Mechanical Approaches Combined With Intra-Arterial Pharmacological Therapy Are Associated With Higher Recanalization Rates Than Either Intervention Alone in Revascularization of Acute Carotid Terminus Occlusion

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Background and Purpose—Acute stroke attributable to internal carotid artery terminus occlusion carries a poor prognosis. Vessel recanalization is crucial to improve clinical outcome. Historically, pharmacological thrombolysis alone has low recanalization rates. We sought to determine whether adjunctive mechanical approaches achieve better vessel recanalization and functional outcome.

Methods—We retrospectively reviewed 75 consecutive endovascular cases of acute internal carotid artery terminus occlusions treated at our center between 1998 and 2008. Mechanical approaches (MERCI retrieval/angioplasty/stent) with and without adjunctive intra-arterial pharmacological therapy (urokinase or tissue plasminogen activator) was compared to intra-arterial lysies alone. Univariate and multivariate analyses were performed to determine predictors of recanalization (thrombolysis in myocardial infarction grades 2 to 3) and favorable functional outcome (modified Rankin score ≤2) at 3 months.

Results—Lowest recanalization rates were observed with intra-arterial lysies alone (3/17, 17.6%). MERCI embolectomy combined with intra-arterial lysies was associated with the highest recanalization rates (18/21, 85.7%; P<0.0001). MERCI embolectomy alone achieved 46.2% recanalization rates (6/13; P=0.23). Angioplasty or stenting and intra-arterial lysies achieved 25% (2/8; P=0.65) and 40% (4/10; P=0.085) recanalization, respectively. In multivariate analysis, combination of MERCI embolectomy with intra-arterial lysies (OR, 16.2; CI, 4.6–77.6), or any mechanical technique with intra-arterial lysies (OR, 6.7; CI, 2.5–19.5) independently predicted thrombolysis in myocardial infarction 2 to 3 recanalization. Clinically significant parenchymal hemorrhage rates were 7.5% with combination (3/38) and 12.5% with pharmacological therapies (2/16; P=0.46). Using stepwise logistic regression, age (OR, 0.95; CI, 0.90–0.995), baseline NIHSS (OR, 0.82; CI, 0.70–0.96), and thrombolysis in myocardial infarction 2 to 3 recanalization (OR, 4.0; CI, 1.1–14.4) were associated with favorable functional outcome.

Conclusions—Combined mechanical and intra-arterial pharmacological therapy is associated with higher recanalization rates than either intervention alone in acute internal carotid artery terminus occlusion revascularization. (Stroke. 2009; 40:2092-2097.)

Key Words: carotid terminus ◦ intra-arterial ◦ mechanical

Acute ischemic stroke attributable to internal carotid artery terminus (TICA) occlusion is associated with a high rate of mortality and poor functional outcome in survivors.1 TICA occlusion both reduces collateral circulation capacity through the circle of Willis and is often associated with a high clot burden.1,2 Vessel recanalization is essential to improve outcome in this condition. Pharmacological treatment using intravenous (IV) or intra-arterial (IA) thrombolysis has historically been associated with low recanalization rates.1–5 Higher recanalization rates have been reported with mechanical approaches (MERCI retrieval6,7 or stents8) but experience with combined mechanical and pharmacological treatment is limited.6,9,10 We sought to determine whether combination approaches using mechanical modalities and IA thrombolysis are superior to either intervention alone for treatment of acute TICA occlusions by comparing the rates of recanalization and functional outcome at 3 months in a single-center consecutive case series.
Materials and Methods
We retrospectively analyzed data on 75 consecutive cases of acute ischemic stroke attributable to TICA occlusions treated endovascularly at our center between October 1998 and June 2008. This study was conducted with institutional Investigational Review Board approval. Demographic, clinical, CT, angiographic, and follow-up data were analyzed. The anatomic occlusion site was confirmed by angiography. Lesion types were classified as type 1 (T-shape) if occlusion of the internal carotid artery (ICA) terminus extends into both the anterior cerebral artery A1 and the middle cerebral artery M1 segments, or type 2 (L-shape) if the terminal ICA lesion extends into either A1 or M1 segment only. All patients presenting with acute ischemic stroke were initially evaluated with CT, whereas most patients underwent additional imaging to assess vessel and perfusion status using CT angiography and perfusion or MR diffusion and perfusion studies. Patients who presented within 3 hours of symptom onset were initially treated with IV tissue plasminogen activator (TPA) if there were no contraindications. Twenty-nine percent (5/17) patients received bridging dose and 70.6% (12/17) patients received full-dose TPA. When deemed appropriate based on clinical and imaging characteristics, cases with no neurological improvement after completion of IV-TPA infusion and persistent vessel occlusion were treated with IA therapy. Patients who presented beyond 3 hours from symptom onset or with contraindication to IV-TPA were evaluated for IA therapy using pharmacological or mechanical approaches. In general, patients were selected for IA therapy if CT showed less than one-third hypodensity within the middle cerebral artery territory. More recently, patients were considered for IA therapy if baseline CT revealed an Alberta Stroke Program Early CT Score (ASPECTS) 11 of >7 or if the extent of infarcted brain was ≤30% than the hypoperfused but viable brain, based on visual inspection of the imaging studies by the treating stroke neurologist and the interventionalist.

The general approach to treating patients at our center has been described previously.9 We categorized our IA treatments as IA pharmacological only, IA mechanical only, and IA combined pharmacological and mechanical. IA thrombolysis with UK (N=10) and TPA (N=32) was used as first-line therapy if the patient arrived within 6 hours from symptom onset. The median dose of UK was 625 000 U (range, 500 000–750 000 U) for IA pharmacological only and 1 000 000 U (range, 250 000–1 000 000 U) for combined IA pharmacological and mechanical group. The median dose of TPA was 20 mg (range, 5–40 mg) for IA pharmacological-only and 10 mg (range, 5–25 mg) for combined IA pharmacological and mechanical group. Because of higher intracerebral hemorrhage rates observed with IA UK administration,12 we currently use TPA for thrombolysis. Most patients were treated with intravenous heparin (range, 3000–5000 U with goal-activated clotting time of ≥250). If recanalization failed to occur with IA-TPA/UK, mechanical approaches such as MERCI retriever system (the X series in 7 patients; L series in 29 patients; Concentric Medical), angioplasty balloon catheters (Stormer coronary balloon catheter, Medtronic, Inc; N=7; Voyager coronary balloon catheter, Guidant Corp, N=4; Maverick balloon catheter, Boston Scientific, N=1), stents (Multilink Minivision stent, Guidant Corp, N=7; Driver stent, Medtronic, Inc, N=3; Neuroform stents, Smart Therapeutics Inc, N=1) were used. An IA pharmacological thrombolysis approach was primarily used in cases early in the series before mechanical approaches became available. Patients with tandem extracranial high-grade carotid stenosis or occlusions were treated first with angioplasty and stenting of the proximal lesion to improve distal flow through collaterals and to gain access to the ICA terminus lesion.13 An intravenous bolus of integrilin (180 µg/kg), a glycoprotein IIb/IIIa receptor antagonist, was administered as an adjunct without maintenance dosing for large clot burden or when a stent was deployed. Patients who arrived beyond 6 hours were initially treated with mechanical embolectomy; IA lysics were used if the lesions failed to recanalize and in cases in which the infarct burden and the corresponding risk of symptomatic hemorrhage was deemed low. The antiplatelet regimen used in this population included aspirin, which started 24 hours after the intervention. Patients who received a stent received aspirin and Plavix combination for at least 30 days.

Recanalization was defined as TIMI grade 2 to 3.14 TIMI 3 was defined as patency in ICA, anterior cerebral artery, and all middle cerebral artery branches with good distal perfusion. TIMI 2 was defined as recanalization of the ICA terminus, M1 segment, and at least 1 division of the M2 segments and A1 segment. The interventionalists determined the recanalization status at the end of the case and the data were recorded prospectively in our IA database. Postintervention CT/MRI scans were reviewed for evidence of intracranial hemorrhage by an author (R.L.) blinded to the treatment modality. Because most patients remained intubated and sedated, making preprocedure and postprocedure comparison of NIHSS difficult, we considered clinically significant hemorrhage as CT/MRI evidence of parenchymal hematoma (PH)13 associated with clinical worsening. We considered all type 2 PH and subsets of type 1 PH associated with neurological worsening as clinically significant. The modified Rankin scale was used to assess functional outcome at 3 months after treatment. Outcome assessment was determined from chart review of follow-up clinical visits (N=41) or by phone (N=34). Favorable clinical outcome was defined as modified Rankin scale score of 0 to 2.

Statistics
Statistical analysis was performed using JMP 5.1.2 statistical software (SAS Institute, Inc). Baseline characteristics among various intervention treatment groups were analyzed using ANOVA. Differences between individual subgroups were compared using the Fisher exact test for categorical variables and Student t test for continuous variables. Nonparametric variables were compared using Wilcoxon test. Multivariate analyses were performed using stepwise logistic regression to determine independent predictors of recanalization and favorable functional outcome at 3 months.

Results
Seventy-five consecutive acute strokes attributable to TICA lesions were treated endovascularly between October 1998 and June 2008. Sixty-one cases (81.3%) were of type 1 (T-shape) and 14 cases (18.7%) were type 2 (L-shape) lesions. Eighteen (24%) cases were associated with tandem high-grade or critical proximal ICA stenosis (N=3, 4%) or ICA occlusions (N=15, 20%). Predominantly IA pharmacological therapies (with or without IV thrombolysis) were used to treat TICA lesions before the use of MERCI embolectomy at our center (11 cases before and 5 cases since January 2005), whereas mechanical-type therapies (MERCI retriever, angioplasty, and stents) were mainly used later in the series (9 cases before and 50 cases since January 2005). Table 1 shows the baseline patient characteristics and the types of intervention. Admission NIHSS scores, stroke etiologies, stroke risk factors, and times to intervention and recanalization were not significantly different among the different treatment groups. TIMI 2 to 3 recanalization rate in the IA pharmacological-only treatment group was 17.6% (3/17; Figure). Within this group, 2 out of 8 patients (25%) who received both IV-TPA and IA-TPA/UK achieved TIMI 2 to 3 recanalization. Patients treated with the MERCI clot retriever and IA lytic achieved the highest rate of recanalization (18/21, 85.7%; P<0.0001). MERCI embolectomy alone achieved 46.2% recanalization rates (6/13; P=0.23). Angioplasty with IA thrombolysis achieved 25% (2/8; P=0.65) recanalization rate, whereas stent-assisted recanalization with IA lytic resulted in 40% (4/10, P=0.085) recanalization rate based on an intent-to-treat analysis. Balloon-mounted coronary stents

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were undeliverable in 4 cases attributable to extreme ICA tortuosity. In those patients who had successful stent placement and IA lysis, 67% resulted in TIMI 2 to 3 recanalization (P=0.003).

Overall, the use of mechanical techniques combined with IA pharmacological thrombolysis achieved significantly better rate of recanalization than IA lytic alone (26/40, 65%; P<0.0001). A multivariate analysis showed that treatment with IA lytic plus MERCI retriever (OR, 16.2; CI, 4.6–77.6), or IA lytic plus any mechanical therapy (OR, 6.7; CI, 2.5–19.5) were independent predictors of vessel recanalization in acute TICA occlusions. The mean time to recanalization with combined mechanical and IA lytics (124±61 minutes) was higher than either mechanical (111±53 minutes) or pharmacological (98±41 minutes) therapy alone, although the differences were not statistically significant (ANOVA; P=0.35).

Interventions for acute TICA occlusions were associated with 10.8% rate of type-2 parenchymal hematoma (N=8). There were no statistically significant differences among treatment groups in the rate of type-2 PH (P=0.56; Table 2). Six patients (8%) had type-1 PH, although none had associated worsening from their baseline stroke deficits. There was 37.3% (N=28) overall mortality rate, which was not statistically different among the various treatment groups. The rate of favorable clinical outcome (modified Rankin scale, 0–2) at 90 days was 34.4% among patients with TIMI 2 to 3 recanalization compared to 15% in patients who did not recanalize (P=0.09). Forty one percent of patients with TIMI 2 to 3 recanalization achieved modified Rankin scale 0 to 3 compared to 17.5% who did not recanalize (P=0.037). Overall, modified Rankin scale of 0 to 2 was achieved in 17 patients (23%). Using stepwise logistic regression model, age (OR, 0.95; CI, 0.90–0.995), admission NIHSS (OR, 0.82; CI, 0.70–0.96) and TIMI 2 to 3 recanalization (OR, 4.0; CI, 1.1–14.4) were independent predictors of clinical outcome. There was a difference in the rates of recanalization (27/61, 44.3% vs 8/14, 57.1%; P=0.55) and 3-month favorable outcome (12/59, 20.3% vs 5/13, 38.5%; P=0.28) between the T-type and the L-type ICA lesions, but the difference did not reach statistical significance.

**Discussion**

Among all possible occlusion sites within the anterior circulation, acute TICA occlusions carry the worst prognosis. Depending on the location and extent of the thrombus (T-shape or L-shape lesions), TICA lesions obstruct Willissian collaterals, retrograde ophthalmic circulation, and lead to reduced leptomeningeal collateral capacity from the ipsilateral anterior cerebral artery if the anterior communicating artery is absent or the contralateral A1 is hypoplastic/atretic. Furthermore, if the thrombus is extensive enough to occlude the origin of a large posterior communicating artery, leptomeningeal collateral supply from the posterior cerebral artery may also be compromised. The combined rates of mortality and poor outcome have been reported up to 84% in various series, even when treated with IA thrombolysis. The only intervention that has been shown to improve outcome is rapid recanalization. It is therefore imperative to define the most rapid and successful strategies for recanalization in this stroke type. In our series, pharmacological IA-only approach using TPA/UK was the least effective, associated with 17.6% recanalization rate. This rate was similar to previously reported recanalization rates for IA pharmacological therapy alone. Mechanical approaches achieved higher rate of vessel recanalization, with rates of 46.2% in the group treated with MERCI retriever only, 85.7% with MERCI retriever plus adjunctive IA lytics, and 67% with stent plus IA lytics in

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>IA-Pharm Only (N=17)</th>
<th>Mechanical Only (N=18)</th>
<th>IA-Pharm Plus Mechanical (N=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (SD)</td>
<td>63 (13)</td>
<td>71 (13)</td>
<td>68 (13)</td>
<td>0.26</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>9 (52.9)</td>
<td>10 (55.6)</td>
<td>19 (47.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>HTN, N (%)</td>
<td>11 (64.7)</td>
<td>11 (61.1)</td>
<td>23 (57.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>DM, N (%)</td>
<td>3 (17.7)</td>
<td>2 (22.2)</td>
<td>14 (35)</td>
<td>0.33</td>
</tr>
<tr>
<td>CHOL, N (%)</td>
<td>3 (17.7)</td>
<td>5 (27.8)</td>
<td>8 (20)</td>
<td>0.73</td>
</tr>
<tr>
<td>CAD, N (%)</td>
<td>4 (23.5)</td>
<td>6 (33.3)</td>
<td>12 (30)</td>
<td>0.81</td>
</tr>
<tr>
<td>Smoker, N (%)</td>
<td>5 (35.7)</td>
<td>5 (35.7)</td>
<td>9 (24.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>Previous stroke, N (%)</td>
<td>1 (5.9)</td>
<td>2 (11.1)</td>
<td>5 (12.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Baseline NIHSS, median (range)</td>
<td>17 (8–24)</td>
<td>18 (10–29)</td>
<td>17 (6–25)</td>
<td>0.39</td>
</tr>
<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid occlusion</td>
<td>6 (35.3)</td>
<td>1 (5.6)</td>
<td>12 (30)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>8 (47.1)</td>
<td>14 (77.8)</td>
<td>23 (57.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline ASPECTS score, median (range)</td>
<td>8 (4–10)</td>
<td>8 (3–10)</td>
<td>9 (4–10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Time to intervention, min (SD)</td>
<td>338 (141)</td>
<td>374 (248)</td>
<td>343 (199)</td>
<td>0.84</td>
</tr>
<tr>
<td>Angio time, min (SD)</td>
<td>98 (41)</td>
<td>111 (53)</td>
<td>124 (61)</td>
<td>0.35</td>
</tr>
<tr>
<td>Time to recanalization, min (SD)</td>
<td>449 (148)</td>
<td>492 (263)</td>
<td>483 (201)</td>
<td>0.85</td>
</tr>
</tbody>
</table>
cases in which the stents could be navigated through the lesions. Recanalization rate with combination of Merci plus TPA plus angioplasty was based on only 3 patients, which was lower (67%) but not statistically different from Merci plus IA lytic alone ($P=0.54$). In our series of 75 consecutive patients with acute TICA occlusions, even though mechanical intervention alone achieved higher recanalization rates compared to pharmacological-only therapy, neither intervention alone seems to achieve satisfactory recanalization and combination of both approaches may be necessary. The time to recanalization between treatment approaches was longer in the combined treatment group but the differences were not statistically significant. This difference may be explained by our observation that combination approaches were more likely to occur when single treatment modality failed, and may reflect underlying clots that were more resilient to recanalization. The rates of TIMI 3 recanalization among each treatment approach was 11.76% (2/17) for IA lytics only, 30.8% (4/13) for Merci only, 33.3% (7/21) for IA lytic plus Merci only, 33.3% (1/3) for IA lytic plus Merci plus angioplasty with no significant intergroup differences ($P=0.25$). The lower rates of complete recanalization underscored the high clot burden seen.

### Table 2. Hemorrhage and Mortality Rates

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>IA-Pharm Only</th>
<th>Mechanical Only</th>
<th>IA-Pharm Plus Mechanical</th>
<th>Total</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal Hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH-1, N (%)</td>
<td>1 (5.9)</td>
<td>1 (5.6)</td>
<td>4 (10.3)</td>
<td>6 (8.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>PH-2, N (%)</td>
<td>2 (12.5)</td>
<td>3 (16.7)</td>
<td>3 (7.5)</td>
<td>8 (10.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mortality, N (%)</td>
<td>6 (35.3)</td>
<td>8 (44.4)</td>
<td>14 (35)</td>
<td>28 (37.3)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

PH-1 indicates type 1 parenchymal hemorrhage; PH-2, type-2 parenchymal hemorrhage.
with TICA lesions. As endovascular treatment modalities evolve, it is possible that in the future, improved mechanical devices may lead to reduction of current dosage of lytics and improved recanalization.

In our case series, angioplasty combined with IA lysis was not significantly better than IA lysis alone in achieving recanalization. This may be attributable to thrombus prolapse into the vessel lumen after balloon deflation or reocclusion attributable to angioplasty-induced intimal disruption. Our experience, therefore, suggests that whenever a stent can be navigated past the occlusive lesion, it is more effective than angioplasty alone in the treatment of TICA lesions. Our case series involves mainly balloon mounted coronary stents and one case with neuroform stent. The advent of self-expanding stents has made possible stent delivery and deployment in most patients with promising results with respect to vessel recanalization. However, whether stenting is superior to mechanical embolectomy or suction embolectomy remains to be established.

The higher recanalization rates we observed using MERCI plus IA lytics for acute TICA lesions were consistent with the previous pooled results from the MERCI and Multi-MERCI trials, which reported 53% and 63% TIMI 2 to 3 recanalization rates with MERCI retriever alone and MERCI plus adjunctive IV-TPA, respectively, in a stroke population with intracranial internal carotid occlusions. One possible reason the mechanical retriever device may be especially useful for TICA lesions is that the clot burden is often extensive. The occlusions often span the ICA terminus, M1, and often A1, markedly reducing antegrade blood flow and limiting clot exposure to TPA, thus making systemic thrombolysis practically ineffective. Reduced antegrade flow also limits exposure of the clot surface to locally infused TPA because the lytic is more likely to diffuse away through open side branches proximal to the thrombus. When using the MERCI system, aspiration from the proximal occluding base catheter in conjunction with mechanical thrombus retrieval creates a gradient favorable to thrombus movement into the base catheter and away from the brain. Mechanical retrieval is also effective in reducing the clot burden, resulting in improved efficacy of IA lysis. Softening of the clot by prior IA/IV thrombolysis may also enhance the clot retriever’s effectiveness. This may explain the improved effectiveness of MERCI plus IA pharmacological adjunct compared to MERCI embolectomy alone. Our study did not address whether the sequence of IA-TPA and MERCI embolectomy influence the effectiveness of TICA recanalization but this is an important point to clarify in the future.

The overall rate of clinically significant symptomatic hemorrhage in this study was 10.8%, associated with type-2 PH. This rate was comparable to the rates of symptomatic hemorrhage in large intracranial intervention trials. There were no significant differences in the rates of parenchymal hematoma between treatment groups, although the number of patients in some groups was small. The overall mortality in our series was 37.3% and no significant differences in mortality were found between treatment groups. Death occurred most commonly because of cerebral edema and progressive herniation, symptomatic hemorrhage, medical complications, and withdrawal of care by family’s requests.

This study has several limitations. Although our database is entered prospectively, the data were analyzed retrospectively and the treatment groups were not randomized. Therefore, we could not exclude the possibility of case selection bias. The various treatment approaches were not evaluated concurrently (most of the IA pharmacological-only treatment was performed before the first MERCI case in January 2005); therefore, we could not exclude time-associated factors (including cumulative case experience) that could influence the measured outcome. Additionally, with a limited total and subgroup sample size, some baseline factors may not be evenly distributed. However, the differences in what we feel are the most relevant baseline patient variables were not statistically different and were adjusted for in the multivariable analysis. This study represents the largest single-center case series to date on acute interventions for TICA occlusions. However, given these limitations, our findings should be interpreted as hypothesis generating on treatment approaches for TICA occlusions and await confirmation by future prospective trials.

Disclosures

None.

References


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