Endovascular Treatment of Tandem Extracranial/Intracranial Anterior Circulation Occlusions
Preliminary Single-Center Experience

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Background and Purpose—Acute ischemic stroke due to tandem occlusions of the extracranial internal carotid artery and intracranial arteries has a poor natural history. We aimed to evaluate our single-center experience with endovascular treatment of this unique stroke population.

Methods—Consecutive patients with tandem occlusions of the internal carotid artery origin and an intracranial artery (ie, internal carotid artery terminus, M1 middle cerebral artery, or M2 middle cerebral artery) were studied retrospectively. Treatment consisted of proximal revascularization with angioplasty and stenting followed by intracranial intervention. Endpoints were recanalization of both extracranial and intracranial vessels (Thrombolysis In Myocardial Ischemia ≥2), parenchymal hematoma, and good clinical outcome (modified Rankin Scale ≤2) at 3 months.

Results—We identified 77 patients with tandem occlusions. Recanalization occurred in 58 cases (75.3%) and parenchymal hematoma occurred in 8 cases (10.4%). Distal embolization occurred in 3 cases (3.9%). In 18 of 77 patients (23.4%), distal (ie, intracranial) recanalization was observed after proximal recanalization, obviating the need for distal intervention. Good clinical outcomes were achieved in 32 patients (41.6%). In multivariate analysis, Thrombolysis In Myocardial Ischemia ≥2 recanalization, baseline National Institutes of Health Stroke Scale score, baseline Alberta Stroke Programme Early CT score, and age were significantly associated with good outcome.

Conclusions—Endovascular therapy of tandem occlusions using extracranial internal carotid artery revascularization as the first step is technically feasible, has a high recanalization rate, and results in an acceptable rate of good clinical outcome. Future randomized, prospective studies should clarify the role of this approach. (Stroke. 2011;42:00-00.)

Key Words: acute stroke ■ angioplasty and stenting ■ endovascular treatment ■ stenting ■ stents

Endovascular recanalization strategies in acute ischemic stroke have been mainly described for intracranial occlusions. However, some patients are found to have tandem occlusions of the extracranial internal carotid artery (ICA) origin and intracranial ICA or middle cerebral artery (MCA). These lesions have responded poorly to intravenous tissue plasminogen activator (tPA). Consequently, endovascular treatment has become a more frequently used approach with or without prior intravenous tPA. Given the presence of two sites of occlusion (ie, extracranial and intracranial), the most appropriate reperfusion strategy in this setting, including the sequence of vessels treated, is not well established. Our standard approach, previously shown to be technically feasible, is to perform angioplasty and stenting of the proximal ICA origin occlusion first followed by treatment of the intracranial occlusion second. The aim of this study is to evaluate safety, recanalization rates, and clinical outcomes when patients with tandem occlusions are treated according to this approach at our institution.

Methods

With institutional Investigational Review Board approval, we retrospectively reviewed case records of patients who underwent endovascular therapy for acute ischemic stroke at the University of Pittsburgh Medical Center from July 1999 to April 2010. The study included patients with a concomitant complete ICA origin occlusion and occlusion of the intracranial ICA, M1 MCA, or M2 MCA segments. We collected data on pertinent stroke risk factors, clinical and neuroimaging findings, site of intracranial occlusion, and type of intracranial interventions.

In most cases, patients were selected based on visual inspection of MRI or CT perfusion scans performed before the procedure demonstrating mismatch between presumably irreversibly compromised brain (diffusion-weighted imaging or CT perfusion cerebral blood volume lesion) and inadequately perfused brain (cerebral blood flow,
mean transit time, or time to peak MRI or CT perfusion maps; Figure 1). The amount of mismatch that qualified the patient for intervention was determined in each individual case by the treating stroke neurologist and interventionalist according to patient specific characteristics. In general, however, evidence of "infarct core" (diffusion-weighted imaging or CT perfusion cerebral blood volume lesion) involving greater than one-third MCA territory constituted a reason for exclusion from treatment. Prior to intervention, a diagnostic cerebral angiogram was performed to establish collateral pathways in the affected hemisphere and identify the site of intracranial occlusion.

Figure 1. A Preprocedure noncontrast head CT showing loss of gray–white differentiation in anterior right insula. B, C, and D, respectively, show a preprocedure CT perfusion cerebral blood volume (CBV) map suggesting an infarct confined to the right frontal area that is significantly smaller than the critically hypoperfused area illustrated by the cerebral blood flow (CBF) and mean transit time (MTT) maps.

Carotid stenting was then performed with embolic protection using the Accunet (Guidant, Minneapolis, MN) or Spider (ev3 Neurovascular, Irvine, CA) systems. Pre-stenting balloon angioplasty was employed when necessary using 3.0- to 3.5-mm angioplasty balloons. Stenting was performed with the Acculink (Guidant), ProtegÉ (ev3 Neurovascular), Precise (Cordis Corporation, Bridgewater, NJ), or the WALLSTENT (Boston Scientific, Natick, MA). Post-stenting angioplasty was then performed with 4.5- to 5.0-mm balloons. The procedure occurred under systemic heparinization with activated clotting time goals of 200 to 250 seconds. Initially, patients received an intravenous bolus of eptifibatide (ie, 180 μg/kg) at the time of stenting followed by an oral load of clopidogrel and aspirin if hemorrhage was absent on postprocedure neuroimaging. Recently, we have changed our approach to forgoing GPIIb/IIIa inhibition in favor of administration of oral aspirin (ie, 325 mg) and clopidogrel (ie, 600 mg) loading doses through a nasogastric tube before stenting.

Intracranial interventions were performed if there was a persistent intracranial occlusion in the ICA terminus, M1 MCA, or M2 MCA segments after proximal revascularization. Pharmacological intra-arterial (IA) treatments included the infusion of tPA or urokinase. Mechanical IA treatments included mechanical embolectomy with the Merci clot retriever device (Concentric Medical, Mountain View, CA; Figure 2), continuous aspiration with the Penumbra system (Penumbra Inc, Alameda, CA), manual aspiration thrombectomy with the distal access catheters (Concentric Medical) or Penumbra reperfusion catheter, or intracranial angioplasty with or without stenting. For analysis purposes, these intracranial interventions are grouped as IA pharmacological therapy, IA mechanical therapy, or combined IA pharmacological and mechanical therapy. Postprocedure MRI or CT imaging was obtained to determine the extent of infarction (Figure 3).

Endpoints included successful extracranial and intracranial recanalization defined as Thrombolysis in Myocardial Infarction (TIMI) score ≥2, postprocedure parenchymal hematoma (PH), and good functional outcome defined as a modified Rankin Scale (mRS) score ≤2 at 3 months. Because complete recanalization of the extracranial occlusion was encountered in all cases, TIMI scores were applied primarily in reference to the intracranial occlusion. Thus, successful (ie, TIMI ≥2) recanalization implied recanalization of the intracranial lesion in addition to the extracranial occlusion. Distal embolization (DE) was a secondary endpoint and was determined from a distal common carotid artery base catheter injection after stenting of the ICA origin. DE was defined as a new site of occlusion in the intracranial ICA, anterior carotid artery region, or posterior circulation.

Figure 2. Proximal (extracranial) and distal (intracranial) intervention. A, Right CCA injection, anteroposterior view, identifies the right internal carotid artery occlusion (ICAO). The right ICA reconstitutes intracranially and the right middle cerebral artery (MCA) M1 segment is occluded (arrow). B, A stent has been placed in the proximal ICA after pre-stenting angioplasty under cerebral protection. C, L5 Merci retriever device (Concentric Medical, Mountain View, CA) has been placed into the right MCA. D, After 2 passes with the Merci retriever, Thrombolysis in Myocardial Infarction (TIMI) grade 2 recanalization is achieved.
cerebral artery (ACA), or M1 MCA or M2 MCA segments as compared with the diagnostic cerebral angiogram before stenting.

Functional outcomes were available in all patients and were obtained by vascular neurologists during outpatient clinic visits or through phone interviews.

Statistics

Statistical analysis was done using the STATA/IC 10 software package. In univariate analysis, variables of interest were correlated to the following binary outcome measures: good functional outcome and the presence of PH. For each endpoint, all covariates with \( P/0.20 \) were then entered into a multivariate logistic regression model, respectively. Significant association was considered at \( P/0.05 \).

Results

We treated 77 patients with clinical characteristics summarized in Table 1. Thirty (39.0%) patients were intubated for the procedure. Eleven of the patients reported here have been reported as part of an earlier series.2

Proximal revascularization was successful in 100% of cases and the stented ICA origin remained patent in 76 of 77 (98.7%) patients at 24 hours postprocedure. In-stent restenosis was determined in all patients by follow-up imaging through carotid Doppler ultrasonography, CT angiography, or cerebral angiogram. Long-term (ie, 30 days or later) in-stent restenosis rate was 2 of 27 (7.4%) in patients with available follow-up imaging. Of the remaining 50 patients without follow-up imaging, 18 patients had died by 90 days. The remaining 32 patients were not able to present for follow-up imaging for various reasons.

Twenty patients (26.0%) underwent only proximal stenting. Of these patients, 18 (90.0%) were observed to have spontaneous intracranial recanalization immediately after proximal revascularization, making further interventions unnecessary. The remaining 2 patients did not undergo intracranial revascularization because of hemodynamic instability or concern about an already completed large infarct during the procedure.

Table 2 summarizes the primary endpoints of successful recanalization, postprocedure PH, and good functional outcome as well as the secondary endpoint of distal embolization. Higher recanalization rates were seen in patients with intracranial occlusions of the M1 MCA or M2 MCA compared with those with an ICA terminus occlusion (43 of 51 [84.3%] versus 15 of 26 [57.7%]; \( P=0.02 \)). In 1 patient with a M2 MCA occlusion, we noted DE to the ICA terminus after proximal stenting. He was treated with IA tPA, achieved TIMI 2 recanalization, and achieved a good functional outcome.

#### Table 1. Patient Clinical Characteristics (n=77)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>No. (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.4 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>14.8 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>ASPECT score</td>
<td>8.5 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (67.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>31 (40.3)</td>
<td></td>
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</tbody>
</table>

#### Table 2. Primary and Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>No.</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>TIMI ≥2</td>
<td>58/77</td>
<td>75.3</td>
</tr>
<tr>
<td>ICA terminus</td>
<td>15/26</td>
<td>57.7</td>
</tr>
<tr>
<td>MCA M1</td>
<td>26/33</td>
<td>78.8</td>
</tr>
<tr>
<td>MCA M2</td>
<td>17/18</td>
<td>94.4</td>
</tr>
<tr>
<td>PH, postprocedure</td>
<td>8/77</td>
<td>10.4</td>
</tr>
<tr>
<td>HI, postprocedure</td>
<td>23/77</td>
<td>29.9</td>
</tr>
<tr>
<td>mRS ≤2 at 90 d</td>
<td>32/77</td>
<td>41.6</td>
</tr>
<tr>
<td>Distal embolization</td>
<td>3/77</td>
<td>3.9</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis in Myocardial Infarction; ICA, internal carotid artery; MCA, middle cerebral artery; PH, parenchymal hematoma; mRS, modified Rankin Scale.
oclusion experienced DE to the ICA terminus. He was treated with mechanical embolectomy but did not recanalize and subsequently died. The third patient had ICA terminus occlusion with DE to the M1 MCA segment. She was treated with IA tPA and Merci embolectomy, achieved TIMI 3 recanalization, and achieved a good functional outcome without hemorrhagic complications.

A postprocedure PH was associated with poor functional outcome (ie, mRS ≥3; OR for good outcome, 0.023; 95% CI, 0.001 to 0.055; P = 0.02) and with increased mortality (OR, 32.3; 95% CI, 2.52 to 413.7; P = 0.01). Of the 19 patients (24.7%) who died in our series, 4 patients (21.1%) had PH. Age, baseline Alberta Stroke Programme Early CT (ASPECT) score, intravenous tPA use, time to start of the procedure, and treatment modality (pharmacological or mechanical lysis) were not associated with PH formation. The use of intravenous GPIIb/IIa inhibitors was not associated with higher incidence of PH because this occurred in 5 of 34 (14.7%) cases without GPIIb/IIa inhibition versus 3 of 43 (6.7%) cases with GPIIb/IIa inhibition (P = 0.45). In multivariate analysis, the only variable significantly associated with PH was the presence of a carotid terminus occlusion (OR, 7.35; 95% CI, 1.36 to 39.5; P = 0.02).

A significant relationship between recanalization and favorable functional outcome at 3 months was noted. Successful recanalization was seen in 28 of 32 (87.5%) patients with good functional outcome, whereas a good functional outcome was noted only in 4 of 32 (12.5%) patients who did not recanalize (P = 0.04). In multivariate analysis, TIMI ≥2 recanalization (OR, 5.6; 95% CI, 1.12 to 28.77; P = 0.03), baseline NIHSS score (OR, 0.70; 95% CI, 0.57 to 0.85; P = 0.001), baseline ASPECT score (OR, 2.11; 95% CI, 1.21 to 3.65; P = 0.008), and age (OR, 0.85; 95% CI, 0.78 to 0.92; P = 0.001) were significantly associated with good functional outcome.

Discussion
To our knowledge, this report represents the only case series focused entirely on proximal and distal recanalization of anterior circulation tandem occlusion. Our preliminary data suggest that angioplasty and stenting of the proximal occlusion followed by intracranial intervention appears to be associated with higher rates of recanalization and at least comparable rates of good functional outcome compared with the natural history of this disease or treatment with intravenous thrombolysis.1 Moreover, our case series may provide pilot data for future comparisons of our approach with other treatment methods for this condition, including alternative endovascular approaches.

In our series, angioplasty and stenting of the acute ICA origin occlusion was performed with high technical success. The feasibility of passing a microwire across this lesion in a high proportion of cases has been previously reported and may reflect a similar situation to that demonstrated in acute coronary syndromes in which vessel occlusion often represents thrombus formation associated with rupture of a pre-existing plaque of underlying noncritical stenosis.2,3 Hence, at least some occlusive lesions of the ICA origin in the acute setting may represent focal lesions with fresh unorganized thrombus resulting in relatively easy passage of a microwire through the lesion.

Endovascular strategies different than the ones presented here focus on revascularization of the intracranial lesion only by passing a microcatheter distal to the proximal occlusion to infuse a thrombolytic agent or using circle of Willis collaterals (most commonly the anterior communicating artery) to access the MCA occlusion for drug infusion.4,5 Due to the overall low number of patients studied with these approaches, we feel that a reliable comparison between them is difficult. However, proximal recanalization as the initial step confers some advantages. Increased distal perfusion through collaterals from enhanced proximal flow may increase the likelihood of successful distal recanalization,7 which may explain why a significant proportion of patients (23.4%) experienced intracranial recanalization after ICA origin stenting only. Another advantage of proximal recanalization is improved access for treatment of intracranial lesions, which allows for better support when trying to access an intracranial occlusion resulting in better ways of deploying mechanical devices.6 An additional advantage to proximal recanalization is the lower risk of stroke recurrence in patients who make a good recovery because persistent carotid occlusion is associated with a significant risk of subsequent stroke. Carotid occlusion with hemorrhagic infarction heralds a worse prognosis and is associated with early clinical deterioration and late stroke recurrence risk.9 The 7.4% rate of restenosis observed in our series provides some reassurance with regard to the durability of this approach. However, our ability to accurately determine the restenosis rate is limited by the fact that in a significant proportion of patients in our cohort, assessment of stent patency beyond the acute stage was not available.

Proximal recanalization as the first step is fraught with theoretical disadvantages. The risk of DE is one major safety concern associated with this approach; however, in our case series, the rate of DE was relatively low at 3.9%. This finding could be attributable to the use of emboli protection devices in almost all of our cases. Our definition of DE was a new occlusion of a large intracranial vessel (ie, ICA, ACA, or M1 MCA or M2 MCA segments); as such, it is possible that the rate of distal embolization may have been higher because involvement of smaller vessels may have also occurred. Our DE definition was used because new occlusions in larger caliber vessels are more reliably detected on angiography and also because they are associated with worse outcomes compared with occlusions of smaller branches and thus may be more clinically relevant.10

Another theoretical shortcoming of this revascularization sequence is the increased time to restoration of flow in the intracranial circulation. An argument can be made that proximal prior to distal interventions may be too time-consuming. However, some of the procedural steps such as groin access and other steps necessary for base catheter placement are common for both approaches and therefore the extra steps necessary to revascularize the proximal occlusion do not cause a significant delay. Another concern derived from this reperfusion approach is the requirement of dual antiplatelet therapy after proximal stent placement that may precipitate hemorrhagic complications in those patients with a large stroke. An option could be to perform proximal angioplasty without stenting, although the immediate and
long-term durability of carotid angioplasty alone is likely to be lower than with stenting.

In our cohort, successful recanalization was independently associated with improved clinical outcome, a finding that is consistent with findings from multiple other studies. Similar to the experience gained from intravenous tPA, in our case series recanalization was dependent on the site of intracranial occlusion. The ICA terminus was more resistant to the thrombolytic strategies available over the entire duration of the study. More recently, with improved thrombolytic devices, we have been able to achieve higher recanalization rates in terminal ICA occlusions, but this technology was not available during the entire period of this study.

Patients with large territory infarcts can deteriorate due to a multitude of factors aside from hemorrhage. Some of the cases in our series were performed under general anesthesia and therefore a proportion of patients were still intubated by 24 to 48 hours, making a comparison of pre- and postprocedure neurological status difficult. Another potential confounding factor is the presence of stagnant contrast in the brain after intervention because it sometimes cannot be distinguished from blood on CT. For all these reasons, we chose to define symptomatic hemorrhage as any PH on follow-up imaging because we felt this would confer the highest degree of uniformity and accuracy in ascribing this complication.

However, we recognize that this definition may not be identical to that used in past IA trials. Nevertheless, the ominous nature of PH in our series is underscored by the high rate of poor outcomes and death in patients experiencing this event. The incidence of PH in this study is comparable to that noted in other studies. Contrary to earlier reports, we could not detect a significant association between extent of preprocedure infarction on CT and PH. This finding may be attributed to the small sample size along with the fact that most patients were selected for treatment based on a low infarct burden (ie, selection bias). Although no significant association could be detected between PH and the use of any single antithrombotic drug, we postulate that PH is mainly a consequence of reperfusion injury in conjunction with combined use of antithrombotic drugs. Thus, strategies that aim to treat patients with low preprocedure infarct burden along with a reduction in the use of any antithrombotic drugs are likely to result in lower PH rates.

The main limitation of our study derives from its non-randomized single-center, retrospective design. Endovascular treatment modalities have varied over the time course of our series, which makes standardization of our treatment approaches difficult. Furthermore, the number of patients included in the analysis is relatively small. However, we do not feel that these shortcomings have altered the main findings of this analysis in a fundamental way. We found that in using our approach of proximal followed by distal intervention, recanalization rates are comparable to those observed with endovascular strategies for intracranial occlusions only. In confirming findings from multiple other endovascular case series in patients with acute stroke, recanalization in addition to age, baseline stroke severity, and ischemic burden on preprocedure CT was correlated with favorable outcomes. Ultimately, knowledge of the best reperfusion strategies for tandem occlusions can only be gained through studying different reperfusion strategies compared with the best medical therapy. Thus, the results of this study may be useful in providing the necessary framework for the design of prospective trials addressing the best management strategy for this complex vascular problem.

Disclosures

L.R.W. is a consultant for Abbott Vascular, Lundbeck, and Ferrer and has ownership interest in NeuroInterventional Therapeutics Inc. M.B.H. is a consultant for ev3 Neurovascular. T.G.J. is a consultant for Concentric Medical, Co-Axia Inc, Micrus Inc, and ev3 Neurovascular and has ownership interest in NeuroInterventional Therapeutics Inc.

References

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