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Original Article

Effects of nimodipine combined with transcatheter arterial embolization intervention on cerebral aneurysm hemorrhage and prognosis

Meizhen Xu[1], Laishu Luo[2], Guohua Mao[3]

[1]Cardiac Intervention Room, [2]Comprehensive Intervention Room, [3]Department of Neurosurgery, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

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Abstract: To explore the effect of nimodipine in combination with TAE intervention on cerebral aneurysm hemorrhage and prognosis. Total of 65 patients with intracranial aneurysm rupture underwent endovascular embolization were divided into the control group (CG, n=34) that underwent TAE intervention alone and the test group (TG, n=31) which received nimodipine in addition to TAE so as to compare the efficacy of the both groups. The incidences of cerebral vasospasm and delayed cerebral infarction were lower in the TG than those in the CG (P<0.05). The levels of S100 protein and NSE in CSF were markedly elevated in both groups after treatment, but the degree of increase in the TG was significantly lower than that in the CG (P<0.05). The blood flow velocity in the proximal and distal ends of the MCA with those in the TG was significantly higher than those in the CG (P<0.05). Administration of nimodipine in the intervention treatment of cerebral aneurysms has important clinical application value and is worth promoting.

Keywords: Nimodipine, transcatheter arterial embolization, cerebral aneurysm hemorrhage, intracranial aneurysm, prognosis

Introduction

Cerebral aneurysm, also known as intracranial aneurysm [1], is a protrusion of the artery wall caused by local abnormal enlargement of the cerebral artery lumen. These aneurysms are caused mostly by local congenital defects of the cerebral arterial wall and increased intraluminal pressure, resulting in a cystic bulge, which is the leading cause of subarachnoid hemorrhage. Transcatheter arterial embolization (TAE) is a method commonly used to treat subarachnoid hemorrhage caused by cerebral aneurysm hemorrhage [2].

TAE is one of the most important basic techniques in interventional radiology; it entails dropping a substance into a blood vessel through a catheter and blocking the vessel to achieve the desired therapeutic purpose under X-ray television fluoroscopy. Compared with transarterial chemoembolization, this treatment method causes lesser pain and lesser trauma, and is safer. The accuracy and controllability of embolization are greatly enhanced by imaging guidance throughout the procedure and selective target vessel intubation [3]. Bloomston et al. [4] found that TAE combined with chemotherapy can effectively control the condition of patients with advanced liver cancer, and it plays an effective role in the treatment of liver malignancies by causing ischemia in the tumors and delivering high-dose chemotherapy simultaneously. Kinoshita et al. [5] revealed that subjective symptoms of anorectal malignant melanoma decreased after TAE, which indicates that TAE has a positive effect in the treatment of malignant tumors. Because of the strong advantages of TAE, it has begun to be performed for treating intracranial aneurysms [6].

After interventional embolization for intracranial aneurysms, vasospasm and delayed cerebral infarction are common complications [7] that can worsen patient's prognosis. Vasospasm is one of the main causes of hemorrhage and disability from cerebral aneurysms; there-

Table 1. General information

Factors	CG (*n*=34)	TG (*n*=31)	X^2/F	*P*
Age	58.6±12.5	57.5±13.2	0.3450	0.7312
Course of disease	4.5±1.2	4.0±1.5	1.449	0.1525
BMI	24.1±1.8	23.6±1.5	1.188	0.2395
Weight	70.3±9.8	69.42±10.01	0.350	0.7277
Gender			1.342	0.3118
Male	18 (52.94%)	16 (51.61%)		
Female	16 (47.06%)	15 (48.39%)		
Hunt-Hess grade			0.1799	0.8660
I	10 (29.41%)	10 (32.26%)		
II	19 (55.88%)	17 (54.84%)		
III	5 (14.71%)	4 (12.90%)		
Disease classification			0.5846	0.5801
Middle cerebral aneurysm	10 (29.41%)	8 (25.81%)		
Anterior cerebral aneurysm	8 (23.53%)	7 (22.58%)		
Internal carotid artery-posterior communicating aneurysm	10 (29.41%)	10 (32.26%)		
Vertebral basal aneurysm	6 (17.65%)	6 (19.35%)		

fore, controlling the occurrence of vasospasm and delayed cerebral infarction is an effective way to improve patient's prognosis. Clinical treatment of vasospasm involves nimodipine, a calcium channel inhibitor initially used for blood pressure management. Nimodipine crosses the blood-brain barrier and causes dilation of vascular smooth muscle cells [8]. In this study, nimodipine was included in the treatment of cerebral aneurysm hemorrhage in combination with TAE in an attempt to improve the efficacy and prognosis of this disease.

Materials and methods

Patient characteristics

In total, 65 patients with intracranial aneurysm rupture, aged 18-65 years, who underwent endovascular embolization in our hospital from January 2017 to January 2018 participated in this study. All patients were randomly assigned to one of the two groups by stratified random sampling with the use of a random number table: 34 patients underwent TAE alone (18 male and 16 female) served as the CG; their average age was 58.6 years (standard deviation, 12.5). The other 31 patients (16 male and 15 female) received nimodipine in combination with TAE and served as the TG; their average age was 57.5 years (standard deviation, 13.2). Other general data of patients in the two groups were not significantly different (*P* value of >0.05; **Table 1**).

Inclusion and exclusion criteria

Inclusive criteria were as follows: (1) the time from onset of symptoms to admission was <72 hours; (2) intracranial aneurysms were diagnosed by computed tomographic angiography or digital subtraction angiography, and cerebral vasospasm was caused by aneurysm rupture; (3) Hunt and Hess grade of subarachnoid hemorrhage [9] was I-III; (4) patients underwent TAE; and (5) research methods were in line with ethical standards and were approved by the medical ethics committee of our hospital. Written informed consent was obtained after patients were fully informed about the study.

Exclusion criteria were as follows: (1) the presence of primary diseases such as those of the cardiovascular, liver, kidney and blood system; (2) cerebrovascular obstruction caused by hematopathy, hypertension, amyloid angiopathy, cerebral arteritis, abnormal vascular network at the base of the brain, or tumor metastasis; (3) presence of metabolic diseases and mental disorders; (4) contraindications to the drugs used in this study; and (5) presence of severe vital signs disorder, respiratory system failure, or circulatory system failure at the time of admission.

Treatment

All patients underwent TAE under general anesthesia, and intracranial pressure was reduced before surgery. The anesthesiologist monitored the vital signs of the patient during the surgery. The right femoral artery was punctured by the Seldinger technique [10], and a 6F artery sheath and 6F guiding catheter were inserted simultaneously. Systemic heparinization was initiated (intravenous injection of heparin, 3000 IU, followed by an additional 1000 IU per hour); then, normal saline was injected into the coaxial catheter to prevent intracatheter coagulation and cerebral thrombosis. The microcatheters were shaped according to the location, size, and shape of the aneurysm, aneurysmal neck, and angle of the parent artery at the site of the arterial bulge. First, the aneurysm cavity was simply packed with a microspring coil into a basket. If the coil could not be stably inserted into the aneurysm cavity, it was positioned with double microtubules, auxiliary balloons, or auxiliary stents. After successful embolization, hypervolemic hypertensive hemodilution were routinely assessed to prevent insufficient blood perfusion in the affected brain tissue. All patients were treated according to these methods; the patients in the TG were, in addition, administered 25 mg of nimodipine (Bayer Healthcare Pharmaceuticals AG, Berlin Germany; Stage Drug Approval No.: J20100002) intravenously at a rate of 0.5 μg/kg/min for 2 weeks.

Outcome measures

The total clinical effectiveness rates in the two groups were observed and compared. According to the relevant standards of the *Chinese Expert Consensus on Vascular Interventional Therapy for Intracranial Aneurysms*, formulated in 2013 by the neurointerventional group of the neurosurgery branch of the Chinese Medical Association, therapeutic efficacy was graded as markedly effective, effective, or ineffective. Treatment was considered markedly effective if the clinical symptoms and signs disappeared and if the patient's score on assessment of neurological impairment improved by >46%. Treatment was considered effective if the clinical symptoms and signs were significantly improved and the neurological impairment score improved by 18-46%. Treatment was considered ineffective if the clinical symptoms and signs of the patient did not change or worsened. The total clinical effectiveness rate was calculated as the sum of the number of patients in whom treatment was markedly effective and the number of those in whom it was effective divided by the total number of patients and then multiplied by 100%.

The occurrences of cerebral vasospasm and delayed cerebral infarction as well as adverse reactions to treatment were monitored in the two groups, and the prognosis of the patients 3 months after the surgery was evaluated according to the Glasgow Outcome Scale (GOS) [11], with a score of 1 representing death, a score of 2 representing persistent vegetative state, a score of 3 representing severe disability, a score of 4 representing moderate disability, and a score of 5 representing good recovery. For detecting S100 protein (CSFSS100) in cerebrospinal fluid, 3 mL of CSF was collected before and 7 days after the surgery, and the presence of S100 protein was determined by enzyme-linked immunosorbent assay (ELISA). Simultaneously, to measure neuron-specific enolase (NSE) levels in serum, 2 mL of venous blood was collected and placed in an SC-2542 centrifuge at 335.37×*g* and 4°C for 10 min to separate the serum. Then, the serum NSE level was measured by ELISA. The detection kits were purchased from CanAg (Gothenburg, Sweden), and the relevant inspection was conducted strictly according to the manufacturer's instructions. To measure the velocity of blood flow in the proximal and distal ends and the center of the middle cerebral artery (MCA), a microvascular ultrasonic Doppler probe (DW company, Germany) was used, and the relevant parameters were set as follows: ultrasonic depth of 1.8 mm, power of 1.4 μW, and a filter of 300 Hz.

Statistical analysis

Logistic regression analysis was applied to analyze the risk factors responsible for a poor prognosis. The experimental data were analyzed using the SPSS 20.0 software (Shanghai Yuchuang Network Technology Co., Ltd., Shanghai, China). The measurement data were expressed as mean ± standard deviation, and the count data were compared using a χ^2 test. GraphPad Prism 6 (Emerald Biotechnology Co., Ltd., Hangzhou, China) was used for picture rendering of this experiment. A P value of <0.05 indicated that the difference was statistically significant.

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

Groups	*n*	Markedly effective	Effective	Ineffective	Total effective rate (%)
TG	31	12 (38.71%)	16 (51.61%)	3 (9.68%)	28 (90.32%)
CG	34	13 (38.24%)	13 (38.23%)	8 (23.53%)	26 (76.47%)
X^2		0.282	0.372		
P		0.804	0.746		

Table 3. Comparison of the incidence of vasospasm and delayed cerebral infarction between the two groups [n (%)]

Groups	*n*	Symptomatic vasospasm	Asymptomatic vasospasm	Total occurrence of vasospasm	Delayed cerebral infarction
TG	31	5 (16.13%)	3 (9.70%)	8 (25.81%)	3 (9.68%)
CG	34	8 (23.53%)	6 (17.65%)	14 (41.18%)	5 (14.71%)
X^2		22.306	21.360	23.935	24.665
P		0.002	0.003	0.002	0.001

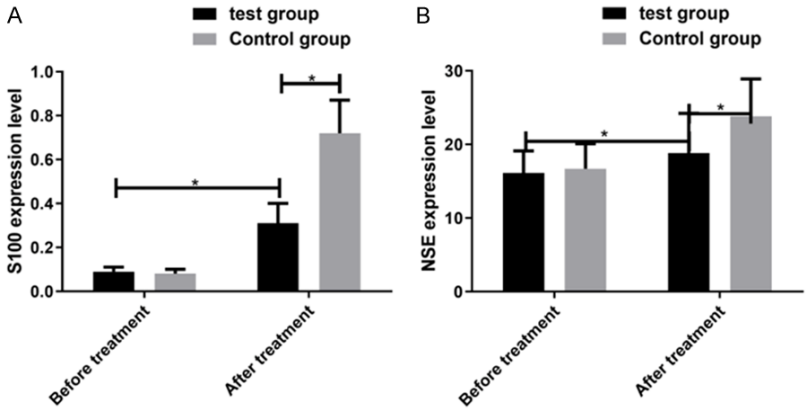

Figure 1. Comparison of S100 protein and serum neuron-specific enolase (NSE) levels in cerebrospinal fluid between the two groups. A. S100 protein expression before and after treatment in the two groups. B. NSE expression before and after treatment in the two groups. *P<0.05.

Results

Nimodipine combined with TAE achieves better clinical treatment effects

The total clinical effectiveness rate was markedly higher in the TG (90.32%) than that in the CG (76.47%; P<0.05; **Table 2**).

Nimodipine combined with TAE has lower incidence of complications

In the TG, the incidence of cerebral vasospasm was 25.81% and that of delayed cerebral infarction was 9.68; however, in the CG, these incidences were 41.18% and 14.71%, respectively. Thus, the incidences of these two complications were significantly lower in the TG than those in the CG (P<0.05; **Table 3**).

Nimodipine combined with TAE inhibits abnormal increases in S100 protein and serum NSE levels in CSF

The levels of S100 protein in CSF and of NSE in serum were remarkably elevated after treatment in both groups (P<0.01), but the degree of increase in the TG was significantly lower than that in the CG (P<0.05; **Figure 1**).

Nimodipine combined with TAE improves the proximal and distal blood flow velocity

The blood flow velocity in the proximal and distal ends of the MCA in the two groups was significantly higher after treatment than that before treatment, and the blood flow velocity before treatment in the TG was significantly higher than that in the CG (P<0.05). The blood flow velocity in the middle of the MCA did not differ significantly between the two groups after treatment (P> 0.05; **Figure 2**).

Nimodipine combined with TAE improves prognosis

Three months after the surgery, the proportions of patients with GOS scores of 5 and 4 in the TG were remarkably higher than those in the CG (P<0.05; **Table 4**).

Adverse reactions

The total incidence of adverse reactions in the two groups, 12.90% in the TG and 17.65% in

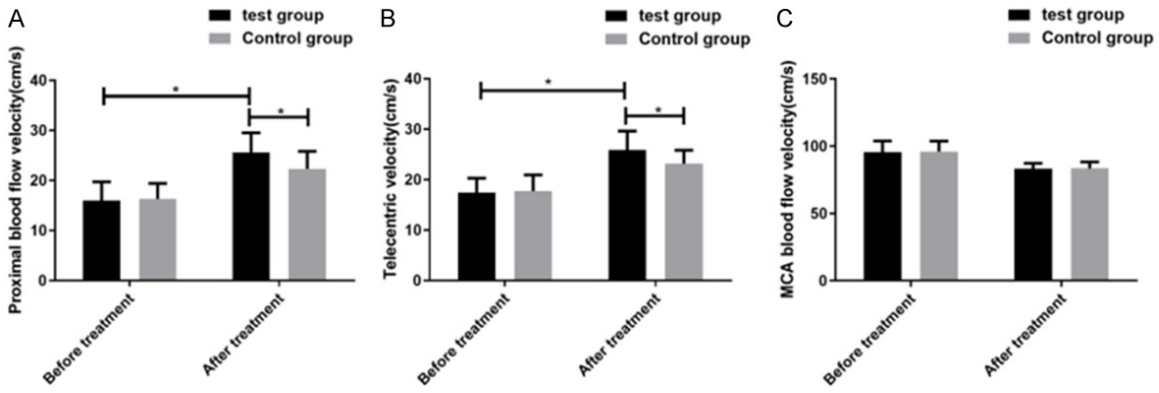

Figure 2. Comparison of blood flow velocity between two groups. A. Ratio of proximal blood flow velocity before and after treatment in the two groups. B. Ratio of distal flow velocity before and after treatment in the two groups. C. Ratio of middle cerebral artery (MCA) blood flow velocity before and after treatment in the two groups. *P<0.05.

Table 4. GOS grading of patients in the two groups at 3 months after surgery

Groups	*n*	Grade I	Grade II	Grade III	Grade IV	Grade V
TG	31	0	4	5	6	16
CG	34	2	3	12	8	9
X^2		4.6635	5.635	26.635	20.635	20.215
P		0.362	0.093	0.002	0.003	0.003

Table 5. Comparison of adverse reactions between the two groups

Groups	*n*	Slight decrease in blood pressure	Rash	Increase in alanine aminotransferase	Total
TG	31	1	1	2	4 (12.90%)
CG	34	2	1	3	6 (17.65%)
X^2		6.258	5.935	5.392	4.935
P		0.069	0.163	0.155	0.295

the CG, did not differ significantly (P>0.05; **Table 5**).

Univariate logistics analysis for factors influencing patient prognosis

Univariate logistic regression analysis revealed significant differences in age, number of patients with multiple artery ruptures, number of patients with multiple aneurysms, tumor size, Hunt and Hess grade, and number of patients with intraoperative aneurysm rupture (P<0.05). Conversely, the effects of seven other factors, which included sex, basic medical history, aneurysm location, presence of subarachnoid hemorrhage, arterial block time, operation timing, and operation duration, did not differ statistically (P>0.05; **Table 6**).

Multivariate logistics regression analysis for factors affecting patient prognosis

Multivariate logistic regression analysis demonstrated that of the six factors affecting prognosis according to the univariate analysis, age and intraoperative rupture of the aneurysm had no significant effect on prognosis (P>0.05), but multiple aneurysm ruptures (P=0.014), multiple aneurysms (P=0.004), Hunt and Hess grade (P=0.006), and aneurysm size (P=0.020) seriously affected prognosis; the differences between the TG and CG were statistically significant (P< 0.05). These four factors had the highest effect on prognosis after aneurysm surgery (**Table 7**).

Discussion

After subarachnoid hemorrhage caused by ruptured aneurysm, damage to brain tissue by blood can lead to cerebral artery spasm, and long-term intervention during TAE can also stimulate cerebral vasospasm [12]. Subarachnoid hemorrhage can be spontaneous or traumatic; the former is mostly caused by aneurysm rupture. The overall rate of mortality associated with subarachnoid hemorrhage is exceedingly high (>50%), and subarachnoid hemorrhage accounts for approximately 22-26% of all deaths owing to cerebrovascular disease. Among survivors of subarachnoid hemorrhage,

Table 6. Univariate logistic regression analysis

Factors	*P* value	OR value	95% CI
Gender	0.847	0.910	0.321-2.732
Age	0.008	1.723	1.021-1.109
Basic medical history	0.167	2.275	0.710-7.920
Multiple aneurysm ruptures	0.006	5.721	1.630-20.079
Multiple aneurysms	0.001	6.11	2.139-17.459
Aneurysm location	0.834	0.184	-
Aneurysm size	0.003	1.521	1.105-1.396
Hunt-Hess grade	0.002	4.451	2.410-8.217
Subarachnoid hemorrhage	0.651	1.429	0.383-6.697
Intraoperative rupture	0.005	7.000	2.463-19.891
Arterial block time	0.703	1.004	0.983-1.026
Operation Timing	0.674	0.999	0.997-1.002
Operation time	0.054	1.265	0.996-1.607

Table 7. Logistics regression analysis of multiple factors affecting the prognosis of 65 cases of intracranial aneurysms

Factors	*P* value	OR value	95% CI
Multiple aneurysm ruptures	0.014	52.514	2.238-1232.454
Multiple aneurysms	0.004	26.038	2.790-244.764
Hunt-Hess grade	0.006	3.915	1.469-10.434
Aneurysm size	0.018	1.484	1.058-1.970

>16% are left with severe disability, and of those patients, merely 15-30% showed any recovery [13, 14].

Cerebral vasospasm is an important cause of delayed death after subarachnoid hemorrhage [15]. Cerebral vasospasm after embolization of ruptured intracranial aneurysms results from the change in the lumen structure caused by vascular injury or continuous contraction of smooth muscle of one or more branches of the basilar artery. This change is manifested during arteriography as luminal stenosis. There is evidence that vasospasm after subarachnoid hemorrhage might be the result of multiple factors, such as production of nitric oxide, bilirubin oxidation decomposition products, endothelin, and inflammatory cytokines, each of which plays an important role in the process of vasospasm [16-18]. Skilled technique, gentle surgical manipulation, appropriate operation time, short intubation time, and correct medication are all critical in effectively reducing the incidence of cerebral vasospasm.

Currently, most scholars advocate the administration of nimodipine in the embolization of ruptured intracranial aneurysms. Nimodipine is also currently recommended by the American Stroke Association for the prevention and treatment of cerebral vasospasm [19]. Nimodipine binds to calcium channels in a highly specific reversible manner after it enters brain tissue and regulates calcium ions flowing into nerve cells, thereby protecting neurons, stabilizing their functions, and improving their ischemic tolerance [20, 21]. Calcium ions flowing into vascular smooth muscle cells are also regulated to enhance the ability of blood vessels to resist contraction and ischemia [22]. According to the results of Stullken et al. [23], nimodipine can effectively prevent vascular occlusion of intracranial aneurysms. According to Han et al. [24], continuous infusion of nimodipine during intracranial aneurysm surgery can reduce the occurrence of cerebral vasospasm.

The results of regression analysis indicated that the prognosis of patients with multiple aneurysm ruptures is significantly worse than that of patients with a single rupture and those without aneurysm rupture. The repair of a ruptured aneurysm wall mainly depends on cellulose networks and the generation of new capillaries, but new capillaries are more susceptible to rupture and can bleed again, leading to a vicious circle of bleeding, repair, and rebleeding, and this ultimately results in the enlargement of tumor bodies. Results of some studies revealed that the rate of mortality owing to multiple aneurysm ruptures was significantly increased compared with that owing to single aneurysm ruptures, and the higher the number of aneurysm ruptures, the worse the prognosis and higher the possibility of cerebral infarction [25]. Therefore, most investigators consider postoperative treatment (hypertension, high blood volume, and blood dilution) [26], and the use of calcium antagonists are essential to prevent and minimize brain damage caused by cerebral vasospasm.

The results of this study showed that patients in the TG, who were administered nimodipine in combination with TAE, had a significantly

better prognosis than those in the CG who underwent TAE alone. Furthermore, postoperative levels of S100 protein in CSF and NSE in serum increased significantly in both groups, but the TG presented much lower rates of increase than the CG, and nimodipine effectively controlled the high expression of S100 protein and NSE. S100 protein is a kind of nerve tissue protein, and an abnormal elevation in its levels in an intracranial aneurysm can reflect the degree of central nervous system injury to a certain extent, which is helpful for judging brain tissue injury [27, 28]. NSE is specific to nerve cells and participates in glycolysis. Normally, the levels of NSE in the CSF and blood are exceedingly low, but when brain injury occurs, NSE is released into the CSF in large quantities, after which it enters the blood stream through the injured blood-brain barrier. This results in an abnormal increase in serum NSE levels, which reflects the degree of brain tissue damage [29].

In summary, administration of nimodipine in the surgical treatment of cerebral aneurysm can produce a good clinical effect. It can significantly reduce the incidence of cerebral vasospasm in patients, improve the proximal and distal blood flow velocity, and inhibit abnormal increases in S100 protein and serum NSE levels in CSF. Thus, it has important clinical value and should be applied widely.

Disclosure of conflict of interest

None.

Address correspondence to: Laishu Luo, Comprehensive Intervention Room, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Nanchang 330006, Jiangxi, China. Tel: +86-0791-86299873; E-mail: dh3lnw@163.com

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