Intra-arterial Tirofiban Infusion for Partial Recanalization with Stagnant Flow in Hyperacute Cerebral Ischemic Stroke

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Summary

Early reocclusion is a major concern associated with poor clinical outcomes in patients with an ischemic cerebral stroke. This occurs most frequently in patients with partial initial recanalization. This study focuses on partial recanalization with stagnant antegrade flow after intravenous (IV) tPA or spontaneously, treated with the administration of intra-arterial (IA) tirofiban. Three patients with initial M1 occlusion on diagnostic studies had an occluded segment that was recanalized with stagnant flow after IV tPA or spontaneously. In all cases, IA tirofiban was administered. We evaluated the distal blood flow and the degree of vascular narrowing in the pre and post-procedure angiography and at follow-up in addition to the clinical status. In all patients, severe vascular narrowing with stagnation of blood flow was detected in the initial M1. After infusion of IA tirofiban, improvement of the distal blood flow was achieved rapidly within 40 minutes in all patients. The severe vascular narrowing resolved rapidly in two patients without residual stenosis. In one patient, moderate vascular narrowing was still present. The median baseline National Institutes of Health Stroke Scale (NIHSS) scores were 18 and the median post-procedural NIHSS scores were 2 at two weeks. No intracerebral hemorrhage occurred in any of the patients. Treatment with IA tirofiban was safe and effective in patients with partial initial recanalization. It can be suggested that detection of any partial recanalization is time for administration of glycoprotein IIb-IIIa receptor inhibitor in hyperacute ischemic stroke.

Introduction

Early reocclusion is a common cause of early clinical worsening after thrombolytic therapy in patients with an acute ischemic stroke. This can lead to a poor clinical outcome and higher in-hospital mortality^{1,2}. Reocclusion has been reported to occur in 16%-34% of patients who underwent IA or IV thrombolysis¹⁻⁴.

The mechanism of reocclusion after IA or IV thrombolysis for stroke patients remains to be determined. However, reocclusion in stroke patients appears to be most likely due to partial initial recanalization⁵. These patients may be prone to repeated thrombosis and artery to artery reembolization^{4,5}.

Three patients with hyperacute cerebral infarction that appeared as partial recanalization with stagnant antegrade flow after IV tPA or spontaneously were recently treated. After IA administration of tirofiban (Aggrastat, Merck, Whitehouse Station, NJ, USA) only, rapid and complete recanalization without complications was achieved. Here, these cases are described with the strategy for successful IA use of tirofiban in acute cerebral ischemic stroke.

Material and Methods

Patients

Three (n=3) patients were retrospectively identified who presented with the initial symptoms of hyperacute occlusion of the middle cerebral artery (MCA) on magnetic resonance an-

giography (MRA) or computed tomography angiography (CTA). The occluded segment appeared to have partial recanalization with stagnant antegrade flow on the initial catheter angiography. In two cases, IV tPA was administered and in one case the recanalization occurred spontaneously. The definition of a partial recanalization was grade 2 according to the Thrombolysis in Cerebral Infarction (TICI) score where the contrast material passed beyond the obstruction and opacified the arterial bed distal to the obstruction. However, the rate of entry of the contrast material into the vessel distal to the obstruction and/or its rate of clearance from the distal bed were perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel; e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction as defined by Higashida et al⁶.

In all three patients, treatment with superselective IA tirofiban infusion with a microcatheter was performed to resolve the thrombi and/or stenosis. Two patients were males and one was female; ages ranged from 32 to 56, with a mean of 42 years of age.

Tirofiban Preparation and IA Infusion

When a partial recanalization with stagnant antegrade flow was encountered at the initial catheter angiography, infusion was started without delay. A dose of 1 mg of tirofiban (4 mL) was diluted with physiologic saline (16 mL) to obtain a 20% dilution. A slow continuous infusion of the solution at a rate of 1 mL/min (0.2 mL/min tirofiban 0.05 mg/min tirofiban) was achieved by manual injection. Two 1 mL syringes were used for this infusion. The IA administration of tirofiban was infused over 20 minutes for 1 mg of tirofiban. In addition, it was administered as incremental injections of 0.25 mg (5 cc of 20% dilution)/5 min up to a maximum dose of a high IV loading dose (25 µg/kg) for the catheter-based revascularization during myocardial infarction⁷. Depending on the thrombus or embolus burden, doses of 0.5 to 1.5 mg were infused intra-arterially via a microcatheter near the clot. Angiography was then used to assess the clot status and arterial flow. When the arterial flow improved and the thrombi and/or stenosis were resolved, the infusion was discontinued and angiography was performed immediately and after ten minutes. IA infusions with a microcatheter were used without a continuous IV maintenance dose. All patients received

half a loading bolus of heparin (35 IU/kg) during angiography and thrombolysis.

Post-Procedure Antiplatelet Medication

After IA tirofiban was administered at a loading dose, aspirin (8-125 mg/d orally) and clopidogrel (300 mg orally and then 75 mg/day) were provided for at least three months.

Efficacy and Safety

The degree of arterial recanalization was graded according to the TICI classification⁶. Post-procedure magnetic resonance imaging (MRI) and/or computed tomography (CT) were obtained to assess for cerebral infarction or intracranial hemorrhage. The clinical outcomes were determined using the NIHSS score (baseline, one week and two weeks) and a modified Rankin score at 90 days.

Results

Three patients (two men, one woman; median age, 42 years; range, 32 to 56) were treated with either IA tirofiban (one patient) only or a combined IV tPA/IA tirofiban (two patients) infusion. The procedural characteristics and outcomes are summarized in Table 1.

Angiography Outcomes

All three patients initially had symptomatic hyperacute occlusion in the M1 mid-portion of the MCA on MRA or CTA; a partial recanalization with stagnant antegrade flow was found on the initial catheter angiography in all patients.

Severe focal vascular narrowing was detected in the M1 mid-portion in all patients. Intra-arterially infused tirofiban doses ranged from 0.5 to 1.5 mg, which corresponded to 33 to 100% of the recommended IV high loading dose in percutaneous coronary intervention (25 µg/kg)⁷. Improvement of the distal blood flow was rapidly achieved in all patients after IA administration of tirofiban (TICI grade 3 in all patients).

The severe focal vascular narrowing resolved rapidly in two patients without residual stenosis within 26 and 35 minutes. In one patient, there was moderate residual thrombus and/or residual stenosis on the post-procedural angiography 40 minutes after the start of the infusion with tirofiban; the condition improved to mild stenosis on the follow up MRA ten months later (Figures 1-3).

Figure 1 Case 3. Middle cerebral artery occlusion treated with intra-arterial tirofiban only. A) Initial CTA shows occlusion of the left M1 segment. B) CTA source image reveals a subtle low density in the left basal ganglia and left frontal lobe. C) Initial catheter angiography reveals partial recanalization with a focal M1 narrowing and antegrade stagnant flow without any medication. D) After infusion of 0.25 mg of tirofiban, improvement of the distal blood flow was noted. E) After infusion of 0.5 mg of tirofiban, mild resolution of focal stenosis and the new appearance of another lenticulostriate artery were noted. F) After infusion of 0.75 mg of tirofiban, complete resolution of focal stenosis, and new appearance of another lenticulostriate artery as well as another MCA division with occlusion of the M2 distal segment was noted. G) After infusion of 1 mg of tirofiban, no missing arteries were noted and blood flow through the M2 segment was completely restored. H) The post-procedural diffusion weighted image reveals high signal intensity in the left basal ganglia and left frontal lobe. No intracerebral hemorrhage or new infarction occurred.

Clinical Outcome

The median baseline NIHSS scores were 18 and the median post-procedural NIHSS scores were 5 at one week and 1 at two weeks.

The modified Rankin score at 90 days was 1, 0, and 0 respectively. No intracerebral hemorrhage or new infarction was noted in any of the patients on the post-procedure MRI and/or CT.

Table 1 Clinical characteristics of patients

Patient No.	1	2	3
Age(yr)/Sex	56/M	38/M	32/F
Onset time	1 hour	2.5 hours	5.5 hours
Site	Left M1	Right M1	Left M1
Initial NIHSS	21	13	20
Initial TICI	0	0	0
Initial treatment	tPA 0.9mg/kg	tPA 0.9mg/kg	none
Pre-TICI	2	2	2
Pre-vessel narrowing	severe	severe	severe
Tirofiban	1.5 mg	0.5 mg	1.0 mg
Resolving time	40 min	26 min	35 min
Post-vessel narrowing	moderate	none	none
Post-TICI	3	3	3
Post CT/MRI	No hemorrhage	No hemorrhage	No hemorrhage
Post-NIHSS (1/2 weeks)	8/3	2/1	5/0
MRS (90days)	1	0	0

NIHSS: National Institutes of Health Stroke Scale. TICI: Thrombolysis in Cerebral Infarction score. MRS: modified Rankin score.

Discussion

A high rate of early arterial reocclusion has been reported with standard IV tPA therapy for acute ischemic stroke. One third of patients with early recanalization experienced reocclusion within two hours of the tPA bolus. In addition, two thirds of the patients with deterioration, following improvement, had early reocclusion. These results suggest that early reocclusion may be the most common mechanism of early clinical deterioration after thrombolytic therapy for acute ischemic stroke ^{3,4}.

The mechanism of reocclusion after thrombolysis in stroke patients remains unclear. However, reocclusion in stroke patients appears to be most likely associated with partial initial recanalization ⁵. These patients may be prone to repeated thrombosis and artery to artery reembolization ^{4,5}.

Prevention of reocclusion after thrombolysis

and endovascular intervention may prove critical to further improve the efficacy of reperfusion strategies for stroke. Platelet-mediated thrombotic mechanisms probably play a key role in rethrombosis. Therefore, platelet membrane glycoprotein IIb-IIIa inhibitors could dissolve the platelet-rich thrombus rapidly ⁴.

Three patients with hyperacute cerebral infarction with partial recanalization and stagnant antegrade flow after IV tPA or spontaneous are reported here. With IA administration of tirofiban only, rapid and complete recanalization was achieved without complications. This is the first report on IA infusion for partial recanalization in patients with acute ischemic stroke.

Glycoprotein IIb-IIIa Inhibitors

Glycoprotein IIb-IIIa inhibitors are used alone or in combination with fibrinolytics to treat patients with acute myocardial or cerebral ischemia. The combination of glycoprotein IIb-

Table 2 Parenteral glycoprotein IIb-IIIa inhibitors (modified from references 10, 11)

	Abciximab	Tirofiban	Eptifibatide
Structure	Antibody Fab fragment	Non-peptide	Cyclic heptapeptide
Molecular weight	47615 Da	495 Da	832 Da
Reversibility	Irreversible	Reversible	Reversible
Cross reactivity with other integrin	Yes	No	No
Plasma half life	10-30 min	2 h	2.5h
Inhibition of platelet aggregation	>80%	>90%	>90%
Platelet recovery	<48 hr (>50% aggregation block)	< 4-8 h (near baseline)	4 hr (>50% aggregation block)
Elimination route	Senescent	Mostly renal	50% renal
Reversal of effect	Platelet transfusion	Discontinuation of infusion	Discontinuation of infusion
Usual dosage	0.25 mg/kg+0.125 µg/kg/min	* 25 µg/kg (10 µg/kg)+ 0.15 µg/kg/min ** 0.4 µg/kg/min+ + 0.1 µg/kg/min	180 µg/kg + 2.0 µg/kg/min

* High dose (low dose) in percutaneous coronary intervention. ** Label-recommended intravenous dose.

← *Figure 2* Case 2. Middle cerebral artery occlusion treated with IV tPA and IA tirofiban. A) Initial MRA shows occlusion of the right M1 segment. B) Diffusion-weighted image reveals a subtle high signal intensity in the right basal ganglia and right occipital lobe. C) Initial catheter angiography reveals partial recanalization with a focal filling defect in the M1. D) Oblique angiography shows focal narrowing of the M1 mid-portion. E) After infusion of 0.5 mg of tirofiban, near complete resolution of the focal filling defect and focal vascular narrowing in the right M1 was noted. F) Post-procedural diffusion-weighted image reveals no interval change, compared to the initial diffusion-weighted image.

IIIa inhibitors with thrombolytics enhances the effects on clot lysis. This treatment appears to prevent reocclusion of partially recanalized vessels, preserving microcirculation patency, and alters the no-reflow phenomenon ⁸.

Among glycoprotein IIb-IIIa inhibitors, three commonly used inhibitors include abciximab, eptifibatide and tirofiban (Table 2) ⁹⁻¹¹. Abciximab, a rapidly acting monoclonal antibody, can inhibit platelet aggregation within

ten minutes of delivery. Platelet activity usually returns to normal within 48 hours, although antibody binding may last as long as 15 days. However, a recent phase III study did not demonstrate either the safety or efficacy of intravenous administration of abciximab for the treatment of patients with acute ischemic stroke. There was an increased rate of symptomatic and fatal intracranial hemorrhage in the primary and wake-up cohorts¹².

In contrast to abciximab, and similar to eptifibatide, tirofiban exerts a competitive and rapidly reversible antagonism. The terminal elimination half-life of tirofiban is very short (about 2h) with median bleeding times returning to near normal levels within three hours. The

ADP-induced platelet aggregation reaches near-baseline levels eight hours after cessation of the infusion. Therefore, tirofiban provides an advantage when the rapid reversal of antiplatelet action is required such as in cases at high risk for hemorrhage or in combined treatment with thrombolytics¹³⁻¹⁵.

Junghan et al. reported that tirofiban was not associated with a significantly increased cerebral bleeding rate in patients with acute ischemic stroke¹⁴. In patients with acute ischemic stroke, tirofiban is used because of its shorter biological half-life and the reversible activity of tirofiban compared to abciximab. In this case series, no hemorrhagic complications occurred.

Figure 3 Case 1. Middle cerebral artery occlusion treated with IV tPA and IA tirofiban. A) Initial CTA shows occlusion of the left M1 segment. B) CTA source image reveals a subtle low density in the left basal ganglia and insular cortex area. C) Initial catheter angiography reveals partial recanalization with a focal M1 narrowing and antegrade stagnant flow after IV tPA. D) After infusion of 1.5 mg of tirofiban, improvement of the distal blood flow was noted. However, moderate vascular narrowing remained. E) Moderate vascular narrowing improved to mild stenosis on follow up MRA 10 months later.

IA Use of Tirofiban

Compared with IV administration, IA use of tirofiban has several obvious advantages. First, high doses of tirofiban can be delivered to the target thrombi; rapid and effective prevention of reocclusion can be achieved and a prompt reduction of the thrombus size or complete resolution within 40 minutes. Second, a lower IA dose may theoretically achieve the same local receptor inhibition effect as an IV dose, and it may lead to a lower systemic level of receptor inhibition. This may decrease subsequent systemic bleeding complications. The three patients presented here did not have any bleeding complications. And intra-arterially infused ti-

rofiban doses ranged from 0.5 to 1.5 mg corresponding to 33 to 100% of the recommended IV high loading dose. Third, the tirofiban dose can be adjusted according to response as incremental injections of small amounts are used (0.25 mg/5 min)^{16,17}.

Other Pharmacological Effects of Tirofiban

In addition to preventing fibrinogen cross-linking and platelet aggregation, glycoprotein IIb-IIIa inhibitors have other pharmacological properties. The glycoprotein IIb-IIIa inhibitors can disaggregate newly formed platelet clusters *in vitro*, even when their potential fibrinolytic activity is ruled out. Because enzyme-dependent fibrinolysis does not appear to be involved

in this setting, competitive removal of fibrinogen by the receptor antagonists is a likely mechanism associated with the production of dispersal of the clot. Other mechanisms of action attributed to the platelet glycoprotein IIb-IIIa inhibitors that could potentially affect their efficacy *in vivo* are their ability to prevent fibrinogen-mediated aggregation and inhibit platelet-dependent prothrombinase activity as well as thrombin generation in a concentration-dependent manner.

They may have some function as anticoagulants, and they may also promote fibrinolysis. The mechanisms are not well known but may involve a decrease in fibrin production, a decrease in inhibition of rtPA, or an increase in urokinase production¹⁷.

In this case series, after infusion of incremental doses of IA tirofiban, the severe focal vascular narrowing with residual thrombus and/or stenosis was dissolved rapidly in two patients without residual stenosis. The severe focal vascular narrowing was caused by residual thrombus formation that consisted of multiple elements, including platelets, thrombin, and fibrin more than tandem residual stenosis. There is strong evidence suggesting the direct thrombolytic effect of tirofiban.

Stent Placement or Angioplasty in Acute Ischemic Stroke

In this study, severe focal vascular narrowing was detected in the M1 mid-portion in all patients on initial catheter angiography. The configuration of M1 appears as an underlying tandem lesion. However, after infusion with the IA tirofiban, the severe focal vascular narrowing was dissolved rapidly in two patients without residual stenosis.

In one patient, there were moderate residual thrombus and/or residual stenosis on the post-procedural angiography; this improved to mild stenosis on follow-up MRA ten months later. Some of the severe focal vascular narrowing

may not be a tandem residual stenosis but rather a residual thrombus and/or emboli in patients with an acute ischemic stroke.

These findings underscore the importance of careful stent placement and angioplasty during the acute phase of treatment.

Any Partial Recanalization in Acute Ischemic Stroke

In patients with an acute ischemic stroke, development of a platelet-rich thrombus should be expected after any partial recanalization or reocclusion or in patients undergoing neurointerventional procedures such as:

- (1) Partial recanalization observed after thrombolysis including mechanical thrombolysis or spontaneous events;
- (2) Intravascular non-occlusive thrombus;
- (3) Reocclusion during or after thrombolysis;

or

- (4) Thrombi or emboli were detected during neurointerventional procedures such as coil embolization of a cerebral aneurysm^{18,19}. In selected patient populations, IA tirofiban may be more effective and should be considered as a treatment strategy. However, confirmation of its safety and efficacy is needed in large well-controlled studies.

Conclusion

Treatment with IA tirofiban was safe and effective in patients with partial initial recanalization. It can be suggested that detection of any partial recanalization is time for administration of glycoprotein IIb-IIIa receptor inhibitor in hyperacute ischemic stroke.

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