

Registry Report on Kinetics of Rescue Antiplatelet Treatment to Abolish Cerebral Microemboli After Carotid Endarterectomy

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Background and Purpose—Cerebral microemboli signals (MES) are associated with increased risk of acute stroke syndromes. We compared the effects on cerebral microemboli after carotid endarterectomy of tirofiban with dextran-40.

Methods—We used transcranial Doppler ultrasound to study transient MES acutely after carotid endarterectomy between August 2000 and December 2010 in 128 subjects refractory to preoperative antiplatelet treatment. Antithrombotic treatment was given for MES ≥ 50 hour⁻¹ (tirofiban: 40 patients [age 74 ± 1 {SEM}, males 27, and white 38]; dextran-40: 34 patients [age 69 ± 2 , males 22, white 30]). In 54 patients with MES < 50 hour⁻¹ (age 71 ± 1 , male 36, white 52), MES were monitored during their spontaneous resolution (controls). Data are median (interquartile range).

Results—The time to 50% reduction in MES (tirofiban 23 minutes [15–28]; dextran-56 [43–83]; controls 30 [22–38]; $P < 0.001$, Kruskal-Wallis analysis) and for complete MES resolution (tirofiban 68 minutes [53–94]; dextran-113 [79–146]; controls 53 [49–68]; $P < 0.001$, Kruskal-Wallis analysis) were shorter with tirofiban. The early cardiovascular event rate was similar with tirofiban compared with controls but increased in patients who received dextran.

Conclusions—These findings suggest that transcranial Doppler-directed tirofiban therapy is more effective than dextran-40 in suppression of cerebral microemboli after carotid endarterectomy. (*Stroke*. 2012;44:000-000.)

Key Words: carotid endarterectomy ■ microemboli ■ platelets ■ stroke ■ transcranial Doppler

In patients with symptomatic carotid stenosis, cerebral embolization from the carotid plaque is associated with increased risk of stroke.¹ Transcranial Doppler (TCD) detected cerebral microemboli are biomarkers of risk of stroke syndromes in symptomatic carotid stenosis and after carotid endarterectomy (CEA).² There is no consensus on which antiplatelet therapy is most effective in abolishing microemboli. Pharmacological agents effective in acute coronary syndromes could be beneficial in carotid disease to prevent stroke syndromes.²

We aimed to compare effects of the glycoprotein IIb/IIIa receptor antagonist tirofiban^{3,4} with the antithrombotic polysaccharide dextran-40 in patients with high microembolic rates after CEA.

Subjects and Methods

Our Carotid Registry comprises 576 patients who underwent elective CEA⁵ between August 2000 and December 2010 and were monitored by TCD⁶ after surgery. It has been our unit policy to use TCD-directed intravenous antiplatelet agents in all patients with microemboli signals (MES) rate ≥ 50 hour⁻¹. Prior to 2002, we used TCD dextran-40 and after that date we used tirofiban. We report retrospectively on 74 patients with postsurgery MES rate ≥ 50 hour⁻¹ and given either dextran-40 (n=34) or tirofiban (n=40) and on 54 patients with MES rate < 50 hour⁻¹ resolving spontaneously. All patients had preoperative single or dual oral antiplatelet treatment (aspirin+clopidogrel

or aspirin+dipyridamole—tirofiban: single n=32, dual n=8; dextran: single n=32, dual n=2; for patients with spontaneous MES resolution: single n=36, dual n=18).

Immediately patients recovered from anesthesia, TCD⁶ (PC Dop 842, SciMed, Bristol, UK) was used to monitor the middle cerebral artery ipsilateral to the operated artery, or in patients lacking an acoustic temporal window, transorbital monitoring of the carotid siphon was used.⁶ The microemboli⁷ rate was calculated at 15-minute intervals. We added treatment with tirofiban⁸ or dextran-40 in patients with MES rate > 50 hour⁻¹.⁹

Tirofiban¹⁰ (Aggrastat; MSD, Hoddeson, UK) was given intravenously 0.4 mcg/kg per minute for 30 minutes then 0.1 mcg/kg per minute for 18 hours.

For dextran-40¹¹ (10% Gentran-40 [Baxter Healthcare, Thetford, UK] in 5% glucose solution), after a 20-mL bolus, dextran-40 infusion was continued at 20 mL/h for 18 hours. For TCD evidence of persistent high MES rates, the dextran-40 infusion was increased at increments of 20 mL/h until MES reduced.

The local ethics department advised that, as a registry report using previously collected, nonidentifiable information with no randomization of drug therapies, this work did not fall under the remit of the National Health Service Research Ethics Committee.

Demographic and laboratory variables are expressed as mean \pm SEM. MES are expressed as median and interquartile range (IQR). Nonparametric unpaired data were analyzed using Kruskal-Wallis analysis for multiple groups or Mann-Whitney (MW) *U* test for 2 group comparisons. Categorical variables were analyzed using χ^2 test or Fisher's exact test. A *P*-value of < 0.05 was considered significant.

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Results

The demographic profile, cardiovascular risk factor (Table 1), and preoperative blood results were similar in the 3 groups, other than family history of cardiovascular disease being more common in patients with MES on tirofiban, or with spontaneous resolution.

MES Kinetics After CEA

In view of group differences in preoperative antiplatelet treatment, we analyzed data both for all subjects and separately for those only on single antiplatelet treatment preoperatively.

Initial MES rates were similar in dextran-40 and tirofiban-treated patients (dextran-40 102 minutes [IQR 79–150], tirofiban 88 [68–134], $P=0.234$, MW).

The Figure demonstrates the rapid initial reduction in MES in patients receiving tirofiban compared with patients with no additional antiplatelet treatment, despite almost 4 times higher initial MES rate postsurgery (tirofiban 88 (68–134), spontaneous resolution 24 (16–36), $P<0.001$, MW).

Time to 50% reduction in MES rate was shorter in patients receiving tirofiban compared with dextran-40 (tirofiban 23 (15–28), dextran-40 56 (43–83), $P<0.001$, MW).

Results for patients who received only single antiplatelet therapy before CEA were similar to those for the overall analysis. For tirofiban versus dextran-40, half-life for MES was shorter (23 minutes (15–28) versus 60 (43–83), $P<0.001$, MW); and time to resolution shorter (68 [53–98] versus 113 [71–154], $P<0.001$, MW) (Table 2).

Time to Resolution

Patients receiving tirofiban achieved earlier complete MES resolution compared with dextran-40 (Log Rank [Mantel-Cox], 2-way $P<0.001$) (Table 2).

Complications

Twenty-Four Hours Postsurgery

In 5 patients who developed transient ischemic attack or stroke, despite dextran-40, the MES rate was initially 60% higher and remained markedly raised during infusion (Figure), compared with patients in whom MES resolved uneventfully following dextran-40 ($n=29$).

Thirty Days Postsurgery

Ischemic stroke occurred in 1 tirofiban-treated patient 1 week after surgery. Two fatal myocardial infarctions occurred in dextran-40-treated patients, 1 fatal myocardial infarction in a tirofiban-treated patient, and 1 fatal myocardial infarction in a patient who did not receive rescue antiplatelet treatment. One tirofiban-treated patient died from intracerebral hemorrhage 4 days postsurgery. In the immediate postoperative phase, this patient had received an intravenous nitrate infusion for hypertension and a hyperperfusion syndrome. Platelet count was normal before the hemorrhagic event.

Late Events (30 Days to 1 Year)

One fatal myocardial infarction and 1 intracerebral hemorrhage occurred in different patients in the spontaneous resolution group.

Discussion

Despite antiplatelet therapy before CEA, patients may develop microemboli acutely postsurgery and so be at marked increased risk of postoperative stroke.⁹

Our results showed that in patients refractory to single or dual antiplatelet treatment, compared with dextran-40,⁹ tirofiban resulted in a large reduction in half-life MES and time to MES resolution. This advantage of tirofiban was not explained by differences in cardiovascular risk factor burden (Table 1). Until this study, it had not been clear whether tirofiban

Table 1. Demographic and Clinical Profile

	Spontaneous Resolution n=54 (%)	Tirofiban n=40 (%)	Dextran-40 n=34 (%)	χ^2 Test P Value
Age (mean \pm SEM)	71 \pm 1	74 \pm 1	69 \pm 2	0.199
Male	36 (67)	27 (66)	22 (65)	0.199
White	52 (96)	38 (95)	30 (88)	0.199
Asian	2 (4)	2 (5)	4 (12)	0.223
Hypertension	47 (87)	31 (78)	27 (79)	0.442
Never smoked	15 (28)	19 (47)	12 (38)	
Current smoker	12 (22)	13 (33)	9 (24)	0.143
Ex-smoker	27 (50)	8 (20)	13 (38)	
Ischemic heart disease	24 (44)	14 (35)	14 (41)	0.611
Type 2 diabetes mellitus	16 (30)	10 (25)	6 (18)	0.45
Hypercholesterolemia	30 (56)	26 (65)	15 (44)	0.197
Peripheral vascular disease	8 (15)	8 (20)	10 (29)	0.253
Cerebrovascular disease	13 (24)	12 (30)	5 (15)	0.299
Family history	25 (46)	13 (33)	4 (12)	0.04
Cholesterol (mmol/L)	4.6 \pm 0.1 (n=43)	4.6 \pm 0.2 (n=32)	4.6 \pm 0.5 (n=12)	0.97
Glucose (mmol/L)	5.3 \pm 0.2 (n=41)	5.3 \pm 0.3 (n=30)	5.9 \pm 0.5 (n=9)	0.571

Table 2. Comparison of MES Decay for Tirofiban vs Dextran-40 in Patients on Single or Dual Antiplatelet Therapy Before Carotid Surgery

	Single Antiplatelet Therapy			Dual Antiplatelet Therapy		
	Tirofiban (n=32)	Dextran-40 (n=32)	Mann-Whitney U Test	Tirofiban (n=8)	Dextran-40 (n=2)	Mann-Whitney U Test
	Median (IQR)	Median (IQR)	P Value	Median (IQR)	Median (IQR)	P Value
Initial MES rate (MES h ⁻¹)	96 (69–136)	104 (81–150)	0.268	81 (65–123)	77 (76)	0.6
Half-life of MES decay, min	23 (15–30)	60 (40–83)	<0.001	19 (15–23)	49 (45)	0.29
Time to MES resolution, min	68 (53–98)	113 (71–154)	<0.001	53 (53–79)	105 (83)	0.48

MES indicates microemboli signals; IQR, interquartile range.

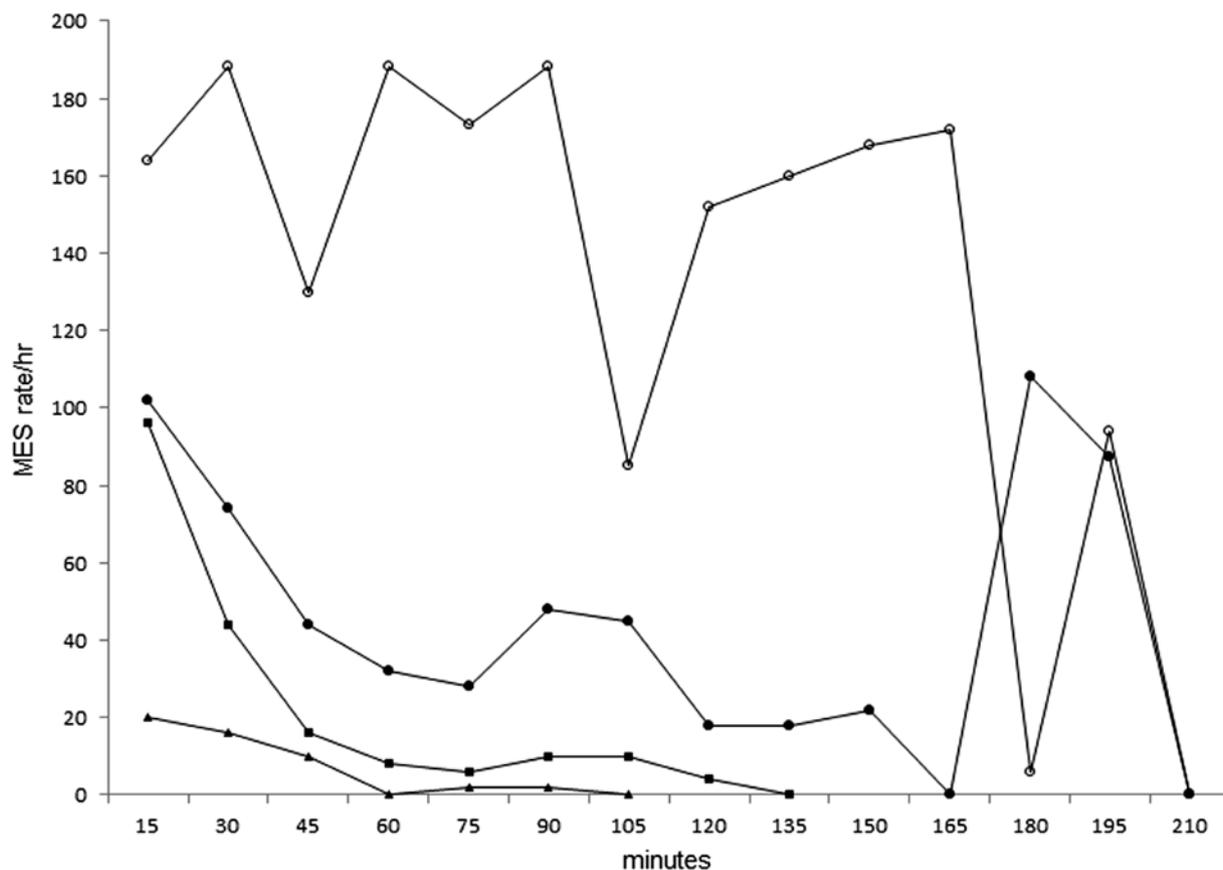


Figure. Microemboli signals after carotid endarterectomy in patients on single antiplatelet therapy before surgery. (●) dextran-40 (n=28); (○) patients (n=4) who developed early stroke, despite dextran-40 infusion; (■) tirofiban (n=32); (▲) no additional antiplatelet treatment (n=36).

would have benefits over dextran-40 treatment. Tirofiban also provides an effective treatment option in patients resistant to aspirin and clopidogrel.¹²

No patients had transient ischemic attack or acute stroke while on tirofiban, whereas 5 of 34 patients had adverse neurological outcomes, despite dextran-40. In our study, the tirofiban-associated bleeding rates were comparable with a trial of tirofiban in the setting of acute stroke.⁴

Conclusions

Our report provides support for randomized controlled trials of the clinical and cost-effectiveness of tirofiban in reducing stroke incidence after CEA.

Disclosures

None.

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