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Original Article

Clinical efficacy and prognosis of endovascular embolization in the treatment of ruptured tiny intracranial aneurysms

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Abstract: Objective: Tiny intracranial aneurysms pose a great therapeutic challenge for endovascular embolization due to the difficulties in coil packing and risk of intraoperative aneurysm re-rupture. These aneurysms are defined as the maximum diameter of less than or equal to 3 mm. This study was designed to explore the clinical efficacy and prognosis of endovascular embolization in the treatment of ruptured tiny intracranial aneurysms. Method: A total of 46 patients with 46 ruptured tiny intracranial aneurysms admitted to our hospital were retrospectively analyzed and evaluated for clinical efficacy and follow-up results by the Modified Rankin Scale (MRS). Clinical efficacy was assessed by the embolization degree of aneurysms and perioperative complications. According to patients' MRS scores at 12 months after discharge, univariate analysis was performed for gender, age, hypertension, diabetes, smoking, Hunt-Hess grade (HHG), Modified Fisher Scale (MFS), time from admission to embolization, aneurysm location, embolization method, embolization degree and perioperative complications, and factors with statistically significant differences were included in multivariate logistic regression analysis. Results: There were 37 patients (80.4%) with complete embolization. Of the remaining 9 patients, 4 patients (8.7%) were found with sub-complete embolization and 5 patients (10.9%) with incomplete embolization. In the process of embolization, there were 4 cases (8.7%) of cerebral vasospasm, 3 cases (6.5%) of acute thrombosis and 3 cases of intraoperative aneurysm re-rupture. The postoperative complications included cerebral infarction in 2 cases (4.3%), serious hydrocephalus in 1 case (2.2%) and severe pulmonary infection in 1 case (2.2%). After treatment, the proportion of MRS score 0 and 1 was significantly higher than that at admission ($P<0.05$). During the follow-up of all patients for 12 months, 35 patients (76.1%) had good prognosis and 11 patients (23.9%) had poor prognosis. Univariate analysis showed that HHG, MFS and perioperative complications were the factors affecting the prognosis of patients ($P<0.05$), and were the independent risk factors affecting the prognosis of patients with ruptured tiny intracranial aneurysms ($P<0.05$). Conclusion: Endovascular embolization has been proven effective in the treatment of patients with ruptured tiny intracranial aneurysms. HHG, MFS and perioperative complications are significantly correlated to poor prognosis of patients, which is worthy of attention.

Keywords: Endovascular embolization, ruptured tiny intracranial aneurysms, risk factors, efficacy, prognosis

Introduction

Intracranial aneurysms refer to abnormal dilations of the intracranial arteries, which can be divided into ruptured aneurysms and unruptured aneurysms, and the former cause subarachnoid hemorrhage (SAH). Ruptured aneurysms provide significant rates of disability and mortality [1]. The overall prevalence of intracranial aneurysms is estimated to be 3.2%, and there are roughly equal numbers of men and women affected with a mean age of 50 years [2]. Intracranial aneurysms occur more frequently at cerebral bifurcations because of the higher hemodynamic shear stress and stronger flow acceleration. The most common sites are the anterior communicating artery, middle cerebral artery bifurcations, posterior communicating artery and basilar artery terminus [3]. At present, the treatment methods of intracranial aneurysms mainly include endovascular embolization and surgical clipping. Tiny intracranial aneurysms are a special type of aneurysms, which have been studied for many years, but there is still no consensus on their prevalence [4-6]. The International Subarachnoid Aneurysm Trial (ISAT) demonstrated that endovascular embolization is more effective than surgical clipping for ruptured aneurysms [7]. But tiny aneurysms were not included in this study. Endovascular embolization or surgical clipping, deciding which treatment method is more suitable for tiny ruptured aneurysms, may need further research. The tiny size increases the difficulties for endovascular embolization. These difficulties are related to the inability for microcatheter to obtain a stable position, increased risk of intraoperative aneurysm rupture and instability of detached coils in aneurysm. However, with the improvement of devices and the increasing experience of surgeons, various embolization techniques have been widely adopted [8]. Many scholars like endovascular embolization, which has been proved to be safe and reliable [9-11]. Even thought, the risk factors affecting the prognosis of patients with tiny ruptured aneurysm after embolization have not been determined [12, 13]. In this study, 46 patients with ruptured tiny intracranial aneurysms were included to analyze the treatment efficacy and risk factors affecting the prognosis.

Materials and methods

Patients' data

A total of 46 patients with 46 ruptured tiny intracranial aneurysms from May 2014 to April 2020 were treated in our hospital and retrospective analyzed in this study. There were 21 males and 25 females with an age range from 36 and 73 years, with the mean age of (52.6± 8.2) years. There were 27 patients under the age of 50 and 19 patients over the age of 50. Among all 46 patients, 31 had hypertension and 10 had diabetes. There were 7 patients with both hypertension and diabetes. Fourteen patients had a history of smoking. All patients presented with headache as the first symptom and were diagnosed with SAH by computed tomography (CT) scan. The Hunt-Hess grade (HHG) was used to assess the patients' medical condition on admission. The results were grade I in 11 patients, grade II in 23 patients, grade III in 7 patients and grade IV in 5 patients. The Modified Fisher Scale (MFS) was applied to evaluate the risk of cerebral vasospasms, and there were 4 patients identified as grade 1, 11 patients as grade 2, 24 patients as grade 3, 7 patients as grade 4 and no patients as grade 0. There were 35 patients who received endovascular embolization within 24 hours after admission and another 11 patients who received endovascular embolization later than 24 hours after admission. As for the location of these aneurysms, 40 aneurysms were located in the anterior circulation and 6 aneurysms were located in the posterior circulation. The basic information of patients including gender, age, hypertension, diabetes, HHG, MFS, aneurysm location, antiepileptic treatment, time from admission to surgery, embolism degree, and severe complications were compared between the two groups. This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University. The research subjects and their families were informed and signed a fully-informed consent form.

Inclusion criteria

Patients with the maximal aneurysm diameter of ≤3 mm based on digital subtraction angiography (DSA); those with ruptured aneurysm; and those who were treated by endovascular embolization and successfully followed up were included.

Exclusion criteria

Patients with recurrence of aneurysm; those with multiple aneurysms; those aged ≥85; those complicated with vascular malformations and other cerebrovascular or severe systematic diseases; those with no aneurysm found at the first DSA or computed tomography angiography (CTA); and those who failed to complete the follow-up were excluded.

Endovascular procedures

Endovascular procedures were performed after patients underwent general anesthesia. A 6F catheter sheath (Terumo, Japan) was placed in the right femoral artery. A 6F guide catheter (Envoy, Codman, USA) was positioned in the internal carotid artery or vertebral artery. To image the ruptured aneurysm from different angles, the size and shape of the aneurysm were measured and reconstructed. The geometric relationship between the aneurysm and

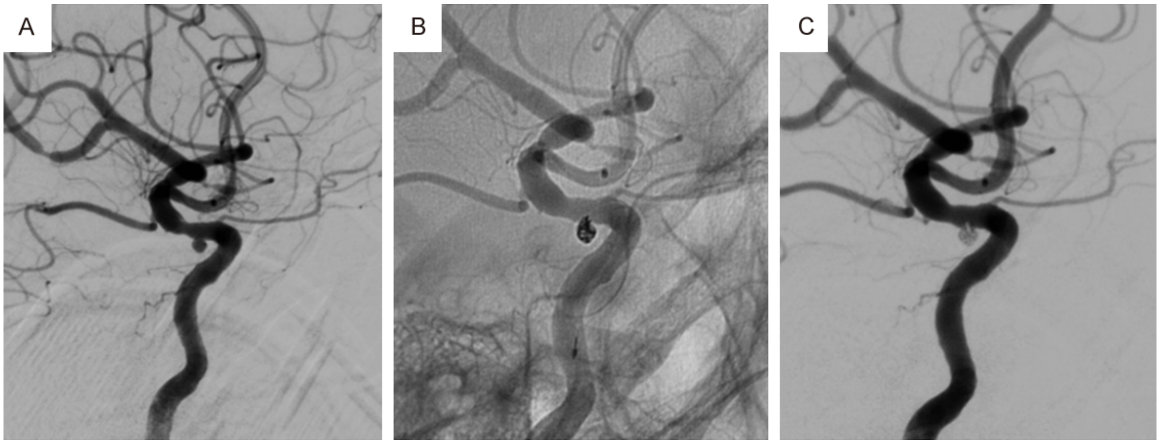

Figure 1. Female, 41 years old, tiny aneurysm (2.3×2.1×1.8 mm) in the ophthalmic segment of right internal carotid artery, no stent used (A: before embolization; B: during embolization; C: after embolization).

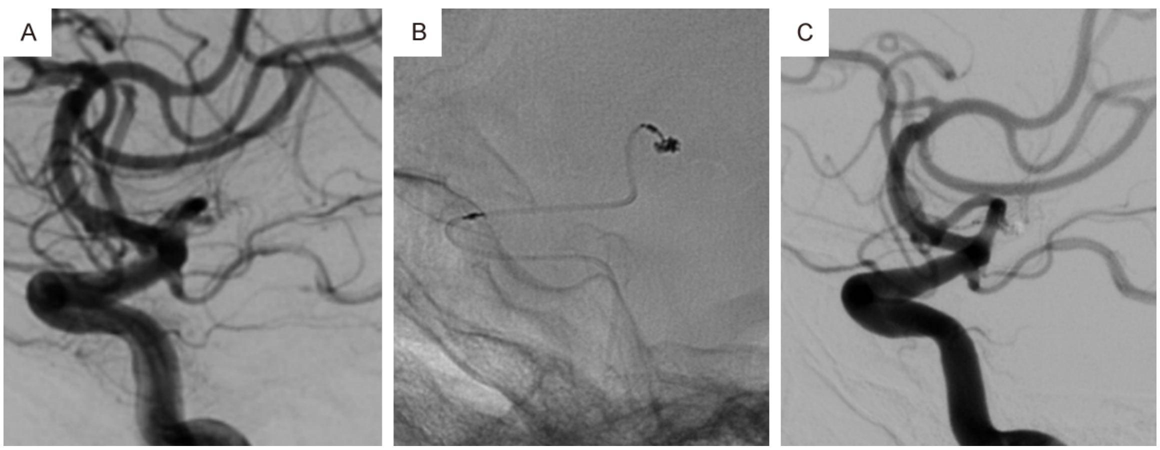

Figure 2. Male, 52 years old, tiny aneurysm (2.2×1.3×1.2 mm) in the A1 segment of the right anterior cerebral artery, no stent used (A: before embolization; B: during embolization; C: after embolization).

the parent artery was established by 3D-DSA and 3D-DSA reconstruction. After systemic heparinization, 17 patients underwent coil embolization without a stent used (**Figures 1**, **2**). Under the roadmap, a micro-guidewire (Synchro, Stryker, USA) guided the shaped microcatheter (Echelon, Ev3, USA) to the aneurysm neck. After confirming the relative position of microcatheter tip and aneurysm neck, Coils (Axium, Ev3, USA) were filled in the aneurysm body until optimal results were obtained. Twenty-nine patients had coil embolization difficulties due to special angles or shape of aneurysms who were provided with a stent (**Figures 3**, **4**). Four hours before embolization, 300 mg of aspirin and 300 mg of clopidogrel were given to these patients orally. The stent was selected according to the measured size of the aneurysm neck and parent artery. Under the roadmap, a micro-guidewire led the stent catheter (Headway, Microvention, USA) to the distal part of parent artery. After the aneurysm was filled with coils, the stent (Lvis, Microvention, USA) was delivered through the stent catheter and released across the aneurysm neck. After embolization, patients continued to take aspirin at the dose of 100 mg and clopidogrel at the dose of 75 mg per day for 3 months followed by aspirin only at the dose of 100 mg for 1 year. The time of medication was adjusted according to patients' medical conditions.

Evaluation criteria

The embolization degree was evaluated by DSA based on the Raymond-Roy Occlusion Class-

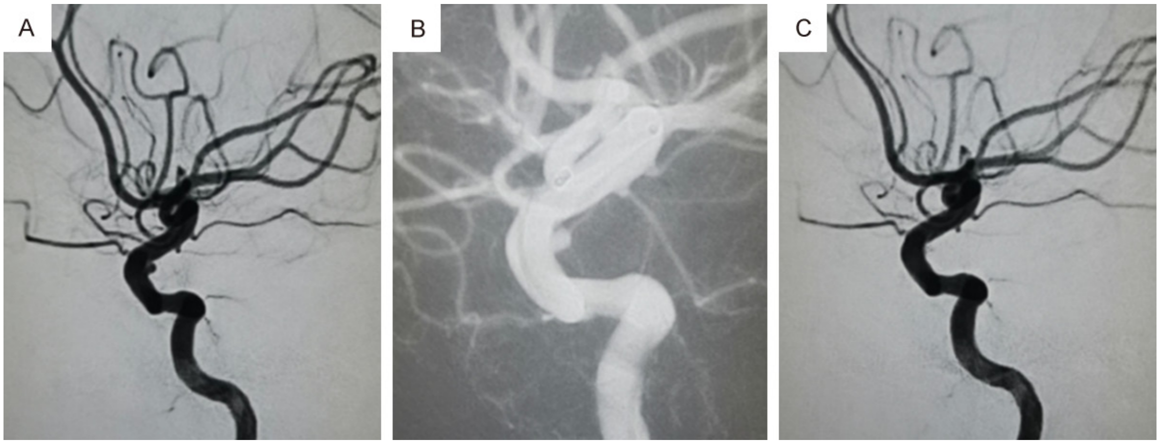

Figure 3. Female, 57 years old, tiny aneurysm (1.8×1.5×1.6 mm) in the clinoid segment of right internal carotid artery, Lvis stent (3.5×15 mm) used (A: before embolization; B: during embolization; C: after embolization).

Figure 4. Female, 41 years old, tiny aneurysm (1.3×1.5×1.8 mm) in the right posterior communicating artery, Lvis stent (3.5×15 mm) used (A: before embolization; B: during embolization; C: after embolization).

ification (RROC). Grade I, complete embolization, is defined as the aneurysm neck and aneurysm body are not filled with contrast medium; grade II, sub-complete embolization, is defined as the contrast medium fills up the aneurysm neck but not the aneurysm body; grade III, incomplete embolization, is defined as the aneurysm body is clearly filled with contrast medium. Follow-up was performed through phone calls and return visits. All patients were evaluated by the Modified Rankin Scale (MRS) scores for prognosis at 12 months after discharge. MRS scores: 0: no symptoms; 1: no significant disability; 2: slight disability; 3: moderate disability; 4: moderately severe disability; 5: severe disability; 6: dead. These patients were divided into a good prognosis group and a poor prognosis group.

Factor evaluation

The clinical efficacy was evaluated by embolization degree and perioperative complications such as cerebral vasospasm, acute thrombosis during embolization, intraoperative aneurysm rerupture, postoperative cerebral infarction, hydrocephalus, aneurysm rerupture and pulmonary infection. MRS was used to evaluate the prognosis. The MRS scores of 0-2 were defined as good prognosis and 3-6 were defined as poor prognosis. Gender (male and female), age (<50 years old and 50-73 years old), hypertension (no and yes), diabetes (no and yes), smoking (no and yes), HHG (grade I, grade II, grade III and grade IV), MFS (grade 1, grade 2, grade 3 and grade 4), time from admission to embolization (≤24 h and >24 h), aneurysm location (anterior circulation and posterior circulation), embolization method (coiling alone and stent-assisted coiling), embolization degree (complete, sub-complete and incomplete) and perioperative complications (no and yes) were the factors affecting the prognosis of patients. The HHG and MFS were obtained by the patients' condition and first CT scan on admission.

Statistical analysis

Statistical analysis was performed with SPSS 24.0. Measurement data were expressed as mean ± standard deviation (mean ± SD) and analyzed by paired t test. Counting data were subject to Chi-squared test and analyzed by Fisher's exact probability test if conditions were not satisfied. For factors with statistically significant differences in univariate analyses, multivariate logistic regression analysis was performed. For all statistical comparisons, significance was defined as $P<0.05$.

Results

Treatment effect

All 46 patients underwent endovascular embolization successfully by coiling alone and stent-assisted coiling. The success rate of embolization was 100%. Seventeen patients with aneurysms were embolized by coiling alone and 29 patients by stent-assisted coiling embolization. Assessed by the postoperative RROC, there were 37 patients with grade I, 4 patients with grade II and 5 patients with grade III. The rate of complete embolization was 80.4%. Perioperative complications occurred in 12 patients, with a complication rate of 26.1%. In the process of embolization, 4 patients had cerebral vasospasms and local stenosis was significantly improved after transcatheter injection of Nimodipine. Three patients had acute thrombosis, of which 2 cases occurred after stent placement; another case occurred after coils were detached and part of the coils flew out of the aneurysm neck. Then stent was immediately placed to isolate coils from the parent artery. All 3 patients with acute thrombosis were injected with Tirofiban through catheter and thrombus dissolved significantly. Of the 7 patients with cerebral vasospasm and acute thrombosis, 2 had symptom of limb weakness after embolization. They were diagnosed with acute cerebral infarction confirmed by Magnetic Resonance Imaging + Diffusion Weighted Imaging (MRI + DWI), and antiplatelet therapy was applied. Intraoperative aneurysm re-rupture occurred in 3 patients and continued coil packing in the aneurysm was performed to stop bleeding; among them, 2 patients exhibited good clinical outcome. All patients had lumbar puncture for replacement of cerebrospinal fluid to prevent hydrocephalus. However, 1 patient developed serious hydrocephalus and underwent ventriculo-peritonal shunt (VPS). One patient had severe pulmonary infection and died of respiratory failure even after antibiotic therapy.

Conditions of prognosis

The MRS scale was used to evaluate the neurological status of enrolled patients at admission and after treatment. The MRS scale was modified on the basis of the RANKIN scale, which was divided into 6 grades of 0-5 points, among which 0 points represented a complete absence of symptoms and 5 points represented severe disability. A higher score indicated worse neurological status of the subjects. The patients were evaluated at admission and after treatment, and the proportions of each grade were calculated and the curve was analyzed. The results showed that the proportions of 0 and 1 scores after treatment were significantly increased compared with those at admission, and the difference was significant ($P<0.05$) (**Figure 5**).

Follow-up results

All patients received follow-up for 12 months. Thirty-five patients with the MRS scores of 0-2 achieved a good prognosis while 11 patients with the MRS scores of 3-6 achieved a poor prognosis.

Univariate analysis

Through univariate analysis, the prognosis of patients showed no significant difference in gender, age, hypertension, diabetes, smoking, time from admission to embolization, aneurysm location, and embolization method ($P>0.05$), but exhibited a significant difference in HHG, MFS, embolization degree and perioperative complications ($P<0.05$) (**Table 1**).

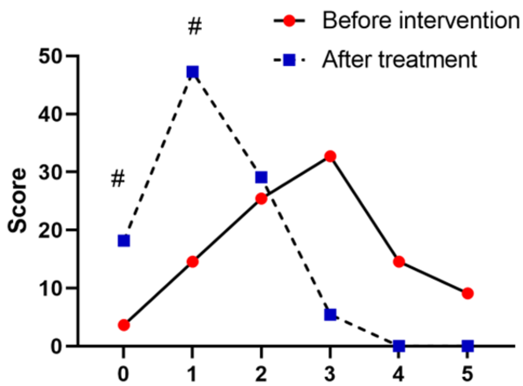

Figure 5. Changes of MRS score before and after intervention. After treatment, the proportions of 0 and 1 score in MRS scale were significantly increased compared with those at admission ($P<0.05$). # indicated statistically significantly different for the same index before and after intervention.

Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed with the prognosis of patients as the dependent variable, and HHG, MFS, embolization degree and perioperative complications as the independent variables. The results showed that HHG, MFS and perioperative complications were the independent risk factors significantly correlated to poor prognosis ($P<0.05$) (**Table 2**).

Discussion

At present, the treatment methods of endovascular embolization or surgical clipping still remain controversial [14], and both methods are more difficult to perform for tiny aneurysms than larger aneurysms. In this study, all patients were treated by endovascular embolization successfully, with the endovascular embolization rate of 100%, complete embolization rate of 80.4% and perioperative complication rate of 26.1%. Our study proved that embolization was effective to treat ruptured tiny intracranial aneurysms.

To improve the clinical efficacy of embolization, the required technical skills of embolization and risk of intraoperative re-rupture should be specially valued. Before embolization, the microcatheter should be shaped appropriately according to the shape of aneurysm and parent artery. The micro-guidewire leads the microcatheter to approach aneurysm, and the micro-guidewire should not be super selective into aneurysm body. SAH may occur because the tip of micro-guidewire may pierce aneurysm. The microcatheter tip should be placed in the aneurysm neck instead of placing it in the aneurysm body. Furthermore, 3D-DSA and 3D-DSA reconstruction are widely used to comprehensively evaluate the size and shape of tiny aneurysms. Rational selection of the coils is crucial to embolize aneurysms and small, short, flexible ones are preferred. If necessary, stent-assisted embolization is required to stabilize the coils in an aneurysm. Low-profile visualized intraluminal supported device (Lvis) is a self-expanding braided stent with the advantages of high visibility, metal coverage and dense mesh. With the metal coverage rate of 23%, the Lvis stent provides great protection across the aneurysm neck and improves flow diversion [15, 16]. The Lvis stent was applied in 29 patients in this study and all stents were successfully released in the proper part of parent artery.

The most serious perioperative complications were intraoperative aneurysm re-rupture and cerebral infarction. Research [5] has shown that endovascular embolization of tiny ruptured aneurysms is more likely to result in re-rupture compared with larger aneurysms. In our study, intraoperative aneurysm rupture in 3 patients was caused by coil puncture. Timely and effective coil packing was performed to stop bleeding. If intraoperative rupture is caused by micro-guidewire puncture, quick coil packing is vitally important. When coil packing in aneurysm failed, embolization should be stopped and measures such as reversal of heparin, compression on carotid artery and lowering blood pressure should be taken immediately until the bleeding stops. Intraoperative re-rupture caused by a micro-guidewire may not be life-threatening and patients' conditions should be closely monitored postoperatively. If a microcatheter puncture caused intraoperative re-rupture, the solutions are the same as above. Aneurysm clipping and decompressive craniectomy may be needed if necessary. About 70% of patients are found with angiographic vasospasm after SAH, leading to delayed cerebral ischemia (DCI) and even cerebral infarction [17]. The clinically detected incidence of DCI is about 30% [18]. To relieve cerebral vasospasms, Nimodipine is usually used in clinical practice and can decrease the rates of symptomatic or asymptom-

Table 1. Univariate analysis for the prognosis of patients with ruptured tiny intracranial aneurysms

Factor		n	Good prognosis (n)	Poor prognosis (n)	*P*
Gender	Male	21	18	3	0.158
	Female	25	17	8	
Age	<50	27	22	5	0.317
	50-73	19	13	6	
Hypertension	No	15	12	3	0.674
	Yes	31	23	8	
Diabetes	No	36	29	7	0.266
	Yes	10	6	4	
Smoking	No	32	27	5	0.089
	Yes	14	8	6	
HHG	I	11	10	1	0.041
	II	23	20	3	
	III	7	4	3	
	IV	5	1	4	
Modified Fisher grade	1	4	3	1	0.011
	2	11	9	2	
	3	24	21	3	
	4	7	2	5	
Time from admission to embolization	≤24 h	35	21	7	0.834
	>24 h	11	14	4	
Aneurysm location	Anterior circulation	40	31	9	0.572
	Posterior circulation	6	4	2	
Embolization method	Coiling alone	17	13	4	0.964
	Stent-assisted coiling	29	22	7	
Embolization degree	Complete	37	31	6	0.020
	Sub-complete	4	1	3	
	Incomplete	5	3	2	
Perioperative complications	No	34	31	3	0.002
	Yes	12	4	8	

Table 2. Multivariate logistic regression analysis

Risk factor	95% CI	*OR*	*P*
HHG	1.207-468.845	23.786	0.037
MFS	0.006-0.899	0.072	0.041
Embolization degree	0.003-1.134	0.054	0.060
Perioperative complications	1.747-43289.554	275.008	0.030

atic vasospasms and delayed cerebral ischemia [19, 20]. It is the only FDA-approved medication with neuroprotective effects and is able to improve outcomes after SAH [21]. Moreover, acute in-stent thrombosis or coil-induced thrombosis could cause disastrous consequences as well. For patients who need stent-assisted embolization, they should take antiplatelet drugs preoperatively. In our experience, 4 hours before embolization, patients orally took 300 mg of aspirin and 300 mg of clopidogrel. Even so, intraoperative acute thrombosis and postoperative acute cerebral infarction may still occur. In this study, there were 4 patients with vasospasms, 3 patients with acute thrombosis and 2 patients with eventual acute cerebral infarction. SAH, vasospasm, acute thrombosis and acute cerebral infarction affect patients' clinical outcomes so as to worsen the prognosis [22, 23]. As a result, clinicians should pay close attention to the postoperative situation of patients.

To evaluate ruptured tiny aneurysms embolization for the clinical prognosis of patients, relevant factors were included. This study found that gender and age was not correlated to the prognosis of patients. Howeve, relevant literature [24, 25] demonstrates that more females suffer from intracranial aneurysm than males and gender could be or could not be correlated to patients' prognosis. Hypertension is not the risk factor for a poor prognosis in this study. It is well known that hypertension could lead to the occurrence, development and even rupture of intracranial tiny aneurysm, but whether hypertension affects the prognosis of patients or not still not known [24, 26, 27] and it may need further research. Literature [28, 29] has indicated that diabetes and smoking affect the prognosis of patients after aneurysmal subarachnoid hemorrhage, which is inconsistent with the results of our study. HHG is an effective assessment method for clinical evaluation of perioperative condition and prognosis of patients with aneurysmal SAH. In this study, 3 of 7 patients with grade III and 4 of 5 patients with grade IV had poor prognosis. This indicated that patients with higher HHG had worse prognosis. Furthermore, this factor was identified as an independent risk factor affecting the prognosis of patients with tiny ruptured aneurysm after embolization. Our result was consistent with some other scholars' study [13, 24, 29]. MFS can be used to predict cerebral vasospasm and provide reference for making treatment strategies. Five of 7 patients with grade 4 had poor prognosis in our results, which proved MFS to be significantly correlated to the prognosis of patients. The higher the FMS was, the worse the prognosis of patients. Studies [13, 30] have demonstrated that the clinical prognosis of patients receiving embolization aneurysm in the early stage is significantly better than those in the later stage. According to the findings in this study, the prognosis for treating ruptured tiny aneurysms was not related to the timing of embolization which were ≤24 h and >24 h. However, if condition permits, the embolization should be performed as early as possible to reduce the risk of aneurysm rerupture. Most of aneurysms are located in the anterior circulation [31], but the risk of treating posterior circulation aneurysms are higher than that of anterior circulation aneurysms due to the former being adjacent to the brain stem. Patients with ruptured posterior circulation aneurysms had poorer prognosis compared with those with anterior circulation aneurysms [13]. However, this study showed that there was no correlation between aneurysm location and prognosis. There is little literature on the relationship between embolization method, embolization degree and the prognosis of patients. This study suggested that embolization method and embolization degree were not risk factors for poor prognosis, but incomplete embolization may lead to postoperative aneurysm re-rupture and stent-assisted coiling embolization may cause in-stent thrombosis. It is known that perioperative complications would affect patients' medical condition and directly or indirectly worsen their prognosis. In our study, there were 12 patients with perioperative complications and 8 of them had poor prognosis. The results showed that perioperative complications were a risk factor for the poor prognosis of patients.

In conclusion, endovascular embolization has demonstrated good clinical efficacy in the treatment of ruptured intracranial tiny aneurysm. In the postoperative period, measures can be adopted to prevent and reduce complications, so as to improve the clinical efficacy of embolization. However, due to the limited number of samples in this study, some factors affecting prognosis may not be included and analyzed. The prospective control study is also necessary. In the future, multicenter prospective control studies based on more samples are preferred to improve the clinical treatment efficacy and prognosis of ruptured intracranial tiny aneurysms.

Disclosure of conflict of interest

None.

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