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Treatment of the acute thromboembolic event during endovascular embolization of intracranial aneurysm

Bing Zhou [a,*], Yang He [a], Jun Cheng [c], XiaoDong Lu [b], MingZhao Zhang [a], Bo Li [a], RongQing Qin [a], ZhongMing Gao [b]

[a] Department of Interventional Neuroradiology, Hangzhou Normal University Hospital, Hangzhou City, Zhejiang Province, China
[b] Department of Neurology, Hangzhou Normal University Hospital, Hangzhou City, Zhejiang Province, China
[c] Department of Neurosurgery, Hangzhou Normal University Hospital, Hangzhou City, Zhejiang Province, China

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ABSTRACT

Objective: The study aimed to discuss the treatment of acute thromboembolic event (TE) during endovascular embolization of intracranial aneurysms.
Methods: Between April 2013 and April 2019, 158 patients with 167 intracranial aneurysms were treated with endovascular embolization in our hospital, in which 9 cases of acute TEs occurred during the embolization procedures. The clinical data, radiological findings and treatments of the 9 patients were reviewed and analyzed.
Results: The TEs occurred at the aneurysmal neck in 3 patients, at distal part of the parent artery in 3, in the stent in 2, and at the proximal part of the parent artery in 1. Intra-arterial (IA) infusion of tirofiban were performed in 6 patients, mechanical thromboectomy (MT) with a stent in 2 patients, and combined use of the two methods in 1 patients. According to the modified Thrombolysis In Cerebral Infarction (mTICI) score, 7 patients had recanalization of 2b/3a, 1 patients had recanalization of 1, and 1 patients had recanalization of 0. At discharge, the mRS score was 0 in 3 patients, 1 in 3 patients, and 2, 3, 4 in 1 patient each. 6 months after the endovascular treatment, the mRS score was 0 in 5 patients, 1 in 2 patients, and 3 in 1 patient.
Conclusions: IA tirofiban and MT are effective remedies for the acute TE during endovascular embolization of intracranial aneurysm, reasonable selection of which may improve the prognosis of patients.

Intracranial aneurysm is a disease caused by the local weakness of the arterial wall. Ruptured aneurysm can cause subarachnoid hemorrhage, cerebral vasospasm, cerebral infarction, and even cerebral hernia, which lead to High mortality and disability. Until now, endovascular embolization has been the first choice for the treatment of intracranial aneurysms due to its minimal invasion, rapid recovery, and low complication.[1–3] In the endovascular procedure, thromboembolic event (TE) is the most common intraoperative adverse event, with an incidence of 2 – 18%.[4] Recanalization of the occluded artery is the most important factor to affect the patient's prognosis. This study intends to explore the remedies of TEs in the aneurysmal endovascular procedure.

1. Materials and methods

1.1. Patients

Between April 2013 and April 2019, 158 consecutive patients with 167 aneurysms were performed with endovascular embolization at our institution. Of these patients, intraoperative acute TE occurred in 9 patients, including 8 patients with ruptured aneurysm and 1 with unruptured aneurysm. Among these patients, there were 3 males and 6 females, aged 27–61 years old. The baseline data of the 9 patients were summarized in Table 1. *The ethics committee of the hospital approved the study, and classified this study as a quality control study and waived the need for obtaining patient informed consent. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki.*

* Corresponding author. Department of Interventional Neuroradiology, Hangzhou Normal University Hospital, No. 126, Wenzhou Road, 310015, Hangzhou City, Zhejiang Province, China.
E-mail address: zbing8888@163.com (B. Zhou).

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Table 1
The baseline data of the patients and their aneurysms.

No	Sex/age	Hunt-hess grade	Fisher score	Characteristics of the aneurysms		
				Location	Size	Shape
1	F/52	3	3	ACOMA	2 mm*3 mm	Saccular/ narrow-necked
2	F/65	2	2	C6 segment of right ICA	3 mm*2.5 mm	Saccular/ wide-necked
3	M/56	3	4	Top of BA	11 mm*8 mm	Saccular/ wide-necked
4	F/45	2	2	C7 segment of right ICA	5.5 mm*4 mm	Irregular/ narrow-necked
5	M/37	2	3	Top of BA	3.5 mm*2.5 mm	Saccular/ wide-necked
6	F/49	1	1	ACOMA	3.2 mm*4.5 mm	Saccular/ narrow-necked
7	F/62	0	0	ACOMA	3.5 mm*5 mm	Irregular/ narrow-necked
8	M/57	2	2	C7 segment of left ICA	4 mm*6 mm	Irregular/ wide-necked/ multiple
9	F/41	1	2	Bifurcation of MCA	2.5 mm*3.5 mm	Irregular/ wide-necked

ACOMA: anterior communicating artery; ICA: internal carotid artery; BA: basic artery; MCA: middle cerebral artery.

1.2. Endovascular treatment

All of the 9 patients underwent the CT angiography after admission, and were diagnosed as intracranial aneurysm. According to the treatment process of the institution, the treatment of ruptured aneurysms was completed within 24 hours as an emergency operation, and un-ruptured aneurysms was completed within 3 days as an selective operation.

Before operation, the neurosurgeons and the neurointerventionalists discussed the treatment plan and reached an agreement on transcranial clipping or embolization. Endovascular treatment was performed in the patients after the signed informed consent forms were obtained from the patient and their families. Under general anesthesia, all procedures were performed with the transfemoral arterial approach. Cerebral angiographies were performed to further definite the size, shape and neck of aneurysms, and to find the best working projection. After angiography, a guiding catheter was advanced to the parent artery followed by systemic heparinization with 3000–5000 units heparin. At the working projection, a micro-catheter was guided by a micro-wire into the aneurysm under the roadmap guidance. According to the size, shape and neck of aneurysms, simple, stent-assisted or balloon-assisted coiling technique was used to embolized the aneurysms. Before the stent implantation, tirofiban was administered intravenously with at a dose of 5 μg/kg. A CT examination of the head was performed immediately after the embolization procedure to determine whether there was intraoperative bleeding.

Regarding the 9 patients with intraoperative TEs, the aneurysms were located at the anterior communicating artery (AComA) in 3 patients, internal carotid artery (ICA) in 3, tip of basilar artery (BA) in 2, and the bifurcation of middle cerebral artery (MCA) in 1. Four aneurysms were embolized with simple coiling and 5 with stent-assisted coiling. Three cases of TEs occurred before aneurysm coiling and 6 occurred during aneurysm coiling. Three cases of thrombus occurred in the distal parent artery of the aneurysms, 3 near the neck of the aneurysms, 2 in the assisted stent, and 1 in the proximal parent artery of the aneurysms. The thrombus was treated by MT in 2 patients, IA tirofiban in 6 patients, and MT combined with IA tirofiban in 1 patients.

According to the time of the TEs occurrence, we choosed the different remedies. If the TE occurred before coiling of the aneurysm or stent implantation, we use MT as the first choice; if the TE occurred during or after coiling of the aneurysm or stent implantation, we use IA tirofiban as the fist choice. Therefore, 3 patients were treated with MT as the first choice and 6 patients with IA tirofiban as the first choice, including 1 patient treated with MT combined with IA tirofiban. A standard procedure of MT was performed with a thrombus removal stent (Solitaire FR, ev3/Covidien, Irvine, CA, USA) in the 3 patients. The microcatheter was inserted into the distal vessel of the thrombus, then the stent was released to cover the thrombus, waiting for 5–10 min to fully integrate the thrombus and stent, and then pull out the stent. In the process of pulling thrombi, the stent passed through the aneurysm as slowly as possible to avoid the aneurysm ruptured. The other 6 patients with TE during aneurysm coiling were treated with IA tirofiban. After the aneurysm was totally embolized, the microcatheter was pulled out to the proximal vessel of the thrombus, and tirofiban was infused through the microcatheter at a dose of 5 μg/kg for 5 min. The infusion was discontinued when the thrombus disappeared or the blood flow significantly improved; otherwise additional tirofiban infusion of the same dosage was continued, with no more than 25 μg/kg of total dose. After IA tirofiban, intravenous administration of tirofiban at a rate of 0.1 μg/kg/min for 24 h, followed by bridging dual antiplatelet treatment 4 hours before discontinuation of tirofiban. The anticoagulant therapy was not used after operation.

After the institutional review board approval, the clinical data were acquired from the Medical Record Department and the imaging data was collected from the Picture Archiving and Communication Systems (PACS). The main observation endpoints of the study included the recanalization rate, the patients' mRS scores at discharge and 6 months after the operation, and the secondary observation endpoints were the complications related to the MT or IA tirofiban, the incidence of cerebral infarction related to TEs, and the results of aneurysm filling. Because of the small sample size of this study, the data was analyzed mainly via descriptive statistics.

2. Results

The data of cerebral angiography, interventional therapy and post-operative follow-up were summarized in Table 2.

Of the 9 patients with thromboembolic event, MT was used to recanalize the occluded artery in 2 patients, MT combined with IA tirofiban in 1, and IA tirofiban in 6. According to the modified Thrombolysis In Cerebral Infarction (mTICI) scale, 7 patients got a 2b/3 scale of recanalization, 1 got a 1 scale of recanalization, and 1 got a 0 scale of recanalization.

In this study, the mRS score was used to assess neurological recovery after stroke. At discharge, the mRS score was 0 in 3 patients, 1 in 2 patients, 2 in 2 patients, and 3, 4 in 1 patient each. 6 months after the endovascular treatment, the mRS score was 0 in 5 patients, 1 in 2 patients, 2 in 1 patients, and 3 in 1 patient.

As to the complications of the recanalization treatments, distal migration of the thrombus and occlusion of the distal artery occurred in 1 case treated with arterial infusion of tirofiban, the involved arterial spasm occurred in 2 cases with mechanical thrombectomy including a severe spasm of the basilar artery in 1 (Fig. 1), and no aneurysmal re-rupture occurred in patients treated with tirofiban. There were no irreversible vascular occlusion complications such as intimal dissection. 5 cases of cerebral infarction was discovered in the postoperative imaging examinations, which including 4 cases of symptomatic (Fig. 2) and 1 of asymptomatic cerebral infarction. The 4 cases of symptomatic cerebral infarction included aphasia in 1 patient, dysarthria in 1, and decreased muscle strength in 2 patients. At 6-months follow-up, the patients with decreased muscle strength and dysarthria were recovered well, but the patients with aphasia was not obvious improved.

Table 2
The results of MT, coiling of aneurysms and follow-up.

No	Embolic site	remedies	TICI score	Cerebral infarction in imaging	Coling		New neurological deficit	mRS of follow-up	
					Method	RS		At discharge	6 months
1	distal parent artery	MT	2b	yes	Simple coiling	3	motor aphasia	2	1
2	Aneurysmal neck	Arterial infusion of tirofiban	2b	no	Simple coiling	3	No	0	0
3	In-stent	Arterial infusion of tirofiban	3	yes	Stent + coiling	3	Dysarthria	1	0
4	distal parent artery	MT + Arterial infusion of tirofiban	3	no	Simple coiling	3	No	1	0
5	proximal parent artery	MT	3	no	Stent + coilin	3	No	0	0
6	Aneurysmal neck	Arterial infusion of tirofiban	1	yes	Simple coiling	3	muscle weakness	3	2
7	In -stent	Arterial infusion of tirofiban	3	no	Stent + coiling	3	no	0	0
8	Aneurysmal neck	Arterial infusion of tirofiban	2b	yes	Stent + coilin	3	no	2	1
9	distal parent artery	Arterial infusion of tirofiban	0	yes	Stent + coilin	3	muscle weakness	4	3

TICI: thrombolysis in cerebral infarction; MT: mechanical thrombectomy; RS: Raymond scale; mRS: modified Rankin Scale.

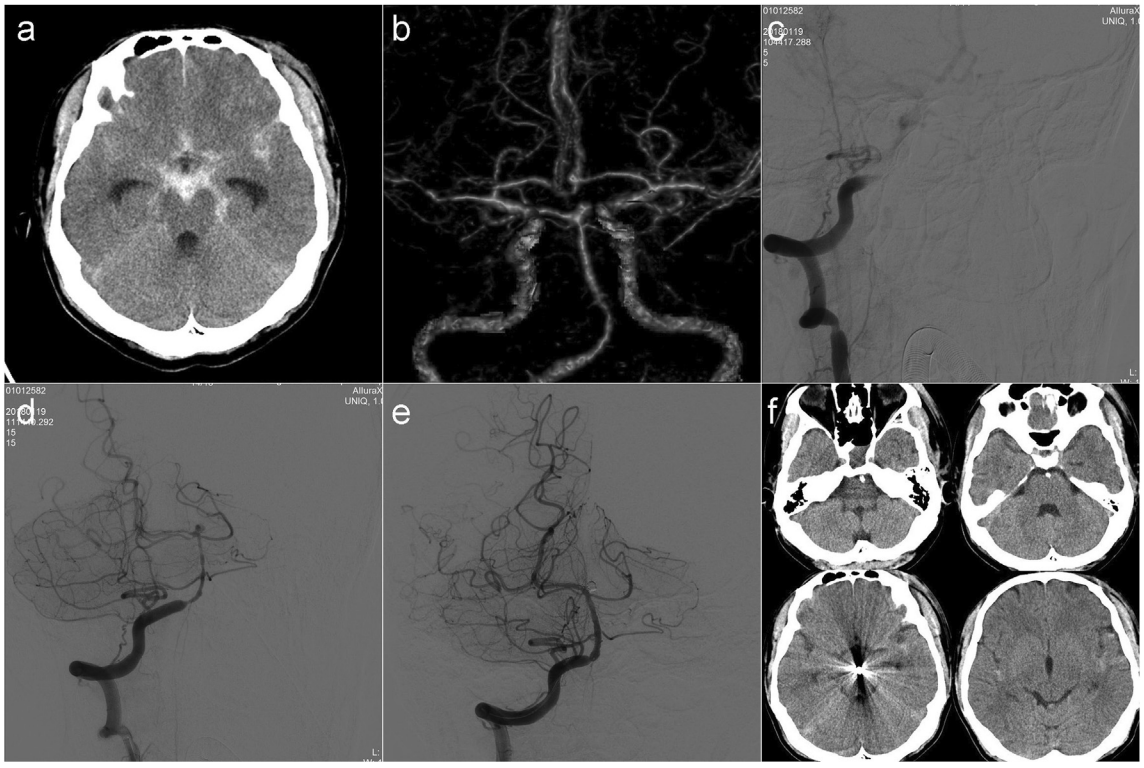

Fig. 1. Images of Case 5. **a and b:** The emergency head CT showed subarachnoid hemorrhage with a Fisher score of 3, and the CT angiography found an aneurysm on the top of BA about 3.5 mm*2.5 mm in size. **c:** The V4 segment of the left vertebral artery and the BA were not visualized anymore after the guiding catheter was placed. **d:** Despite the success of revascularization, severe vasospasm was seen in the BA after MT. **e:** The aneurysm was successfully treated with stent-assisted coiling and the vasospasm of the BA improved significantly. **f:** No obvious cerebral infarction was found in the head CT 5 days after the endovascular treatment.

The aneurysmal embolization was successfully performed in the 9 patients, with 4 simple coilings and 5 stent-assisted coilings. According to the 3-point Raymond scale (RS),[5] all the aneurysms obtained a complete obliteration (Table 2).

3. Discussion

In recent 30 years, with the continuous development of interventional devices and interventional technology, endovascular embolization has gradually become the preferred treatment for intracranial aneurysms due to its small trauma, low recurrence rate, and rapid recovery.[1–3] In the guidelines for treatment of aneurysmal subarachnoid hemorrhage, it is pointed out that for patients who are suitable for endovascular treatment and craniotomy, endovascular treatment is preferred.[1] In recent years, the TE has gradually replaced the intra-operative aneurysm rupture as the most common complication that disturbs neuro-interventionists, with the incidence rate about 2% – 18%.[4] The incidence of TEs assessed via postoperative MR was higher, and the incidence of cerebral infarction

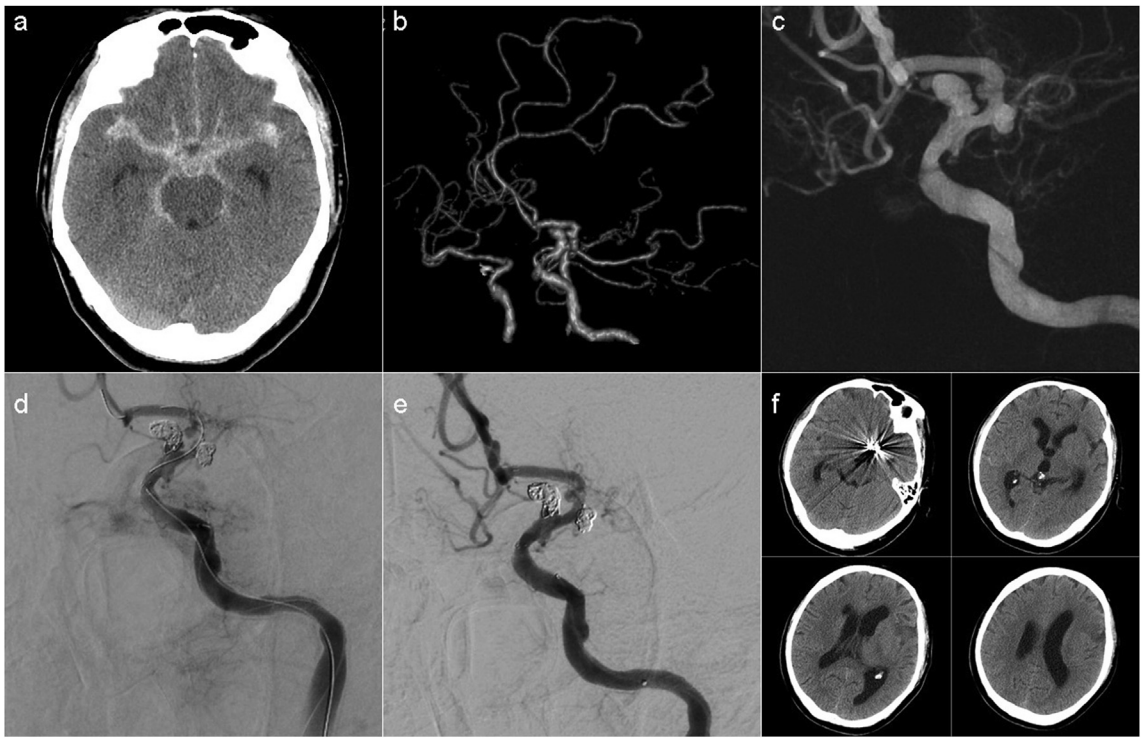

Fig. 2. Images of case 8. **a:** The emergency head CT showed subarachnoid hemorrhage with a Fisher score of 4. **b** and **c:** Preoperative CTA and DSA showed multiple aneurysms in the C7 segment of the left internal carotid artery, and the largest aneurysm was about 4*6 mm. **d:** During the stent-assisted coiling process, the in-stent thrombosis ocurred and the distant vessels of were not well developed. **e:** After IA 300ug tirofiban in 20 min, the thrombus was dissolved and the left ICA was recanalized with a mTICI scale of 3. **f:** Local cerebral infarction was found in the left insular lobe on the postoperative head CT scan.

can be found in as high as 49%–51% patients via postoperative MR examination, although the TEC displayed in MR imaging was mostly asymptomatic.[6]

Mclaughlin N[7] et al. summarized the reasons of the TEs during the endovascular treatment of intracranial aneurysm into the following aspects: insufficient antiplatelet before operation, insufficient systemic heparinization during operation, and violent surgical operation resulting in vascular endometrial damage; insufficient adherence after stent placement; the coils protrude into the parent artery; intraoperative catheterization caused plaque detachment resulting in vascular occlusion; thromboses in the catheter because of insufficient flowing water; and the prolonged operation time.

In this study, we analyzed the causes of the TEs in the 9 patients. According to the formation time, location and shapes of the thromboses and the shapes of the coils and stents, the causes of the TEs were different. Plaque shedding of vascular wall caused by catheter operation was considered in 3 patients because the TEs happened before the coils and the stents were used. Local thrombosis induced by coil or stent was considered in 4 patients, because the thrombus were near the neck of the aneurysm or in the stent. Local thrombosis induced by excessive coiling of the aneurysms in 2 patients, which can be identified in the post-coiling angiography.

At present, many studies have reported the treatment of thromboembolic events in the treatment of aneurysms, but these treatments were mainly based on personal experience, and no consensus has been reached.[8–13] From our view, it is very important to correctly judge the cause of thrombosis. According to the process of an aneurysmal endovascular treatment, TE may happen in the stage of pre-coiling, intra--coiling or post-coiling of the aneurysm. When the TE happens in the stage pre-coiling of the aneurysm, the thrombus is believed to be from the atherosclerotic plaque on the vessel wall, which is shed by the careless manipulation of the catheter or the wire; or from the catheter, which is not fully flushed by the perfusion system. When the TE happens in the stage intra-coiling or post-coiling of the aneurysm, There may be three main causes. The artery is occluded by the thrombus induced by the coil, stent or other assistant devices; the artery is occluded by over packing of the coils or the incomplete stent deployment; or the displacement of thrombi in aneurysms leads to distal arterial embolism. Choosing the right treatment according to the cause of thrombosis may be the most important factor to improve the prognosis.

For the TEs before aneurysm coiling or the thrombus suspected to be from atherosclerotic plaque, mechanical thrombectomy may be the priority because the anticoagulant or thrombolytic drugs are not only ineffective but also easy to induce aneurysm re-rupture. In this group, 3 cases of TEs happened before aneurysm coiling or stent planting, and were recanalized by mechanical thrombectomy without severe complications. The removed thrombus were also identified as old thrombus or plaque. Four cases of TEs diagnosed as local thrombosis were treated with arterial infusion of tirofiban, which showed good efficacy and acceptable safety. There were 2 cases of TEs induced by over packing of the aneurysm, which could lead to local vascular stenosis and blood flow turbulence. In this condition, arterial infusion of tirofiban alone may not achieve satisfactory results because the coil protrusion may block the antegrade flow of the parent artery, which is a key factor in the thrombolytic effect of IA tirofiban. In the 2 patients with over-packed aneurysm, the blocked arteries were not recanalized well after sufficient arterial infusion of tirofiban, with 1 recanalization of mTICI 1 and 1 of mTICI 0.

Tirofiban hydrochloride monohydrate is a kind of reversible antagonist of fibrinogen, which works by antagonizing the glycoprotein IIb/IIIa receptor of platelets.[14] the plasma half-life of tirofiban is two hours and platelet function is almost normalized within four hours after discontinuation. With IA tirofiban infusion, only a couple of hours are needed prior to the surgical procedures.[15] Therefore, for patients who need ventricular drainage, decompressive craniectomy and lumbar cisterna puncture after aneurysm embolization, the effect of tirofiban is

less.[16,17] In our series, there were 4 cases were performed with lumbar cisterna puncture and 1 with ventricular drainage, and no obvious bleeding was found in this patients.

In conclusion, TEs are common complications in the procedure of aneurysm embolization, the pathogeneses of which are different. Improper treatment of the TEs can cause severe neurological dysfunction in patients. Therefore, it is important to identify the pathogenesis of the thrombotic events and take proper treatment strategy, which may lead to be safer and more effective to restore the blood flow and reduce the adverse consequences.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of the manuscript entitled.

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