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Low-Dose Eptifibatide for Tandem Occlusion in Stroke: Safety and Carotid Artery Patency

 A. Jost,  C. Roels,  M. Brown,  R. Janjua, and  D. Heck

ABSTRACT

BACKGROUND AND PURPOSE: Maintaining carotid patency and avoiding symptomatic intracranial hemorrhage are competing concerns in tandem occlusions. This study provides data regarding the safety and efficacy of eptifibatide in stroke from tandem occlusion of the extracranial carotid artery and the intracranial carotid or middle cerebral artery.

MATERIALS AND METHODS: This is a retrospective analysis of 58 consecutive patients who received low-dose eptifibatide (135-mcg/kg bolus, 1-mcg/kg/min infusion) during treatment of tandem occlusions. Brain imaging and carotid sonography were performed at 24–36 hours. mRS was documented at 90 days, and carotid sonography, at 30–60 days.

RESULTS: The median age and NIHSS score were 64 years and 15, respectively. Twenty-five patients (43%) received tPA. ASPECTSs were 8–10 in 47 (81%) and 5–7 in 11 (19%) patients. Thirty-eight patients had angioplasty/stent placement acutely; 20 had angioplasty alone. Symptomatic intracranial hemorrhage occurred in 1 patient (2%). TICI 2b or higher was achieved in 56 patients (96%). Fifty-seven of 58 patients had clinical follow-up at 90 days (1 lost to follow up). The 90-day mRS was 0–2 in 42 patients (72%). There were 4/58 (7%) re-occlusions within 24–36 hours, all originally treated with stent placement. Forty-nine of 53 surviving patients had carotid sonography at 30–60 days, with 3 delayed re-occlusions, 2 with stents and 1 with angioplasty alone. The overall carotid patency at 30–60 days was 42/49 (86%). Carotid re-occlusion was not associated with clinical decline.

CONCLUSIONS: Low-dose eptifibatide seemed to be safe in tandem occlusions (symptomatic intracranial hemorrhage, 2%), although asymptomatic cervical carotid artery re-occlusions still occurred in 14% of patients.

ABBREVIATIONS: mTICI = modified TICI; SICH = symptomatic intracranial hemorrhage

Tandem occlusion presents the simultaneous problem of an intracranial embolic large-vessel occlusion and an acute plaque rupture/thrombotic event in the cervical carotid artery. Tandem occlusion is common, representing between 13% and 32% of patients with large-vessel occlusion.^{1–3} Outcomes in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial were similar between patients with and without tandem occlusions.⁴ The goal of tandem occlusion treatment is to remove the intracranial embolus and re-establish normal flow in the cervical carotid artery without

causing hemorrhage. Optimal conditions for elective carotid stent placement include therapeutic dual-antiplatelet therapy, statin loading, and intraprocedural anticoagulation. Unfortunately, such a strategy, and particularly the use of heparin, increases the risk of intracranial hemorrhage in the setting of acute stroke and particularly tandem occlusion.⁵ In general, following a successful intracranial embolectomy, extracranial carotid re-occlusion is not always associated with neurologic deterioration and poor neurologic outcome, whereas symptomatic intracranial hemorrhage (SICH) almost always is.^{5–7} Avoiding SICH must be the primary consideration. However, re-occlusion of the internal carotid artery may be associated with repeat embolization. Also, direct carotid inflow to support pial collaterals may be beneficial when less-than-perfect results were achieved with intracranial thrombectomy (eg, modified TICI [mTICI] <3). At least 1 retrospective study suggested that re-occlusion is associated with worse clinical outcomes in the tandem occlusion population.⁸ Judicious medical therapy to preserve the patency of the internal carotid artery following angioplasty or stent placement is therefore reasonable, providing this can be accomplished without increasing the risk of

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SICH. This report aims to provide evidence regarding the safety of a specific low-dose eptifibatide antiplatelet strategy in the tandem occlusion population applied uniformly to both patients who were treated with stents and those treated with angioplasty alone and also to provide data regarding carotid artery patency in both the acute phase and the postoperative period.

MATERIALS AND METHODS

The research protocol involving retrospective review of 58 patients was approved by the Novant Health institutional review board. Individual patient consent was not required by the institutional review board due to minimal patient risk and no individual patient identifiers.

Fifty-eight patients with consecutive tandem occlusions treated between February 2016 and January 2020 at Novant Health Forsyth Medical comprehensive stroke center were administered low-dose perioperative eptifibatide (135-mcg/kg bolus, 1-mcg/kg/min infusion) during intracranial thrombectomy and extracranial carotid angioplasty with or without stent placement. All patients had occlusive or near-occlusive atherosclerotic stenosis of the internal carotid artery and an embolus in the internal carotid terminus or middle cerebral artery. A prospective data base was reviewed retrospectively for patient characteristics and clinical and imaging outcomes. SICH was defined as a parenchymal hematoma with mass effect or any hemorrhage associated with a decline in the NIHSS of ≥ 4 points. Management of the intracranial occlusion by contact aspiration (ADAPT, A Direct Aspiration first Pass Technique) or combination therapy with an aspiration catheter and stent retriever (CAPTIVE, Continuous Aspiration Prior To Intracranial Vascular Embolectomy) was according to the physician's choice, as was management of the extracranial lesion with angioplasty and stent placement or angioplasty alone.^{9,10} In general, a distal-to-proximal approach, with angioplasty of the carotid artery and placement of a base catheter just below the skull base to facilitate the thrombectomy, was used first.¹¹ Stents were then placed after the thrombectomy due to the frequent suboptimal results in the cervical carotid occlusion after angioplasty. The eptifibatide infusion was continued until patients were converted to dual oral antiplatelet therapy if the 24-hour sonography and CT demonstrated carotid patency and no concerning hemorrhage. Dual oral antiplatelet therapy consisted of 81–325 mg of aspirin and clopidogrel (load of 300–600 mg) or ticagrelor (180-mg load). No patients received heparin during the procedure.

Preoperative imaging consisted of noncontrast CT and CTA or multiphase CTA. DWI was used in a minority of patients when collaterals were judged to be poor and a large infarct was suspected, and in some patients with unknown time of onset. Patients were selected for intervention on the basis of clinical-imaging mismatch (eg, when the treatment team determined that the clinical deficit was not explained by the size of the estimated core infarct after imaging). The ASPECTS on the preprocedural CT and angiographic mTICI scores were determined by visual inspection by a neuroradiologist. All interventions were performed with the patient under general anesthesia. Patients were admitted to the neuroscience critical care unit postprocedure, with blood pressure goals commensurate with the angiographic

Summary of population and results

Summary	
Age (median) (IQR) (yr)	64 (57–76)
Male (No.) (%)	38 (68%)
Hypertension (No.) (%)	41 (71%)
Diabetes (No.) (%)	17 (29%)
Dyslipidemia (No.) (%)	41 (71%)
Current aspirin use (No.) (%)	22 (38%)
Current clopidogrel use (No.) (%)	6 (10%)
Current/former smoker (No.) (%)	22 (38%)/14 (24%)
Baseline NIHSS (median) (IQR)	15 (11–20)
Baseline ASPECTS 8–10/5–7 (No.) (%)	47 (81%)/11 (19%)
Carotid Terminus occlusion (No.) (%)	25 (43%)
M1 occlusion (No.) (%)	22 (38%)
M2 occlusion, (No.) (%)	11 (19%)
tPA administration (No.) (%)	25 (43%)
Acute angioplasty alone (No.) (%)	20 (34%)
Acute angioplasty and stent placement (No.) (%)	38 (66%)
Delayed stent or endarterectomy within a week (No.) (%)	6 (10%)
mTICI score $> 2a$ (No.) (%)	56 (96%)
Acute carotid artery re-occlusion (No.) (%)	4 (7%)
Any ICH (No.) (%)	18 (31%)
Symptomatic ICH (No.) (%)	1 (2%)
30- to 60-Day carotid patency (No.) (%)	42/49 (86%)
90-Day mRS 0–2 (No.) (%)	42 (72%)

Note:—IQR indicates interquartile range; ICH, intracranial hemorrhage.

outcome (eg, target systolic blood pressure of <140 for mTICI 3 or mTICI 2c; <180 for mTICI 2b or worse). All patients underwent carotid sonography the following day to assess carotid artery patency and residual stenosis and repeat brain imaging with CT, MR imaging, or both. A follow-up clinical visit and carotid sonography were routinely scheduled 30–60 days postprocedure for all surviving patients. mRS scores were determined by a nurse, certified in the test and independent of the care team, in person or by telephone.

RESULTS

Patient population characteristics and results are summarized in the [Table](#).

The median NIHSS score and age were 15 and 64 years, respectively, with tPA use in 25 (43%) patients. Current aspirin use was documented in 22 (38%) patients; clopidogrel as a single therapy in 5 (9%); and clopidogrel with 81 mg of aspirin in just 1 patient. The ASPECTS were 8–10 in 47 (81%) and 5–7 in 11 (19%) patients. Thirty-eight patients had stent placement acutely, while 20 had angioplasty alone. Six patients who originally had angioplasty alone subsequently had elective endarterectomy or stent placement within the first week; these patients were recovering well, had a low stroke burden on imaging, and had persistent, severe stenosis. All patients had brain imaging within 24–36 hours. Any evidence of intracranial hemorrhage was present in 18 (31%) patients, mostly petechial or small subarachnoid hemorrhage, with only 1 case of SICH (2%). Technical success (TICI 2b, 2c, or 3) was achieved in 56 (96%) patients. The mRS at 90 days was documented in 57/58 patients (1 patient was lost to follow-up). Functional independence (mRS 0–2) was achieved in 42 (72%) patients. Five patients (9%) died by 90 days (mRS of 6).

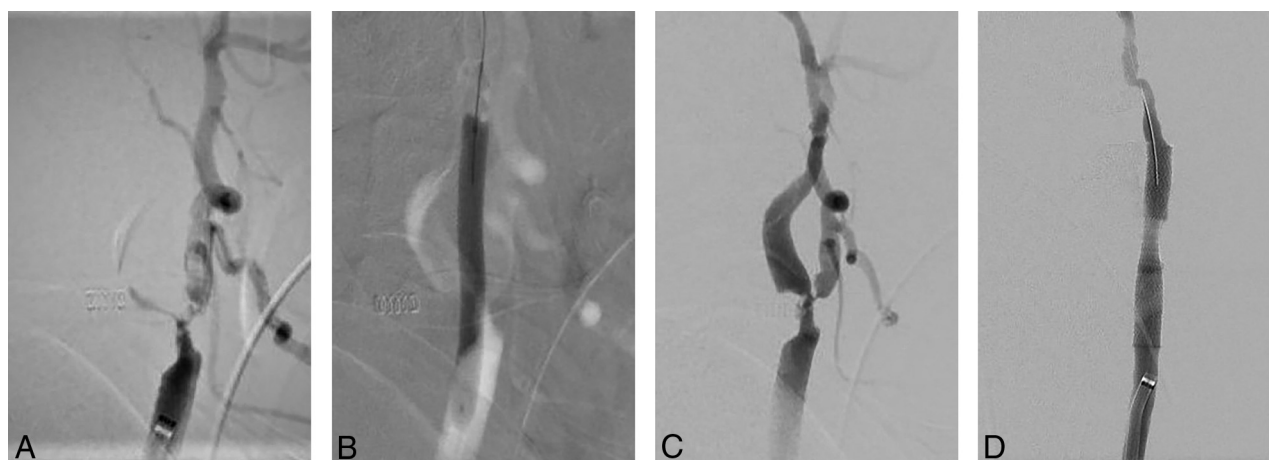


FIGURE. A, Occlusive internal carotid stenosis at the bifurcation; severe external carotid artery stenosis. B, Angioplasty with a 4-mm balloon. C, After successful intracranial thrombectomy, note severe residual stenosis. D, An 8 × 6 × 30 mm stent was placed. Note occlusion of the external carotid artery (the stent was occluded on sonography the next morning).

All patients had carotid sonography within 36 hours. There were 4 (7%) re-occlusions within the first 24 hours, all in patients originally treated with stent placement and all with normal flow at the end of the procedure (Figure). Forty-nine patients had carotid imaging at 30–60 days (5 died, 3 were not scheduled, 1 was lost to follow-up), with an additional 3 re-occlusions (6%): Two had stents and 1 had angioplasty alone. Carotid artery patency for surviving patients imaged at 30–60 days was 86% (42/49). No acute or delayed carotid re-occlusion was associated with neurologic decline, and 5/7 (71%) patients with carotid re-occlusion had a 90-day mRS of 0–2, similar to that in the group as a whole (72%).

DISCUSSION

Full-dose intravenous abciximab may have an unacceptably high rate of SICH, up to 22%, especially in older patients.⁶ Another glycoprotein IIb/IIIa inhibitor, eptifibatide, has the advantage of quicker platelet function return after discontinuation if bleeding complications occur (4–8 hours versus 1–7 days). While abciximab is theoretically reversible with platelet transfusion, in practice this is difficult to accomplish soon enough in the setting of acute intracranial hemorrhage. The choice of the dose of eptifibatide was based on limited available evidence.^{12,13} Our own initial unpublished experience with eptifibatide at a lower dose (135-mcg/kg bolus, but a 0.5-mcg/kg/min infusion) indicated that the drug may be safe but perhaps not efficacious at that dose because a 25% re-occlusion rate within 24 hours was experienced. For the 58 patients in the current study, the same bolus was used, but the infusion rate was increased to 1 mcg/kg/min to achieve greater inhibition of platelet aggregation. The infusion was administered to patients who were treated with stent placement or angioplasty alone because the stroke mechanism of plaque rupture and thromboembolism was considered the same in both groups. The advantages and disadvantages of various antiplatelet medications in tandem occlusion have been recently reviewed.¹¹

No randomized trials comparing techniques or medical therapies for treatment of tandem occlusions exist. The literature consists of retrospective case series in which the techniques and

medical therapies, even within those case series, are often heterogeneous. One might reasonably ask whether any type of intervention in the carotid artery or any addition of antithrombotic therapy is needed in addition to intracranial thrombectomy for patients with tandem occlusion. Papanagiotou et al¹⁴ reported a retrospective review of 482 patients from 18 stroke centers treated for tandem occlusion and found that carotid stent placement plus at least 1 antithrombotic medication resulted in both improved intracranial recanalization and improved clinical outcomes compared with mechanical thrombectomy alone. They also found a non-statistically significant trend toward better recanalization and clinical outcomes when comparing stent placement and antithrombotic medication with stent placement or angioplasty without antithrombotic medication. As one might expect, the medical regimens used varied widely. The overall SICH rate was 5%. Behme et al⁷ reported a retrospective review of 170 patients with tandem occlusions treated between 2007 and 2014 at 4 German centers and noted a 9% incidence of SICH, which had a 73% mortality in the acute phase. The study used 4 different antithrombotic medical strategies at the 4 different centers, one of which used a full-dose (180-mcg/kg) eptifibatide bolus and one of which used another glycoprotein IIb/IIIa inhibitor, tirofiban. They did not note any difference in SICH among the various medical regimens. Stent patency was not reported. A 2017 review and meta-analysis of 11 case series with a total of 237 patients reported 81% successful revascularizations (TICI 2b or TICI 3), a 7% risk of SICH, and good clinical outcomes in 44% (mRS 0–2).¹⁵ A 2018 meta-analysis of 33 studies noted no difference in clinical outcomes of patients treated with thrombectomy and angioplasty alone or stent placement of the cervical carotid lesion; 49% of the time both groups achieved an mRS of ≥ 2 .¹⁶ In their analysis of 395 patients from 17 comprehensive stroke centers, Gory et al¹⁷ noted good clinical outcomes in 52.2%. Stent placement was associated with successful reperfusion, but most interesting, it was not an independent predictor of good clinical outcome.

From a safety perspective, the incidence of SICH in this series was low, just 2%. This result may be for a variety of reasons.

ASPECTSs were high (81% were 8–10, and none were <5), indicating small core infarcts, and revascularization was good (mTICI 2b or better in 96%). Also an indication of small core infarcts and perhaps, more important, of healthy patients at the stroke ictus, the patients did very well clinically (mRS 0–2 in 72%, with just 9% with an mRS of 6). While it may be tempting to discount the safety evidence presented here due to the high ASPECTS, it has been previously noted by Behme et al⁷ that neither procedural timing nor ASPECTS predicted SICH in a tandem occlusion population. In addition to the low incidence of SICH, the favorable clinical outcomes presented here compared with previously published tandem occlusion experience may also be due to an improved technology for thrombectomy (stent retrievers and larger, more easily deliverable aspiration catheters), making the procedures shorter and more effective. Wallocha et al¹⁸ reported similarly good clinical outcomes, 73.6% mRS 0–2 at 90 days in their series.

Reporting of acute in-stent thrombosis or longer-term carotid artery patency has not been routine among case series; therefore, the incidence of acute or subacute stent thrombosis is often not reported. While carotid artery re-occlusions within the first 30 days are rare in elective carotid stent procedures, they are not rare in the tandem occlusion population. In their retrospective review of 163 patients treated for tandem occlusions between 2009 and 2016, Wallocha et al¹⁸ noted 4.9% stent re-occlusion at 24 hours among patients with stents and 42% re-occlusion in patients treated with angioplasty alone. Notably, they administered intravenous aspirin during the procedure to the patients with stents, but not to those with angioplasty alone, who received no additional antithrombotic therapy. Longer-term patency was not reported. In another single-center series of 81 patients with tandem occlusion, Pop et al⁸ reported a 19.1% incidence of delayed stent thrombosis. They used a heterogeneous antithrombotic regimen, with most patients receiving IV aspirin with or without a loading dose of clopidogrel, with none receiving glycoprotein IIb/IIIa inhibitors.

Compared with most published series of patients with tandem occlusion, this report is unique due to the rigorous follow-up for cervical carotid artery patency within the acute phase and the perioperative period. In the present series, acute re-occlusion occurred within the first 24 hours in 4 (7%) patients despite the use of our adjusted eptifibatide protocol, and 3 additional patients re-occluded before the first month, despite being on dual oral antiplatelet therapy. Overall, 7/49 (14%) patients who had follow-up imaging had re-occluded by the 30- to 60-day visit. This finding highlights the different nature of angioplasty and stent placement in a carotid artery in patients undergoing an acute thrombotic event, compared with an elective procedure. Carotid artery patency cannot be assumed in the absence of clinical deterioration. Indeed, none of the re-occlusions were associated with a clinical deterioration.

Placing a stent did not seem to protect against re-occlusion in this series. Of the 4 re-occlusions within the first 24 hours, all patients had stents, and 2 of 3 patients with delayed re-occlusions also had stents. Unlike the experience of Pop et al,⁸ none of the 20 patients initially treated with angioplasty alone re-occluded in the first 24 hours. Within the present series, all of the patients

who underwent angioplasty received the same antiplatelet therapy as the patients who had stents. The data presented here do not inform regarding the superiority of angioplasty alone versus stent placement because there was no attempt to randomize patients to angioplasty alone or stent placement. These decisions were left to the judgment of the interventionalist. It is also not known whether using eptifibatide at this dose results in fewer carotid re-occlusions compared with aspirin alone or any other regimen because no comparisons were made.

Limitations

The study is limited by the small sample size, retrospective nature, and lack of core lab adjudication of outcomes.

CONCLUSIONS

Low-dose eptifibatide (135-mcg/kg bolus, 1-mcg/kg/min infusion) in the population with tandem occlusions seemed safe with a low incidence of SICH. Cervical carotid artery re-occlusions did occur, with an overall 30- to 60-day patency of 86%. Re-occlusion was not associated with clinical decline in any patient. In the absence of a control arm, it is unknown whether cervical carotid patency is improved with low-dose eptifibatide compared with any other regimen. Given the frequently benign course of extracranial carotid re-occlusion compared with the known poor outcomes with SICH, medical therapy to maintain extracranial carotid artery patency should be judicious.

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