). After the treatment, group B had lower levels of ET-1 and VEGF, and higher levels of CGRP compared to group A (*p*<0.05) (Table 2).

There was no significant difference in the comparison of mean blood flow velocity of cerebral arteries between the groups before treatment (*p*>0.05). After treatment, a significant decrease was observed in both the groups

Table-1: Comparison of clinical effect between the groups.

Groups	Significant effective	Effective	Ineffective	Overall response rate
Control group (n=50)	19(38.0)	15(30.0)	16(32.0)	34 (68.0)
Observation group (n=50)	25(50.0)	20(40.0)	5(10.0)	45 (90.0)
z-value				7.294
p-value				0.007

Table-2: Comparison of vascular endothelial function indicators between the groups.

Groups	ET-1 (pg/ml)		CGRP(pg/ml)		VEGF (ng/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=50)	137.33±25.34	95.77±13.65#	38.15±5.10	46.74±6.70#	213.60±34.32	145.11±27.12#
Observation group (n=50)	137.84±23.56	76.81±8.67*#	37.99±5.21	56.21±6.77*#	214.12±33.65	123.39±23.50*#
t-test	0.104	8.291	0.155	7.030	0.077	4.280
p-value	0.917	<0.001	0.877	<0.001	0.939	<0.001

Table-3: Comparison of mean blood flow velocity of cerebral artery between the groups.

Groups	Anterior cerebral artery		Middle cerebral artery		Posterior cerebral artery	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=50)	103.88±7.73	93.61±7.20#	131.70±12.21	101.56±9.37#	76.45±6.59	64.90±5.36#
Observation group (n=50)	102.49±7.38	85.87±7.01*#	130.33±12.94	95.63±9.34*#	75.36±6.83	58.20±5.73*#
t-test	0.920	5.446	0.545	3.170	0.077	4.280
p-value	0.360	<0.001	0.587	0.002	0.939	<0.001

* Significant compared to the control group, # Significant compared to the baseline value.

Table-4: Comparison of peroxiredoxin 2 (PRX2) expression level between the groups.

Groups	Before treatment	1d after treatment	3d after treatment	7d after treatment
Control group (n=50)	1.19±0.02	1.71±0.02	2.01±0.17	2.23±0.14
Observation group (n=50)	1.21±0.19	1.77±0.18	2.11±0.02	2.44±0.13
t-test	0.740	2.342	2.543	7.772
p-value	0.461	0.021	0.013	<0.001

F_{inter}-group=1604.721, P_{inter}-group=0.000
F_{time}=25.469, P_{time}=0.000
$F_{interaction}$=26.518, $P_{interaction}$=0.000
* Significant compared to the control group.

Table-5: Comparison of adverse reactions between the groups [n (%)].

Groups	Rebleeding	Gastrointestinal reactions	Headache and dizziness	Total incidence
Control group (n=50)	3(6.0)	3(6.0)	4(8.0)	10 (20.0)
Observation group (n=50)	1(2.0)	1(2.0)	1(2.0)	3 (6.0)*
x^2				4.332
p-value				0.037

* Significant compared to the control group.

(*p*<0.05). Compared to group A, the mean blood flow velocity of the cerebral arteries was slower in group B (*p*<0.05) (Table 3).

Overall, significant difference was noted in terms of time and interaction effect between the groups (*p*<0.05). Pairwise comparison indicated no significant difference in the comparison of PRX2 expression between the groups (*p*>0.05). On days 1, 3 and 7 after treatment, the expression levels of PRX2 increased in both the groups, but higher levels were observed in group B than group A (*p*<0.05) (Table 4).

The incidence of adverse reactions in group B was 3(6%) compared to 10(20%) in group A (p<0.05) (Table 5).

Discussion

SAH is a common cerebrovascular disease with high incidence rate, which is generally attributed to cerebral artery malformations or rupture of skull basal aneurysms.[12] It also has a high mortality as patients may develop cerebral vasospasm due to an extremely high intracranial pressure after blood flow enters the subarachnoid space directly[13] and even cerebral infarction in the later stage,[14-16] which seriously threatens the patient's quality of life. According to an epidemiological study[17] about one-third of patients with SAH might lose their self-care ability, accompanied by symptoms, such as hemiplegia and aphasia to varying degrees, as well as a series of neurological problems, such as headaches and dizziness. Meanwhile, as reported earlier[18] delayed cerebral vasospasm might occur 21 hours after intracerebral haemorrhage, which generally manifests as adverse vasodilation reaction, leading to ischaemic damage of brain tissue that poses a great challenge with respect to clinical treatment.

It has been documented previously that in an established animal model of SAH, there was a remarkable reduction in the count of red blood cells (RBCs) gathering in cervical lymph nodes, resulting in inflammatory reaction of brain tissues and neurological dysfunction.[19] Notably, nimodipine was confirmed to alleviate neurological damage and improve brain oedema to a certain extent by improving the lymphatic system function of mice with SAH.[20] Simultaneously, study[21] found that daily oral administration of atorvastatin 20mg/d could reduce the incidence of vasospasm and cerebral infarction in patients with aneurysmal SAH (aSAH) aged 60-90 years after surgery. In addition, it has been reported that nimodipine could significantly improve delayed vasospasm in mice.[22] Furthermore, in a randomized double-blind clinical trial, pivastatin could reduce the incidence of cerebral vasospasm to a certain extent despite no significant improvement in delayed ischaemic brain injury and prognosis, highlighting the necessity of using statins in combination with other therapies.[23] In the present study, compared to the control group, the observation group showed better therapeutic outcome and less adverse reactions, with statistically significant differences between the groups. These results support better clinical effect of nimodipine combined with statins in the treatment SAH, with less adverse reactions and high safety.

ET-1 can regulate blood pressure and blood circulation, and there may be risks of vasospasm and thrombosis in subjects with increased content of ET-1, leading to cerebral ischaemic injury.[24] VEGF can promote the differentiation, proliferation and migration of vascular endothelial cells by binding to specific receptors to induce new angiogenesis, leading to cerebral ischaemia and hypoxia consequently.[25] Moreover, CGRP is commonly present in brain tissue and the ischaemic state of brain tissues can be improved when there is a rise in the level of CGRP.[26] In the current study, compared to the control group after treatment, the levels of VEGF, CGRP and ET-1 were all better in the observation group, suggesting that nimodipine combined with statins played a protective role in vascular endothelial function by effectively maintaining the dynamic balance among ET-1, VEGF and CGRP. Concerning the possible causes, nimodipine combined with statins can inhibit the release of VEGF after cerebral ischemia to suppress the growth and proliferation of vascular smooth muscle cells and nerve fibres, thereby effectively protecting neurons. Eventually, this regimen can protect against ischemic brain injury by regulating the dynamic balance among the three indices. At the same time, it is also possible to regulate the ischemic and hypoxic state in vivo by inhibiting platelet aggregation,[27] thus alleviating neuronal damage caused by inflammatory reactions.

Additionally, PRX2 is a novel peroxidase that is highly expressed in various diseases and can reduce oxidative stress damage through antioxidant effects.[28,29] In a prior study[30] under cerebral hypoxia and hypoxia, the administration of PRX recombinant could significantly reduce lipid peroxidation and neuronal apoptosis in brain tissue, and could effectively alleviate oxidative stress induced by cerebral ischaemia and hypoxia. Similarly, a study[31] reported that PRX can significantly improve neuronal damage caused by hypoxia and reoxygenation. In a mice model, a study[32] observed that cerebral infarction mice after drug intervention were detected with increased expression level of PRX2 in brain cells of the infarcted area. In the current study, the expression level of PRX2 in the observation group was significantly higher than that in the control group on days 1, 3 and 7 after treatment. Collectively, the study suggested that nimodipine combined with statins may have a protective effect on patients' brain tissues by upregulating the protein expression of PRX2 to inhibit oxidative stress response.

The current study has limitations as the sample size was not calculated and it was relatively small. Besides, the course of treatment and follow-up duration were short. Further studies are needed to valide that current findings.

Conclusion

The application of nimodipine combined with statins had better clinical effect in the treatment of SAH. The proposed therapeutic regimen could alleviate inflammatory reaction, adjust vascular endothelial function, reduce blood flow velocity of cerebral arteries, and decrease side effects in the treatment process.

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Conflict of Interest: None.

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Author Contribution:

YZ & FM: Design and agreement to be accountable for all aspects of the work.

NG & ZX: Data collection and analysed clinical data.

YJ & JZ: Significantly Revised it.