

Intraarterial Tirofiban Thrombolysis for Thromboembolisms During Coil Embolization for Ruptured Intracranial Aneurysms

Jin Sue Jeon, MD, Seung Hun Sheen, MD, Gyojun Hwang, MD, Suk Hyung Kang, MD,
Dong Hwa Heo, MD, Yong Jun Cho, MD

Department of Neurosurgery, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea

ABSTRACT

Objective: Thromboembolus can occur during endovascular coil embolization. The aim of our study was to show our experience of intraarterial (IA) tirofiban infusion for thromboembolism during coil embolization for ruptured intracranial aneurysms. **Methods:** This retrospective analysis was conducted in 64 patients with ruptured aneurysms who had emergent endovascular coil embolization from May 2007 to April 2011 at a single institute. Thromboembolic events were found in ten patients (15.6%). Anticoagulation treatment with intravenous heparin was started after the first coil deployment in ruptured aneurysmal sac. When a thrombus or embolus was found during the procedure, we tried to resolve them without delay with an initial dosage of 0.3 mg of tirofiban up to 1.2 mg. **Results:** Three patients of four with total occlusion had recanalizations of thrombolysis in myocardial infarction (TIMI) grade III and five of six with partial occlusion had TIMI grade III recanalizations. Eight patients showed good recovery, with modified Rankin Scale (mRS) score of 0 and one showed poor outcome (mRS 3 and 6). There was no hemorrhagic or hematologic complication. **Conclusion:** IA tirofiban can be feasible when thromboembolic clots are found during coil embolization in order to get prompt recanalization, even in patients with subarachnoid hemorrhage.

(*J Cerebrovasc Endovasc Neurosurg*. 2012 Mar;14(1):5-10)

KEY WORDS

Aneurysm coiling · Thromboembolism · Tirofiban · Intracranial aneurysm

INTRODUCTION

Thrombus can occur during endovascular coil embolization in ruptured aneurysms and it can lead to permanent ischemic injury to the brain if it is not combined with proper treatment. Several studies have been per-

formed in order to find method to treat thromboembolus.²⁾⁴⁾⁵⁾⁸⁾⁹⁾¹²⁻¹⁵⁾ With no consensus on optimal thrombolytic drug yet, tirofiban or abciximab have been major treatment for resolving thrombus. The aim of study was to show our experience of intraarterial (IA) tirofiban for thromboembolism during emergent coil embolization in patients with ruptured intracranial aneurysms.

PATIENTS AND METHODS

Patients

This study was performed in patients who underwent endovascular coil embolization for ruptured aneurysm from May 2007 to April 2011 at a single center. A total

Received : 1 December 2011

Revised : 23 December 2011

Accepted : 5 January 2012

Corresponding Author : Seung Hun Sheen, MD

Address : Department of Neurosurgery, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Kyo-Dong, Chuncheon, 200-704, Korea

Tel : (001) 82-33-240-5171 FAX : (001) 82-33-242-9970

E-mail : neurosheen@gmail.com

Table 1. Summary of demographical and clinical information of enrolled patients

No	Sex/Age	H&H	Location	Size(mm)	Type	Procedure	Site	Occlusion
1	F / 43	III	A-com	3,5 × 3,5	Double	packing	A2 (p)	partial
2	M / 51	II	Lt, MCABF	4,7 × 4,7	Double	packing	M2 (p)	total
3	M / 48	II	A-com	3,4 × 2,7	Simple	post EMB	M2 (r)	total
4	F / 46	III	Lt, A1	4 × 3,5	Balloon	selection	M2 (r)	total
5	M / 57	III	A-com	6,3 × 7	Balloon	post EMB	Pericallosal (d)	partial
6	M / 41	IV	A-com	3,8 × 3,2	Simple	selection	A2 (p)	total
7	F / 65	III	A-com	6 × 4,5	Simple	post EMB	A2 (p)	partial
8	M / 48	III	A-com	7 × 5	Simple	packing	Pericallosal (d)	partial
9	M / 48	II	Lt, P-com	3,5 × 2,6	Balloon	balloon	M2 (r)	partial
10	M / 55	II	BA top	9,3 × 9,2	Stent	selection	A1 (p)	partial

*Size indicates the measured aneurismal sac with length × width, H & H = Hunt and Hess grade; F = female; M = Male; A-com = Anterior Communicating Artery; Lt, = Left; MCABF = Middle Cerebral Artery bifurcation; P-com = Posterior Communicating Artery; BA = Basilar Artery; Double = double microcatheter method; Simple = a single microcatheter method; Balloon = balloon assisted coil packing; Stent = stent assisted coil packing; post EMB = the state of post coil embolization; packing = the state of coil packing; selection = the selection procedure of aneurysmal sac; p = proximal thrombus; r = remote thrombus; d = distal thrombus

of 64 patients were included in this study. Thromboembolic events were found in ten patients (15.6%). Any procedures with an elective schedule for the treatment of unruptured aneurysms were excluded. All of the procedures were performed in the emergent situation. Nine of the patients had Fisher grade of III and one had grade of IV. Only two patients had been taking aspirin for hypertension for three and five years, respectively, before the surgery and the other patients had not taken anti-platelet drugs in the past. The demographic information and clinical characteristics of the patients are shown in Table 1.

Patients with ruptured aneurysms were described according to a number of variables such as sex, age, Hunt and Hess (H & H) grade, Fisher grade, location of the aneurysm, type of operation, procedure with which the thrombus was found, the location of thrombus, the severity of the occlusion, the dosage of tirofiban that was used, the infusion route, the Thrombolysis In Myocardial Infarction (TIMI) grade and modified Rankin Scale (mRS) score. The location of the clot was defined according to three sites: proximal, distal or remote. Proximal clot indicates that thrombus was formed at the interface of the coil and parental artery; distal thrombus indicates that clot was found at a portion distal to the

aneurysm within the same vascular territory; remote thrombus was indicated when it is found in other vascular territories during the procedure. The severity of the occlusion was classified as partial or complete by the angiographic findings. A TIMI grade was used to show the degree of recanalization after injections of thrombolytic drugs and mRS three months after discharge was used to express patients' outcomes.

Procedure of coil embolization and thrombolysis with tirofiban

Every procedure, which was done under general anesthesia, was composed of simple, microcatheter-assisted and balloon-assisted coil embolization. After 7-F guiding catheter (Vista brite tip, Cordis Corporation, Miami, FL, USA) was placed in the internal carotid artery or vertebral artery, microcatheter [Excelsior SL (Boston Scientific Corporation, Cork, IRELAND) or Prowler 14 (Cordis Corporation)] was introduced to reach the aneurysmal sac under microwire (Synchro-14, Boston Scientific Corporation) guidance. When balloon-assisted coil embolization was performed, balloon catheter (Hyperform or Hyperglide, ev3 Endovascular, Inc., Plymouth, MN, USA) was used. Several detachable coils [Guglielmi de-

tachable coil, (GDC, Boston Scientific Corporation), Trufil coil (Cordis Corporation), Hypersoft and Hydrosoft coil (Microvention, Inc., Aliso Viejo, CA, USA)] were used. Every angiogram was conducted with the Artis zee Biplane system (SIEMENS Corp., Berlin, Germany).

Anticoagulation with intravenous heparin ranging from

1,000 to 2,000 units was started after the first coil deployment at the ruptured aneurysmal sac, which was followed by intermittent intravenous (IV) bolus injection of 1,000 units of heparin. We continually flushed the guiding catheter with IV infusions of heparin-mixed fluid (1,000 units of heparin in a 1-L sodium chloride solution). When a thrombus or embolus was found during

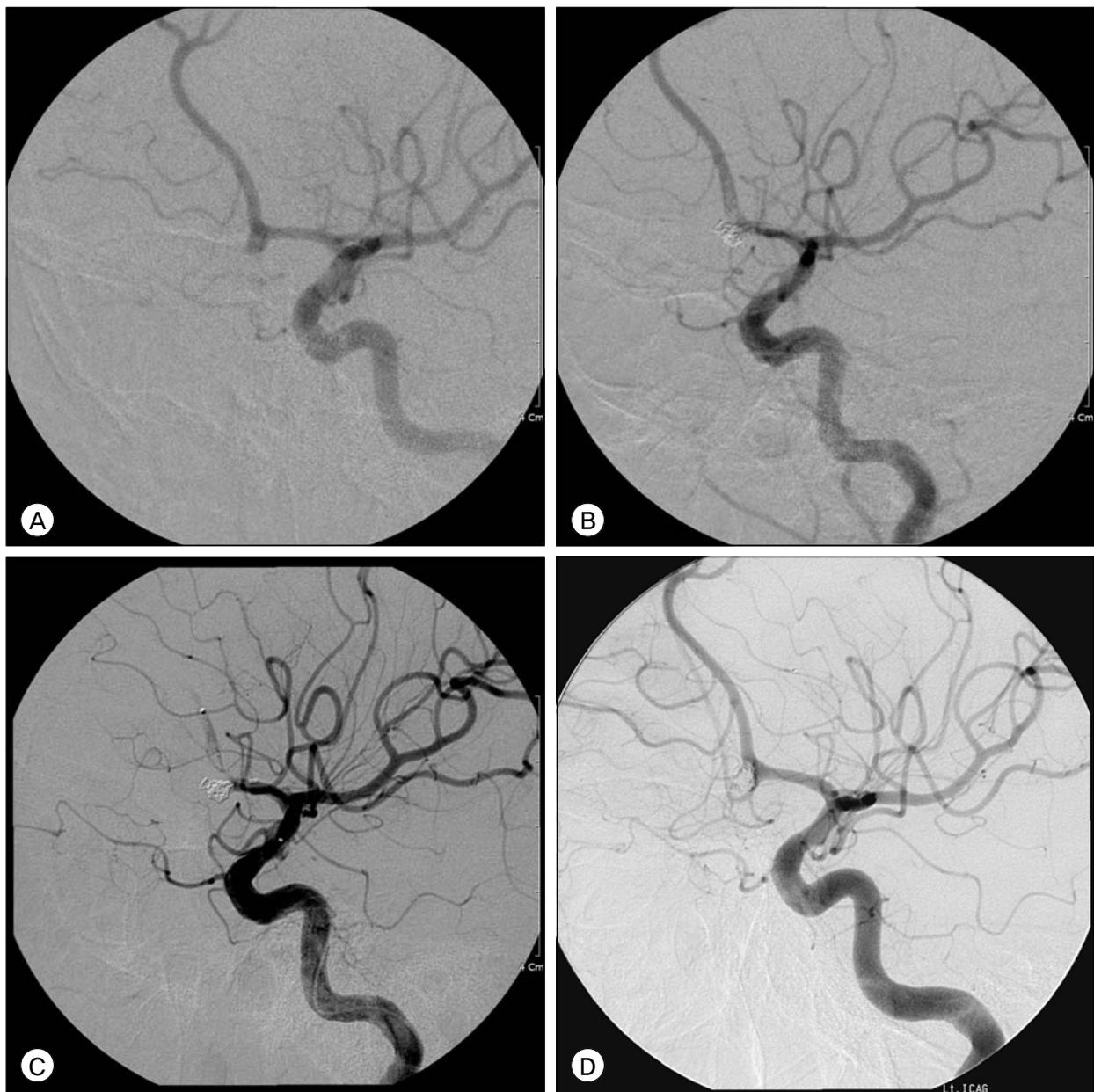


Fig. 1. A 43-year-old female (patient 1) presented with subarachnoid hemorrhage (Hunt and Hess grade III, Fisher grade III). A 3.5 × 3.5 mm-sized aneurysm is found on the anterior communicating artery (A). During coil packing, a thrombus is detected in the proximal A2 lesion of the anterior cerebral artery (B). Nearly complete occlusion of the artery is found (C). The patency of blood flow is restored with an infusion of tirofiban (0.3 mg) (D).

the procedure, we tried to resolve it with no delay. 10 mL of tirofiban (dosage, 12.5 mg/50 mL) was mixed with 40 mL of normal saline and administered from 0.3 mg just proximal to the clot through a microcatheter. Angiography was conducted 10 minutes after the infusion of IA tirofiban in order to confirm the degree of flow patency. When the thrombus or embolus was resolved or blood flow recovered, additional coil embolization followed. When the effect of thrombolysis was not sufficient within 10 min and the clot was resistant to the initial dosage of 0.3 mg of tirofiban, additional tirofiban was infused up to 1.2 mg. When coil embolization was finished, lumbar drainage was performed in all patients. Brain computed tomography (CT) scan was conducted immediately after the procedure in order to evaluate potential post operational intracranial hemorrhage (ICH) and infarction. Additional Diffusion Magnetic resonance imaging (MRI) or CT scans were performed in order to confirm the status of the neurological changes of the patient.

RESULTS

Ten patients received IA tirofiban and one received additional IV tirofiban for 24 hours after procedure for management of superior division of the M2 portion of a

middle cerebral artery occlusion. The characteristics of the clots, the procedural types and medical devices are shown in Table 1.

Complete arterial occlusion was found in four patients. Three of them had TIMI grade III and one had TIMI grade I recanalization according to the subsequent angiogram. Five patients of six with partial occlusion had grade III and one had II recanalization (Table 2).

There was one who underwent by-pass operation due to failure of thrombolysis with IA tirofiban. Every patient underwent diffusion MRI in order to confirm the procedure of infarctions within 1 week. Diffusion restriction was found in six cases. Five patients of six showed small infarctions that were not correlated with their neurological examination, but one presented with significant infarction that lead to mRS score of 3.

Eight patients experienced good functional outcome (mRS score 0) and two showed poor outcome (3 and 6). There were no hemorrhagic and hematologic complications in this study.

DISCUSSION

Thrombi can occur at interface between coil and parental artery or at remote lesions from the ruptured aneurysmal sac during the endovascular coil emboliza-

Table 2. Summary of the result after tirofiban injection

No	Tirofiban (mg)	IA/IV	TIMI	mRS	Infarct (MRI)
1	0,3	IA	III	0	yes
2	0,3	IA	III	0	no
3	0,6	IA/IV	III	0	no
4	1,2	IA	0	3	yes
5	1,2	IA	II	0	yes
6	1,2	IA	III	6	uncheckable
7	0,3	IA	III	0	yes
8	0,6	IA	III	0	yes
9	0,6	IA	III	0	no
10	0,6	IA	III	0	yes

*Tirofiban (mg) indicates the amount of used tirofiban, IA = intra arterial route; IV = intra venous route; TIMI = thrombolysis in myocardial infarction grade; mRS = modified Rankin Scale score; uncheckable = No MRI test due to expire

tion for ruptured aneurysms. Several studies have revealed that thrombolytic agents, such as tirofiban and abciximab, can be effective to resolve thrombus or embolus during the procedure.²⁾⁴⁾⁸⁻¹⁰⁾¹²⁻¹⁵⁾ Tirofiban, which is a nonpeptide antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor, inhibits platelet aggregation. The function of platelets are almost normalized within 4 hours after discontinuation.⁶⁾ Bruening et al.⁴⁾ reported that IV tirofiban was very effective in dissolving intraoperative thrombus formation in ruptured aneurysms in 16 patients. However the infusion time of tirofiban was 31.1 ± 70.3 hours (mean \pm SD). They started IV tirofiban with a loading dosage of 0.4 ug/kg/min for 30 minutes and maintained it at 0.1 ug/kg/min until removal of the thrombus. Additional heparinization was performed from 24 to 48 hours after coil embolization. There were no hemorrhagic complications in their study. However, when urgent surgical operations are needed for ruptured aneurysms, there is the possibility of development of an ICH due to long infusion of tirofiban.¹²⁾ Kang et al.⁸⁾ insisted that IA tirofiban was safe for thromboembolic complications during coil embolization. They experienced 11 cases of ruptured aneurysms and 14 unruptured aneurysms. However, heparinization was started after the near occlusion of the ruptured sac in order to avoid ICH complications. In cases of thrombus formation, further packing of the coil to the aneurysmal sac was advanced rather than the immediate thrombolysis of the clot when its type was not complete occlusion.

Ries et al.¹³⁾ reported that IA or IV abciximab injections were safe in thromboembolic events with aneurysms. This drug did not increase the risk of hemorrhages in patients who were taking prophylactic aspirin or clopidogrel. They suggested that providing abciximab without delay after the detection of a thrombus was effective way to avoid hemorrhagic events.

In this study, anticoagulation with heparin was started just after the first coil was placed within the ruptured sac. When a thrombus or embolus was found during the

procedure, we tried to resolve the clot with no delay with IA tirofiban injection beginning with a dosage of 0.3 mg up to 1.2 mg according to the surgeon's discretion, except in cases of active bleeding in ruptured aneurysmal sac. Because the procedure of persistent coil packing can aggravate the decrease of blood flow by making more thrombi form, the early detection and resolving of a thrombus without delay is important to lower the chance of ischemia in the brain tissue.

Patients with subarachnoid hemorrhages may need further surgical treatments, such as extra ventricular drainage (EVD), removal of intracranial hematomas and decompression surgery in order to control brain swelling. Considering its pharmacologic action and lasting duration, tirofiban is appropriate for these treatments. Tirofiban has several pharmacological advantages over abciximab. It has a short half-life of 2 hours and platelet function is normalized 4 hours after discontinuation.⁶⁾¹¹⁾ Compared to IV infusion of tirofiban, IA injection can be performed directly to the thrombus through a highly selected artery and less of a dose can be used than that needed for the IV route, which is recommended.⁸⁾

There is concern about increasing the risk of hemorrhage when tirofiban was infused during the procedure in patients with aneurysmal SAH.⁴⁾⁸⁾ Although no hemorrhagic or hematologic complications found in this study, complications after using thrombolytic drugs were reported in previous studies.¹⁾³⁾⁷⁾¹²⁾

It is essential to get enough blood flow soon after the development of a thromboembolic event in order to prevent brain infarction. Thus, it is a good strategy to use tirofiban directly through a highly selective artery on a blood clot that was encountered during the operation without delay.

CONCLUSION

IA tirofiban infusion can be a feasible method when procedural thromboembolic complications occur, even in subarachnoid hemorrhage patients. Further investigation

is needed to set clinical indications and dosage limitations of IA injection of tirofiban.

REFERENCES

1. Aster RH, Curtis BR, Bougie DW, Dunkley S, Greinacher A, Warkentin TE, et al. Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors. *J Thromb Haemost*. 2006 Mar;4(3):678-9.
2. Aviv RI, O'Neill R, Patel MC, Colquhoun IR. Abciximab in patients with ruptured intracranial aneurysms. *AJNR Am J Neuroradiol*. 2005 Aug;26(7):1744-50.
3. Bougie DW, Wilker PR, Wuitschick ED, Curtis BR, Malik M, Levine S, et al. Acute thrombocytopenia after treatment with tirofiban or eptifibatid is associated with antibodies specific for ligand-occupied GPIIb/IIIa. *Blood*. 2002 Sep;100(6):2071-6.
4. Bruening R, Mueller-Schunk S, Morhard D, Seelos KC, Brueckmann H, Schmid-Elsaesser R, et al. Intraprocedural thrombus formation during coil placement in ruptured intracranial aneurysms: treatment with systemic application of the glycoprotein IIb/IIIa antagonist tirofiban. *AJNR Am J Neuroradiol*. 2006 Jun-Jul;27(6):1326-31.
5. Cronqvist M, Pierot L, Boulin A, Cognard C, Castaing L, Moret J. Local intraarterial fibrinolysis of thromboemboli occurring during endovascular treatment of intracerebral aneurysm: a comparison of anatomic results and clinical outcome. *AJNR Am J Neuroradiol*. 1998 Jan;19(1):157-65.
6. Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet*. 2004; 43(14):963-81.
7. Hayashi K, Takahata H, Kitagawa N. Ruptured cerebral aneurysm complicated with rebleeding following thrombolysis during endovascular embolization: two case reports. *Neurol Med Chir (Tokyo)*. 2007 Jun;47(6):261-4.
8. Kang HS, Kwon BJ, Roh HG, Yoon SW, Chang HW, Kim JE, et al. Intra-arterial tirofiban infusion for thromboembolism during endovascular treatment of intracranial aneurysms. *Neurosurgery*. 2008 Aug;63(2):230-7; discussion 237-8.
9. Kwon OK, Lee KJ, Han MH, Oh CW, Han DH, Koh YC. Intraarterially administered abciximab as an adjuvant thrombolytic therapy: report of three cases. *AJNR Am J Neuroradiol*. 2002 Mar;23(3):447-51.
10. Liebeskind DS, Pollard JR, Schwartz ED, Cucchiara BL, McGarvey ML, Hurst RW. Vertebrobasilar thrombolysis with intravenous tirofiban: case report. *J Thromb Thrombolysis*. 2002 Apr;13(2):81-4.
11. McClellan KJ, Goa KL. Tirofiban. A review of its use in acute coronary syndromes. *Drugs*. 1998 Dec;56(6):1067-80.
12. Park JH, Kim JE, Sheen SH, Jung CK, Kwon BJ, Kwon OK, et al. Intraarterial abciximab for treatment of thromboembolism during coil embolization of intracranial aneurysms: outcome and fatal hemorrhagic complications. *J Neurosurg*. 2008 Mar;108(3):450-7.
13. Ries T, Siemonsen S, Grzyska U, Zeumer H, Fiehler J. Abciximab is a safe rescue therapy in thromboembolic events complicating cerebral aneurysm coil embolization: single center experience in 42 cases and review of the literature. *Stroke*. 2009 May;40(5):1750-7.
14. Song JK, Niimi Y, Fernandez PM, Brisman JL, Buciu R, Kupersmith MJ, et al. Thrombus formation during intracranial aneurysm coil placement: treatment with intra-arterial abciximab. *AJNR Am J Neuroradiol*. 2004 Aug;25(7):1147-53.
15. Yi HJ, Gupta R, Jovin TG, Tayal A, Genevro J, Gologorsky Y, et al. Initial experience with the use of intravenous eptifibatid bolus during endovascular treatment of intracranial aneurysms. *AJNR Am J Neuroradiol*. 2006 Oct;27(9):1856-60.