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

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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. However, >50% of patients do not demonstrate a favorable clinical response. 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. Complete or partial early arterial recanalization during IV rtPA has been reported to lead to better 3-month outcome.

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. IAT may be superior to IV rtPA. 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.

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. 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. 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. 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 func-
tionally 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. Pa-
ients 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 assess-
ment 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
patients underwent emergent cerebral angiography for possible IAT
within 1 hour of IV rtPA. AMCD was considered in cases before
the IA procedure.26–28 Primary IAT was performed if patients had no recanalization or early arterial reocclusion by ultra-
sonic sound criteria or if there were 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
was inserted 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
following preprocedure. If successful recanalization was achieved (TICI
2a) and the patient was taken to the operating room for craniotomy and
thrombectomy, 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 mul-
tiple 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 interven-
tionalist 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 advanc-
ing 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.3 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 com-
pletion and review of the 24-hour cerebral CT for evidence of hemor-
rhage. 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

| Grade 0 | No perfusion beyond the occlusion |
| Grade 1 | Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory |
| Grade 2a | Partial perfusion with incomplete distal branch filling of <50% of the expected territory |
| Grade 2b | Partial perfusion with incomplete distal branch filling of ≥50%-99% of the expected territory |
| Grade 2c | Near complete perfusion without clearly visible thrombus but with delay in contrast run-off |
| Grade 3 | Full perfusion with normal filling of all distal branches of the expected territory in a normal hemodynamic fashion |

TABLE 2. ICA Occlusion-Segment Description

| Type I | Above ophthalmic artery involving M1 and A1, "T-Occlusion" |
| Type II | Above ophthalmic artery involving M1 or A1 but not both |
| Type III | Proximal to the ophthalmic artery but distal to the common carotid bifurcation |
| Ostium Origin of the ICA |
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 revascularization 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. If those with acute cervical carotid artery revascularization are excluded, the rates of symptomatic ICH are particularly low. The hemorrhages in patients with ICA occlusion were felt to represent reperfusion injury after acute revascularization 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.

**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>
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Our data parallels previous research evaluating safety and efficacy of IAT for the treatment of acute ischemic stroke.29,25,9 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>
<thead>
<tr>
<th>TABLE 4. Clinical and Angiographic Characteristics of Mechanical Clot Disruption Groups</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Mean age (years)± SD</td>
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<tr>
<td>Median (range)</td>
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<tr>
<td>Mean baseline NIHSS± SD</td>
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<td>Median (range)</td>
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<td>Mean time from stroke onset to IA treatment (minutes)± SD</td>
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<tr>
<td>Thrombolytics</td>
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<tr>
<td>MCA (n=14)</td>
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<td>Occlusion segment</td>
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<td>Mean total IA dose</td>
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<tr>
<td>Adjunctive therapy</td>
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<td>Immediate recanalization</td>
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<td>Final TICI</td>
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<tr>
<td>Final recanalization</td>
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<tr>
<td>Symptomatic hemorrhage</td>
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<tr>
<td>Mortality</td>
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<td>Favorable outcome</td>
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*Student t test. †Wilcoxon rank sum. ‡Fisher exact test, 2-sided.
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 hematomas 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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