Aggressive Mechanical Clot Disruption
A Safe Adjunct to Thrombolytic Therapy in Acute Stroke?

Elizabeth A. Noser, MD; Hashem M. Shaltoni, MD; Christiana E. Hall, MD; Andrei V. Alexandrov, MD; Zsolt Garami, MD; Edwin D. Cacayorin, MD; Joon K. Song, MD; James C. Grotta, MD; Morgan S. Campbell III, MD

Background and Purpose—This study evaluated the safety and efficacy of aggressive mechanical clot disruption (AMCD) in acute stroke patients with persisting middle cerebral artery (MCA) or internal carotid artery (ICA) occlusion after thrombolytic therapy.

Methods—Retrospective case series were used from a prospectively collected stroke database on consecutive acute ischemic stroke patients treated with intra-arterial (IA) thrombolytics and mechanical clot disruption during a 5-year interval. Thrombolytic dosage, endovascular techniques, immediate and final recanalization rates, symptomatic hemorrhage, mortality, and outcome were determined.

Results—Thirty-two patients received AMCD. Median baseline National Institutes of Health Stroke Scale (NIHSS) score was 18, and median time to initiation of IA treatment was 261 minutes from symptom onset. ICA occlusion was noted in 16 patients and MCA occlusion in 16 patients: 22 received combined IV/IA thrombolytics, 3 received IV thrombolytics, 6 received IA thrombolytics, and 1 patient received no thrombolytics before AMCD. No immediate periprocedural complications were noted. Immediate recanalization was achieved in 38% (50% MCA, 25% ICA) and final recanalization in 75% (88% MCA, 63% ICA) of patients. Favorable outcome occurred in 19 (59%) patients, symptomatic cerebral hemorrhage in 3 (9.4%) patients, and mortality in 4 (12.5%) patients.

Conclusion—AMCD can be performed safely with comparable intracerebral hemorrhage and mortality rates to other IA therapies even after use of intravenous thrombolytics in selected patients. Early deployment of this technique leads to immediate recanalization in one third of patients. AMCD may potentially shorten the time to flow restoration and improve overall recanalization rates achieved with IA therapy. (Stroke. 2005;36:292-296.)

Key Words: angioplasty, balloon ■ endovascular therapy ■ stroke, acute ■ thrombolytic therapy

Intravenous recombinant tissue plasminogen activator (IV rtPA), the only FDA approved therapy for acute ischemic stroke, has been shown to improve 3-month outcome if given within the first 3 hours of stroke onset.1 However, >50% of patients do not demonstrate a favorable clinical response.2 We previously reported, using noninvasive monitoring with transcranial Doppler, that IV rtPA achieved complete recanalization in 30% of patients, partial recanalization in 48%, and none in 22%; reocclusion occurred in 34% of patients with any initial recanalization.3,4 Complete or partial early arterial recanalization during IV rtPA has been reported to lead to better 3-month outcome.5 Intra-arterial thrombolysis (IAT) may provide multiple benefits in acute stroke treatment, including extending the treatment time window, tailored thrombolytic dosage and delivery, salvage therapy for IV rtPA nonresponders, and combined use with other endovascular techniques.6–13 In the absence of a direct comparative study, an estimated average recanalization rate of 70% for IAT may be superior to IV rtPA.5,6,8,14 Recanalization is an immediate parameter for assessing treatment success, and time to recanalization is likely the most important predictor of clinical outcome regardless of treatment method used.15–18

Aggressive mechanical clot disruption (AMCD) may provide an advantage over “routine” IAT by increasing recanalization rate and speed and reducing total thrombolytic dose. In several series, mechanical clot disruption in conjunction with IAT has been shown to achieve higher rates of recanalization.19–21 Both simple mechanical clot penetration and AMCD are used as salvage therapy for those patients who fail to respond to IAT. Simple mechanical clot penetration with a microwire or microcatheter may more commonly be used than AMCD, such as balloon angioplasty, because of safety concerns including vessel perforation, dissection, or rupture.22–25 Qureshi et al reported an 84% recanalization rate in 19 patients with ischemic stroke who were treated with AMCD by performing snare or balloon angioplasty plus direct IAT with reteplase.19 Patients whose
therapy was delayed longer than 3 hours after stroke onset, those with severe or profound neurological deficits, or those with recent surgery were the predominant candidates for this protocol, with only 2 patients receiving intravenous thrombolytics. At follow-up (1 to 3 months after thrombolysis), a high mortality rate of 53% was noted, with 37% of patients remaining functionally independent.

The safety and effectiveness of AMCD in combination with thrombolytics for the treatment of acute stroke is uncertain. We aimed to determine the safety, recanalization rate, and time-to-flow restoration of AMCD for acute stroke patients who have persistent middle cerebral artery/internal carotid artery (MCA/ICA) occlusion or lack of clinical response after IAT or systemic thrombolytics.

Methods

From February 1998 to July 2003, 94 consecutive acute stroke patients underwent emergent cerebral angiography for possible IAT on the basis of initial evaluation or after IV rtPA under the direction of the University of Texas-Houston, Stroke Treatment Team. Patients who received AMCD for angiographically documented MCA or ICA occlusion were evaluated for this study.

Stroke neurologists and fellows comprising a veteran stroke team at a university-based tertiary care center were responsible for the assessment and treatment of all patients. On admission, the stroke neurologist assessed the neurological status using the National Institutes of Health Stroke Scale (NIHSS) to quantify neurological impairment. All stroke team members are certified in administering this scale. A cerebral computed tomographic (CT) scan was performed in all cases before treatment with thrombolytics. CT exclusion criteria included intracranial hemorrhage, hypodensity consistent with subacute infarct, and significant mass effect with midline shift.

Patients who met standard criteria for IV rtPA were treated with 0.9 mg/kg IV rtPA. One patient outside of the 3-hour time frame was enrolled in an institutional review board–approved protocol of low dose IV rtPA (0.6 mg/kg IV). IAT was considered within 1 hour of IV rtPA if patients had no recanalization or early arterial reocclusion by ultrasound criteria or had no neurological improvement, which was determined as an unchanged NIHSS score from baseline or worsening of the neurological deficit without hemorrhagic changes on repeat CT scan before the IA procedure.26–28 Primary IAT was performed if patients presented after 3 hours from symptom onset had contraindications to IV rtPA or proximal carotid occlusion, including T-type occlusion with rapid symptom worsening. IAT was delivered using a multidisciplinary team approach. The treatment team consisted of interventional neuro- radiologists, an interventional neurologist, and the treating neurologist working in various combinations with at least 2 physicians present making consensus treatment decisions. Diagnostic cerebral angiography was performed through femoral artery approach. A 6-French guide catheter was placed in the ipsilateral ICA or common carotid artery proximal to the occlusion site. A microcatheter and microwire wire were advanced through the guide catheter and navigated to the occluded vessel segment in proximity to the thrombus. The microcatheter tip was placed into the thrombus for thrombolytic infusion. Reteplase was then infused by slow hand push at an approximate rate of 0.1 U aliquots diluted in 1 cc over 1 to 2 minutes. Control angiography was performed approximately after every 0.5 to 1 U of reteplase delivery to evaluate the status of recanalization. The microcatheter was repositioned as needed to maintain placement within the thrombus. In 2 earlier cases before reteplase was readily available at our institution, the IA thrombolytic used was urokinase (n = 1) and rtPA (n = 1).

AMCD was attempted after IAT if there was no significant response or persisting occlusion after repeated administration of reteplase and control angiography. Initially, AMCD was undertaken ∼60 to 90 minutes after suboptimal response to thrombolytics. As the experience of the interventional team with this technique grew, AMCD was often undertaken 30 to 60 minutes after suboptimal thrombolytic response. Remaining doses of thrombolytics after AMCD were administered if required for persisting occlusion or clot at the discretion of the treatment team.

Using standard interventional technique, simple mechanical clot penetration consisting of passage of the microcatheter/microwire through the clot was performed multiple times during catheter positioning for thrombolytic infusion in most cases. AMCD was defined as the utilization of at least one of the following interventional techniques: (a) aggressive microcatheter/microwire clot maceration; (b) percutaneous angioplasty (PTA); (c) stent deployment; or (d) use of a snare device. Aggressive microcatheter/microwire clot maceration consisted of multiple passes of the guide wire through the clot after the tip was manually shaped into a complete J curve approximating the diameter of the vessel. During this process, the microcatheter was often advanced multiple times over the guide wire as well. PTA consisted of balloon angioplasty that could involve multiple dilatations at the discretion of the interventionalist and was performed in patients with persisting occlusion in the ICA and proximal MCA. Balloons were always undersized relative to the estimated lumen diameter of the treated segment. Cervical carotid stent placement was performed in selected patients after angioplasty. No intracranial stents were placed. Finally, utilization of snare devices involved introducing the device through the microcatheter and advancing into the clot matrix. Multiple passes were then made through the thrombus using the fully extended loop of the snare to fragment or capture clot. Snare devices were used in smaller vessels, including distal MCA or proximal vessels, with clot extending into distal vessels not amenable to angioplasty.

All angiograms were analyzed by the same interventional neurologist. For the purpose of this study, we used a thrombolysis in cerebral ischemia (TICI) scale based on the modified thrombolysis in myocardial ischemia (TIMI) criteria to define cerebral perfusion as shown in Table 1. Recanalization was defined as TICI grades 2 or 3. Immediate recanalization was defined as TICI grades 2 or 3 achieved immediately after mechanical manipulation.8 The ICA Occlusion-Segment location was reported as described in Table 2.

All patients were admitted to the Neurology/Neurosurgery Intensive Care Unit or stroke unit and managed by the University of Texas-Houston Stroke Treatment Team. Concomitant antithrombotic therapy was not used. All antiplatelet therapies, including Aggrenox, aspirin, or clopidogrel, were started 24 hours after the procedure and after completion and review of the 24-hour cerebral CT for evidence of hemorrhage. No patients were treated with G2b3a inhibitors. The standard guidelines of blood pressure management for IV rtPA therapy were followed preprocedure. If successful recanalization was achieved (TICI...
II or III), a systolic blood pressure goal of <160 was targeted. Standard orders included acetaminophen for body temperature ≥100°F and regular insulin sliding scale with blood glucose draws every 4 to 6 hours. Repeat cerebral CT scans were routinely obtained after 24 hours or whenever a patient had neurological worsening. Symptomatic intracerebral hemorrhage (ICH) was defined as a homogenous area of hemorrhage on CT scan, with neurological deterioration defined as an increase in NIHSS of >2 points. Favorable outcome was defined as discharge home or to inpatient rehabilitation.

The Student t test and Fisher exact test were used to analyze differences between patients with MCA and ICA occlusion. The Wilcoxon rank sum test was used to analyze nonparametric data. P<0.05 was considered significant. All values are presented as mean±SD or median values.

Results
During the study period, 94 patients with acute ischemic stroke underwent emergent cerebral angiography for possible IAT of whom 50 patients that were found to have MCA or ICA occlusions were treated with endovascular mechanical clot disruption. Of these, 18 patients received simple mechanical clot penetration and 32 patients received AMCD. No demographic differences among the treatment groups were noted (Table 3).

Mean age of the AMCD treatment group (14 females, 18 males) was 59±14 years (median 57, range 26 to 78 years). Seventeen patients were non-Hispanic white, 7 Hispanic, and 8 Black. Baseline median NIHSS was 18 (range 6 to 26). Ninety-one percent of patients had at least 1 vascular risk factor (hypertension, CAD, hyperlipidemia, atrial fibrillation, diabetes mellitus, or smoking) and 59% of patients had 2 or more vascular risk factors. Thrombolytic regimens used were as follows: 22 combined IV rtPA/IA, 6 IAT, 3 IV rtPA, and 1 no thrombolytics. The interval from stroke onset to IA treatment median time was 261 minutes (range 162 to 714). Occlusion sites were MCA (n=16) and ICA (n=16). PTA was performed in 28 patients (5 of whom underwent additional snare maneuvers; 4, stent placement; and 1, stent placement plus AngioJet), aggressive microcatheter/microwire clot maceration in 2 patients, and snare device utilization in 2 patients (one of whom received aggressive microcatheter/microwire clot maceration).

Immediate recanalization occurred in 38% of patients and final recanalization was achieved in 75% of patients. In those patients with MCA occlusion, immediate recanalization occurred in 50%, and final recanalization was achieved in 88%, compared with 25% and 63%, respectively, in those patients presenting with ICA occlusion. Favorable outcome occurred in 59% (n=19) of patients of whom 6 patients were discharged home and 13 to an inpatient rehabilitation unit. Outcome in the remaining patients was as follows: 8 were discharged to a long-term care facility, 1 transferred to an acute care hospital and 4 became mortalities.

In contrast, of the 18 patients who received simple mechanical clot penetration, immediate recanalization occurred in only 1 patient, and final recanalization was achieved in 13 patients (72%). Favorable outcome occurred in 44% (n=8) of patients (1 discharge home, 7 acute inpatient rehabilitation).

No direct procedural complications were noted with AMCD. Symptomatic ICH was noted in 3 (9.4%) patients, and a total of 4 (12.5%) in-hospital deaths occurred. The 3 postprocedural symptomatic ICHs all occurred in patients who underwent cervical carotid recanalization with successful recanalization. Two of these patients underwent cervical carotid stenting with minimal residual lumen stenosis, and a third had PTA only with an 80% residual lumen stenosis.

Baseline characteristics were similar in the MCA and ICA occlusion groups, and no statistically significant difference in outcome measures were observed (Table 4). There was a positive trend for increased immediate and final recanalization rates, lower symptomatic hemorrhage, and mortality rates in the MCA occlusion group.

Discussion
Our study showed that AMCD may be carried out with overall safety comparable to nonaggressive methods. AMCD frequently results in immediate recanalization in patients who fail to respond to IV or IA thrombolytics. Immediate recanalization occurred in 38% of patients, further emphasizing the usefulness of this technique. In contrast, immediate recanalization rarely occurred with simple mechanical clot penetration.

Our rate of symptomatic hemorrhage and mortality is comparable to previously reported rates for thrombolytic therapy using IA and combination IV/IA routes.9,10,19 If those with acute cervical carotid artery recanalization were excluded, the rates of symptomatic ICH are particularly low. The hemorrhages in patients with ICA occlusion were felt to represent reperfusion injury after acute recanalization of atherosclerotic cervical internal carotid occlusions. Thus, cervical carotid occlusions may represent a particularly high-risk group of patients for postprocedure reperfusion hemorrhage, even if normal lumen diameter is not restored. Our mortality rate of 12.5% is lower than previously reported by Qureshi et al who observed a 36.8% mortality at 7 to 10 days after AMCD and low dose IAT for acute stroke patients that failed systemic thrombolytics or were poor candidates for thrombolytics.19

### TABLE 3. Demographics of Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire Population (n=94)</th>
<th>Simple Mechanical Clot Penetration (n=18)</th>
<th>AMCD (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>58 males, 36 females</td>
<td>14 males, 4 females</td>
<td>18 males, 14 females</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>60±15</td>
<td>62±15</td>
<td>59±14</td>
</tr>
<tr>
<td>Median (range), y</td>
<td>59 (26–88)</td>
<td>62 (39–85)</td>
<td>57 (26–78)</td>
</tr>
<tr>
<td>Baseline median NIHSS (range)</td>
<td>18 (3–39), n=90</td>
<td>17 (11–26), n=17</td>
<td>18 (6–26), n=30</td>
</tr>
<tr>
<td>≥1 vascular risk factor</td>
<td>90%</td>
<td>89%</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Notes:**
- SD: Standard Deviation
- NIHSS: National Institutes of Health Stroke Scale
- AMCD: Aggressive Microcatheter/MIcrowave Clot Disruption
- IAT: Intra-Arterial Therapy
- IV: Intravenous
- PTA: Percutaneous Transluminal Angioplasty
Our data parallels previous research evaluating safety and efficacy of IAT for the treatment of acute ischemic stroke.9,25,29 Our data compares favorably to the Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial which reported a symptomatic ICH rate of 10% and mortality of 24%. The PROACT II patients had a median NIHSS score of 17, median time from onset of symptoms to initiation of IA was 5.3 hours, compared with our population with a median NIHSS score of 18 and time to treatment of 4.4 hours. In PROACT II, recanalization rates were 66% after the 2-hour infusion (pro-urokinase) for the treatment group versus 18% for the placebo group, compared with 75% in our patients.9 If we look at the subgroup of our patients with MCA occlusion, the recanalization rate was 87.5%, mortality 6.3%, and symptomatic ICH 0%.

One of the most important predictors of clinical success with IV rtPA is time to treatment, which is a surrogate marker for time to restoration of blood flow, a critical parameter for determining treatment success.3,5,18 A unique aspect of AMCD is the dramatic impact on immediate recanalization. Fifty-nine percent of our patients had favorable outcome, which may be attributable to high recanalization rates achieved in our study.

### TABLE 4. Clinical and Angiographic Characteristics of Mechanical Clot Disruption Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Simple Mechanical Clot Disruption (n=18)</th>
<th>MCA (n=16)</th>
<th>ICA (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)±SD</td>
<td>62.4±15.4</td>
<td>56.6±15.9</td>
<td>60.5±11.6</td>
<td>0.43*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>61.5 (39–85)</td>
<td>55.5 (26–78)</td>
<td>57 (40–77)</td>
<td></td>
</tr>
<tr>
<td>Mean baseline NIHSS±SD</td>
<td>17.7±4.8</td>
<td>16.6±5.7</td>
<td>18.9±4.2</td>
<td>0.31†</td>
</tr>
<tr>
<td>Median (range)</td>
<td>17 (11–26)</td>
<td>17 (6–26)</td>
<td>19.5 (12–25)</td>
<td></td>
</tr>
<tr>
<td>Mean time from stroke onset to IA treatment (minutes)±SD</td>
<td>300±121.7 (5+2 hours)</td>
<td>277±125.9 (4.6±2.1 hours)</td>
<td>275±75.3 (4.6±1.3 hours)</td>
<td></td>
</tr>
<tr>
<td>Thrombolytics</td>
<td>13 IV rtPA/IAT</td>
<td>13 IV rtPA/IAT</td>
<td>9 IV rtPA/IAT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 IAT</td>
<td>3 IAT</td>
<td>3 IV rtPA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 IAT, 1 mechanical only</td>
<td></td>
</tr>
<tr>
<td>Occlusion segment</td>
<td>ICA (n=4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 type I</td>
<td>6 type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 type II</td>
<td>3 type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 type III</td>
<td>2 type III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 M1, 1 M2, 1 M3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total IA dose</td>
<td>Reteplase (n=9)</td>
<td>Reteplase (n=16)</td>
<td>Reteplase (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9±2.7 U</td>
<td>1.9±0.8 U</td>
<td>1.8±0.8 U</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urokinase (n=1)</td>
<td>Urokinase (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 million U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>None</td>
<td>12 PTA (2 w/snare), 2 aggressive wire catheter, 2 snare (1 w/aggressive wire catheter</td>
<td>16 PTA (3 w/snare, 5 w/stent placement)</td>
<td></td>
</tr>
<tr>
<td>Immediate recanalization</td>
<td>1 (5.5%)</td>
<td>8 (50%)</td>
<td>4 (25%)</td>
<td>0.27‡</td>
</tr>
<tr>
<td>Final TICI</td>
<td>TICI 0–1=5</td>
<td>TICI 0–1=2</td>
<td>TICI 0–1=6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TICI 2a=4</td>
<td>TICI 2a=3</td>
<td>TICI 2a=2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TICI 2b=4</td>
<td>TICI 2b=3</td>
<td>TICI 2b=4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TICI 2c=3</td>
<td>TICI 2c=6</td>
<td>TICI 2c=4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TICI 3=2</td>
<td>TICI 3=2</td>
<td>TICI 3=0</td>
<td></td>
</tr>
<tr>
<td>Final recanalization</td>
<td>13 (72.2 %)</td>
<td>14 (87.5%)</td>
<td>10 (62.5%)</td>
<td>0.22‡</td>
</tr>
<tr>
<td>Symptomatic hemorrhage</td>
<td>1 (5.5%)</td>
<td>0</td>
<td>3 (18.8%)</td>
<td>0.23‡</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (5.5%)</td>
<td>1 (6.3%)</td>
<td>3 (18.8%)</td>
<td>0.60‡</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>8 (44.4%)</td>
<td>10 (62.5%)</td>
<td>9 (56.3%)</td>
<td>0.74‡</td>
</tr>
</tbody>
</table>

The P value refers to a comparison between the MCA/ICA occlusion groups.

*Student t test.
†Wilcoxon rank sum.
‡Fisher exact test, 2-sided.

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Limitations
This study is a retrospective study with inherent limitations by design. Most importantly, the treatment regimen was not standardized, there was no randomized comparison group, and our sample size was small. Furthermore, follow-up brain imaging was not carried out routinely in every patient, so that hemorrhages that were not associated with significant clinical worsening may have been missed. Therefore, our results and conclusion should be considered preliminary. Acute stroke and endovascular therapies were performed under the direction of a veteran stroke treatment team and thus may not be generalizable to other settings. Even in our own center, the techniques and timing of AMCD have continued to evolve with increased experience. Finally, long-term outcome data needs to be determined.

Conclusion
AMCD appears safe to administer as an adjunct therapy to IAT in acute ischemic stroke patients and often results in immediate flow restoration. Early consideration of this technique during IAT may decrease time to flow restoration and improve recanalization rates and clinical outcomes in acute stroke patients.

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