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Original Article

Early vascular embolization improves neurological function in patients with intracranial aneurysm

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Abstract: Objectives: To investigate the effect of early vascular embolization for intracranial aneurysms and the effect of matrix metalloproteinase-9 (MMP-9) and nuclear factor-kappa B (NF-κB) on nerve function. Methods: This is a retrospective analysis study. A total of 90 patients with intracranial aneurysms admitted to our hospital from January 2017 to December 2021 were selected as research subjects. The patients were divided into a control group (n=47) and an observation group (n=43) according to different embolization timing. Both groups were treated with vascular embolization, the observation group received vascular embolization within 72 h after onset, while the control group received vascular embolization after 72 h. In addition, both groups were given clopidogrel bisulfate tablets and enteric-coated aspirin tablets from the day after operation for 3 months. The embolization at 3 months after operation, the occurrence of complications, the daily activities and neurological function before and 3 months after operation, serum levels of MMP-9 and NF-κB, the protein expression of MMP-9 and NF-κB, and the prognosis at 3 months after operation were compared between the two groups. Results: The complete embolization rate (90.70%) in observation group was higher than that of the control group (72.34%) at 3 months after operation ($P<0.05$). The postoperative complications in the observation group (9.30%) were lower than those of the control group (27.66%) ($P<0.05$). The improvement in Modified Barthel index score, as well as serum levels of MMP-9 and NF-κB were better in the observation group than those of the control group 3 months after operation (P<0.05). The prognosis of patients in the observation group was better than those of the control group 3 months after operation (P<0.05). Conclusion: Early vascular embolization is an effective approach for intracranial aneurysm. It helps improve patients' neurological function, and reduce their serum and protein levels of both MMP-9 and NF-κB, thereby leading to favorable prognosis.

Keywords: Early vascular embolization, intracranial aneurysm, efficacy, neurological function, matrix metalloproteinase-9, nuclear factor-κB

Introduction

Intracranial aneurysm is caused by the rupture of the blood vessel wall of a local cerebral artery in the human body, causing a continuous rise in intracranial pressure and contributing to subarachnoid hemorrhage [1]. Most patients with intracranial aneurysm have no symptoms, or they may exhibit neurological deficits due to the compression of peripheral nerve structures caused by the enlargement of the aneurysm [2]. The pathogenesis of intracranial aneurysms can be divided into congenital and acquired pathogenesis. Congenital genetic factors include hereditary connective tissue diseases or familial intracranial aneurysms, and acquired pathogenesis is due to arteriosclerosis, vasculitis, or severe hypertension. Some patients have subarachnoid hemorrhage due to the rupture of the aneurysm, which can be life-threatening [3].

At present, aneurysm clipping and vascular intervention are mainly used for the treatment of intracranial aneurysms. However, aneurysm clipping requires craniotomy, so the operation gets more complex, when there is a larger trauma, associated with an increasing number of complications and slow postoperative recovery. As a minimally invasive operation, vascular embolization intervention has the benefits of a high success rate, small trauma, fast postoper-

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ative recovery and fewer complications, and is, therefore, widely applied in the treatment of craniocerebral aneurysms, but the timing of the operation is still controversial [4].

Matrix metalloproteinase-9 (MMP-9) has been shown to be highly expressed in intracranial aneurysms, which can cause vascular injury by degrading the extracellular matrix components of vascular walls. Its expression level changes can predict the prognosis of patients [5]. Nuclear factor kappa B (NF-κB) is a transcription factor with unique biologic characteristics and multi-directionality, which can be activated by a variety of stimuli and is widely involved in the regulation of chemokines, adhesion molecules, inflammatory mediators, and some inflammatory-related enzymes, regulating the immune response and inflammatory response of the body through a variety of pathways. It is closely related to the occurrence and development of intracranial aneurysms, and its level changes are of great significance in the treatment and prognosis of intracranial aneurysms [6].

Therefore, this study included 90 patients with intracranial aneurysms as research subjects and explored the efficacy of early vascular embolization in the treatment of intracranial aneurysms and its influence on neurological function, as well as MMP-9 and NF-κB levels. Our purpose is to provide a reference for clinical treatment.

Data and materials

Clinical data

This is a retrospective analysis study. A total of 90 patients with intracranial aneurysms who were admitted from January 2017 to December 2021 were enrolled as research subjects and divided into a control group (n=47) and an observation group (n=43) based on their surgery time. This study was approved by the ethical institution of Heji Hospital Affiliated to Changzhi Medical College.

Inclusion criteria: (1) patients who underwent vascular embolization according to the Chinese Expert Consensus on Intravascular Interventional Therapy of Intracranial Aneurysms (2013) [7]; (2) patients whose subarachnoid hemorrhage from rupture of intracranial aneurysm was confirmed by intracranial angiography, MRI, CT and digital subtraction angiography (DSA); (3) patients who had indications for surgical treatment; (4) patients with Hunt-Hess grade I-IV; (5) patients with complete data.

Exclusion criteria: (1) patients with autoimmune diseases or other malignant tumors; (2) patients with cerebral infarction, brain trauma, or intracranial metastasis; (3) patients with serious mental illness or consciousness disorder; (4) patients with liver, kidney or cardiopulmonary insufficiency; (5) patients with a recent history of major surgery or trauma; (6) patients with contraindications to surgery; (7) patients with blood coagulation or immune dysfunction; (8) patients with multiple aneurysms.

Methods

Both groups received conventional symptomatic treatment after admission, including intracranial pressure reduction, fluid replacement, blood pressure control, and anti-vasospasm. The two groups also received vascular embolization with specific methods as follows. After general anesthesia with endotracheal intubation, femoral artery puncture and DSA were performed. According to the size, location, shape, and relationship between aneurysms and peripheral blood vessels in the patients, spring-coil microcatheters were delivered into the aneurysm cavity under the guidance of microguide wires according to the specific location of the arterial tumor. An appropriate type of micro-spring coil was chosen for embolization. Afterwards, the embolization situation was evaluated by DSA to confirm the procedure was successful or the cavity was completely filled. The femoral artery was compressed 1 cm above the puncture point for 15 min, and the puncture point was covered by conventional compression dressing. The observation group received vascular embolization within 72 h after onset, while the control group received vascular embolization 72 h after onset. Both groups were given clopidogrel hydrogen sulfate tablets (Sanofi Hangzhou Pharmaceutical Co., Ltd., specification: 75 mg) 75 mg/time on the day after operation, once a day. In addition, patients also took aspirin enteric-coated tablets (Bayer Health Care Co., Ltd., 0.1 g) 100 mg/time, once a day for 3 months.

Evaluation criteria for response

DSA was performed 3 months after surgery to evaluate the response of intracranial aneurysm embolization. Aneurysm embolization of 100% was considered as complete embolization; aneurysm embolization of ≥75% was considered partial embolization; aneurysm embolization of less than 75% was considered non-embolized.

Outcome measures

Primary outcome measures: (1) The complication rate was compared between the two groups. (2) The changes in daily activities and nerve function were observed preoperatively and postoperatively. Modified Barthel index (MBI) score was applied to evaluate the patients' daily activities (score ranged 0-100 points), with a high mark indicating better outcome. Neurological function was evaluated by National Institutes of Health Stroke Scale (NIHSS, score range 0-42), and a higher score representing severer neurological deficits.

Secondary outcome measures: (1) Serum MMP-9 and NF-κB levels were observed before and 3 months after the operation. Peripheral venous blood (5 mL) was collected from the patients before and 3 months after the operation, centrifuged at a speed of 2500 r/min and a radius of 10 cm for 10 min. The serum levels were measured by enzyme linked immunosorbent assay using Human MMP9 ELISA Kit (Abcam, USA) and Human NF-κB (NF-κB) ELISA Kit (Shanghai Jianglai Biology, China). (2) MMP-9 and NF-κB protein expressions in both groups were analyzed by western blot before and 3 months after operation. Tissue lysates were centrifuged, and the total protein concentration was determined. Proteins were then separated using 10% SDS-PAGE and transferred onto PVEF membrane (Bio-RAD, USA). The membranes were blocked at room temperature using 5% skim milk for 2 h. MMP-9 or NF-κB primary antibody (1:500, 1:1000) (Abcam, USA) were added and incubated at room temperature for 2 h, followed by incubation at 4°C overnight. Thereafter, second antibody (Abcam, USA) was added and incubated for 3 h. GAPDH (Abcam, USA) was used as internal reference, and the gray level of protein band expression was analyzed by Quantity One software. (3) The 3-month postoperative prognosis was evaluated in both groups by Glasgow Coma Scale (GOS, score range 1-5 points), in which 5 points indicates the gradual recovery of daily living function and mild defects, and 1 point indicates the death of the patient. Patients with 1-3 GOS points were classified as poor prognosis, and 4-5 points as good prognosis.

Statistical analysis

SPSS 26.0 was adopted for data processing. Measured data were expressed as ($\bar{x} \pm s$). Independent sample t test was used for comparison of measured data between groups, and paired sample t test was used for comparison of measured data before and after treatment within groups. Counted data were represented as *n* (rate) and tested by χ^2. $P<0.05$ was considered a significant difference.

Results

Clinical data

The two groups had non-significant differences in clinical data including gender, age, BMI, lesion site, and Hunt-Hess grade (P>0.05) (**Table 1**).

Comparison of 3-month postoperative embolization rate

The complete embolization rate in the observation group (90.70%) at 3 months after the operation was significantly higher than that of the control group (72.34%) ($P<0.05$) (**Table 2**).

Comparison of postoperative complications

The incidence of postoperative complications in the observation group (9.30%) was lower than that of the control group (27.66%) ($P<0.05$) (**Table 3**).

Comparison of MBI and NIHSS scores

The MBI scores at 3 months after the operation were higher than those preoperatively, while the postoperative NIHSS scores were lower than those before surgery ($P<0.05$). MBI score of the observation group was higher than that of the control group 3 months after surgery, while the NIHSS score was lower than that of the control group ($P<0.05$) (**Table 4**).

Table 1. Comparison of clinical data

Clinical Data	Observation group (n=43)	Control group (n=47)	t/χ^2	*P*
Gender				
Male	25	27	0.004	0.947
Female	18	20		
Age (years, $\bar{x} \pm s$)	57.56±8.18	58.32±7.95	0.447	0.656
Body mass index (kg/m^2, $\bar{x} \pm s$)	22.79±2.09	22.54±2.18	0.554	0.581
Time from onset to surgery (h, $\bar{x} \pm s$)	11.43±2.41	10.87±2.34	1.118	0.267
Lesion location				
Anterior communicating artery	21	23	-0.339	0.735
Posterior communicating artery	13	12		
Vertebrobasilar artery	9	12		
Hunt-Hess Classification				
I	10	12	-0.425	0.671
II	9	14		
III	13	9		
IV	11	12		

Table 2. Comparison of the degree of embolism 3 months after surgery

Group	Number of cases	Complete embolization (%)	Partial embolization (%)	No embolization (%)	Response rate (%)
Observation group	43	39 (90.70)	4 (9.30)	0 (0.000)	39 (90.70)
Control group	47	34 (72.34)	13 (27.66)	0 (0.00)	31 (72.34)
χ^2	-	-	-	-	4.939
P	-	-	-	-	0.026

Table 3. Comparison of postoperative complications between the two groups

Group	Number of cases	Intracranial infection	Thrombosis	Cerebral vasospasm	Hydrocephalus	Incidence (%)
Observation group	43	1	0	2	1	9.30
Control group	47	3	2	6	2	27.66
χ^2	-					4.939
P	-					0.026

Table 4. Comparison of MBI and NIHSS scores between the two groups ($\bar{x} \pm s$, points)

Group	Number of cases	MBI		NIHSS	
		Preoperative	3 months after surgery	Preoperative	3 months after surgery
Observation group	43	60.28±9.94	89.48±5.65*	27.17±5.73	10.24±3.17*
Control group	47	60.71±12.23	78.84±8.47*	26.65±4.45	16.98±4.03*
t	-	0.182	6.943	0.483	8.763
P	-	0.856	<0.001	0.630	<0.001

Note: Compared to preoperative, *$P<0.05$.

Comparison of serum MMP-9 and NF-κB levels

The MMP-9 and NF-κB levels 3 months after surgery were lower than those before surgery in both groups ($P<0.05$). The observation group exhibited lower postoperative MMP-9 and NF-κB levels than the control group did ($P<0.05$) (**Table 5**).

Table 5. Comparison of serum MMP-9 and NF-κB levels between the two groups ($\overline{x} \pm s$)

Group	Number of cases	MMP-9 (μmol/L)		NF-κB (ng/L)	
		Preoperative	3 months after surgery	Preoperative	3 months after surgery
Observation group	43	35.89±5.61	9.42±2.18*	3.24±0.71	1.35±0.37*
Control group	47	36.67±6.57	17.53±4.63*	3.08±0.97	2.01±0.56*
t	-	0.603	10.470	0.886	6.532
P	-	0.548	<0.001	0.378	<0.001

Note: Compared to preoperative, $^{*}P<0.05$.

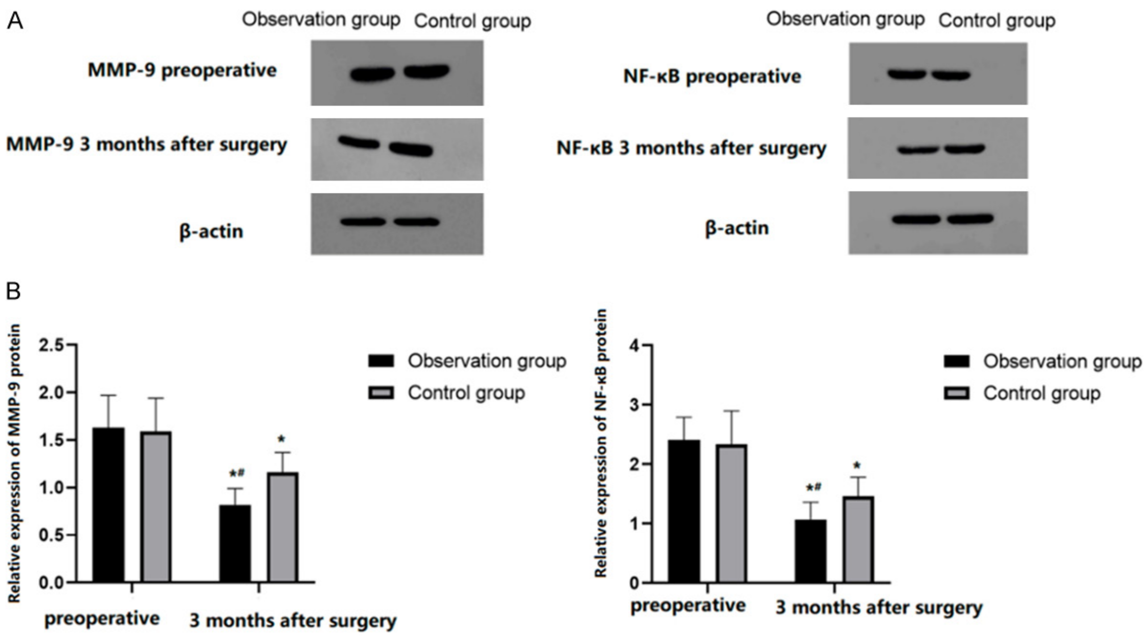

Figure 1. Comparison of expresion values of MMP-9 and NF-κB protein. Note: A: MMP-9 and NF-κB bands before or after treatment. B: Values of MMP-9 and NF-κB protein. 1: Observation group; 2: Control group. Compared to preoperative, $^{*}P<0.05$; Compared to the control group, $^{\#}P<0.05$.

Table 6. Comparison of 3-month prognosis between the two groups

Group	Number of cases	Good prognosis (%)	Poor prognosis (%)
Observation group	43	38 (88.37)	5 (11.63)
Control group	47	33 (70.21)	14 (29.79)
X^2	-	4.446	
P	-	0.035	

Comparison of MMP-9 and NF-κB protein expression between the two groups

The protein expression values of MMP-9 and NF-κB in the two groups at 3 months after operation were both lower than those before operation (*P<0.05*). The expression value of postoperative MMP-9 and NF-κB protein in the observation group was lower than that of the control group (*P<0.05*) (**Figure 1**).

Comparison of 3-month prognosis

The prognosis of the observation group was better than that of the control group (P<0.05) (**Table 6**).

Discussion

Intracranial aneurysm is a cerebral hemangioma-like protrusion caused by localized pathologic expansion of the arterial wall and it is the most common cause of spontaneous subarachnoid hemorrhage, with the disease pathogenesis yet to be entirely elucidated [8]. This condition often manifests as spontaneous cerebral hemorrhage, cerebral vasospasm, or oculomotor nerve palsy. Tumor rupture will lead to local bleeding, and the patient will experience symptoms such as coma, vomiting, headache and even secondary brainstem damage in a short period of time [9, 10]. Therefore, timely and effective treatment for intracranial aneurysm is particularly critical.

Endovascular interventional embolization is a vital method for the treatment of intracranial aneurysms. The purpose is to occlude the aneurysm cavity at an early stage, relieve vasospasm, reduce the amount of blood loss, promote recovery of impaired neurologic function, and improve quality of life in patients [11]. Intracranial aneurysm usually enters the stage of cerebral vasospasm within 3 days of onset, which leads to an aggravation of cerebral edema in patients, and causes great difficulty for dense embolization and a low probability of complete embolization. Early endovascular embolization can reduce the incidence of cerebral vasospasm, the risk of rebleeding, and a recovery time [12]. Spring coil embolization is feasible as long as the microcatheter can pass through the narrow parent artery to the aneurysm cavity. After embolization, the microcatheter is returned to the spastic parent artery and balloon expansion is performed, which is conducive to relieve spasm and prevent aneurysm rupture. However, there is still disagreement regarding the timing of vascular embolization intervention. Some scholars consider that operation at the initial stage of intracranial aneurysm will lead to a higher risk of cerebral vasospasm, and embolization at this time may adversely affect the cerebrovasculature and the prognosis [13]. However, other scholars hold that advancements in interventional techniques ensure effective embolization, even in patients at an initial stage of cerebral vasospasm and when aneurysms are small enough to necessitate microcatheter implantation. With the prolongation of time until treatment, the brain tissue can be seriously damaged, making it difficult for patients to recover neurological function later [14]. This study showed that 3 months after the operation, the observation group demonstrated higher complete embolization rate, lower postoperative complication rate, higher MBI score, and lower NIHSS score compared to the control group. Therefore, surgical treatment within 72 h can increase the complete embolization rate, reduce postoperative complications, and improve patients' ability for daily activities and neurological function.

MMP-9 is an enzyme with the largest molecular weight in the metalloproteinase family produced by mononuclear macrophages, and some inflammatory and epithelial cells. It is regulated by various factors [15, 16]. It has been found that an abnormal increase of MMP-9 expression can damage the internal elastic membrane of the structure maintaining the toughness of the cerebral artery wall and weaken its integrity, allowing the formation of a cerebral aneurysm [17]. NF-κB is a vital transcription factor that has regulatory ability in the process of apoptosis, immunity, and inflammation. It can regulate gene transcription levels, inflammatory responses, and cell biological behaviors by binding to promoters [18]. It was shown that NF-κB is associated with the occurrence of intracranial aneurysm [19]. Besides, oxidative stress and inflammation induced by ruptured intracranial aneurysm can promote the NF-κB pathway, resulting in aggravated inflammatory response, cell damage, and apoptosis in brain tissue [20]. In this research, the 3-month postoperative MMP-9 and NF-κB levels in the observation group were lower than those of the control group, while the protein band levels of MMP-9 and NF-κB were lower than those in the control group, verifying that early vascular embolization can downregulate MMP-9 and NF-κB levels.

However, this study has some limitations, such as relatively small sample size, short observation time, and a small number of observation indicators. In the future, we should increase the sample size, extend the observation time, and expand the observation indicators in multi-center studies, so as to provide more reliable results.

In conclusion, early vascular embolization has a favorable effect towards intracranial aneurysms because it can improve patients' neurological function, reduce serum MMP-9 and NF-κB levels, and downregulate protein expressions of MMP-9 and NF-κB, associating with a good prognosis.

Disclosure of conflict of interest

None.

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