Is Bridging with Intravenous Thrombolysis of Any Benefit in Endovascular Therapy for Acute Ischemic Stroke?

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Key words
- Acute ischemic stroke
- Bridging
- Intra-arterial therapy
- Tissue plasminogen activator

Abbreviations and Acronyms
EMS: Emergency Management of Stroke
IA: Intra-arterial
ICA: Internal carotid artery
IMS: Interventional Management of Stroke
IV: Intravenous
MCA: Middle cerebral artery
mRS: Modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
sICH: Symptomatic intracranial hemorrhage
TIMI: Thrombolysis in Myocardial Infarction
tPA: Tissue plasminogen activator

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OBJECTIVE: **Large vessel occlusions with heavy clot burden are less likely to improve with intravenous (IV) thrombolysis alone. The purpose of this study was to show whether a combination of IV thrombolysis and endovascular therapy was superior to endovascular treatment alone.**

METHODS: **Data for 104 patients with acute large artery occlusion treated between 2005 and 2010 were reviewed. Forty-two received endovascular therapy in combination with IV thrombolysis (bridging group), and 62 received endovascular therapy only. Clinical outcome, mortality rate, and symptomatic intracranial hemorrhage (sICH) rate were compared between the two groups.**

RESULTS: **The two groups had similar demographic and vascular risk factor distribution, as well as National Institutes of Health Stroke Scale score on admission (mean ± SD: 14.8 ± 4.7 and 16.0 ± 5.3; $P = 0.23$). No difference was found in Thrombolysis in Myocardial Infarction recanalization rates (score of 2 or 3) after combined or endovascular therapy alone (83.33% and 79.03%; $P = 0.585$). Favorable outcome, defined as a modified Rankin Scale score of <2 at 90 days, also did not differ between the bridging group and the endovascular-only group (37.5% and 32.76%; $P = 0.643$). There was no difference in mortality rate (19.04% and 29.03%; $P = 0.5618$) and sICH rate (11.9% and 9.68%; $P = 0.734$). A significant difference was found in mean time from symptom onset to treatment in the bridging group and the endovascular-only group (227 ± 88 min vs. 125 ± 40 min; $P < 0.0001$).**

CONCLUSION: **Combining IV thrombolysis with endovascular therapy resulted in similar outcome, revascularization, sICH, and mortality rates compared with endovascular therapy alone. Prospective clinical studies comparing both treatment strategies in acute ischemic stroke are warranted.**

INTRODUCTION

Numerous studies have demonstrated the benefit of intravenous (IV) tissue plasminogen activator (tPA), the only therapy approved by U.S. Food and Drug Administration the for improving outcome of acute ischemic stroke, regardless of ischemic stroke subtype (13). Although differences persist regarding the optimal time window for administration of such therapy, clear benefit has been shown if therapy is initiated within 3 hours of the onset of symptoms (1).

Careful patient selection may allow for less-stringent timing requirements, but earlier intervention is often correlated with better outcomes (19, 20). According to a pooled analysis of several trials, patients receive the greatest benefit from thrombolytic therapy when treatment is initiated within 90 minutes, and time from symptom onset to treatment is an independent predictor of favorable outcome after IV thrombolysis (5).

Although recanalization of a blood vessel does not strictly equal reperfusion, imaging outcomes support a positive response to successful re-establishment of flow (14). Therapy can be life-saving if recanalization is achieved, but rates of partial or complete recanalization in large vessel occlusions with IV tPA alone—the only therapy approved by the U.S. Food and Drug Administration for the treatment of acute stroke—have been shown to be as low as 6% for internal carotid artery (ICA) terminus occlusions. Several studies have shown that the site of occlusion (whether ICA, middle cerebral artery [MCA], or basilar artery) in part determines the response to IV thrombolysis (16). In summary, patients with heavy clot burden in large vessels are less likely to experience improvement with current IV thrombolysis therapy. Therefore, it has been proposed that intra-arterial (IA) or combined IV-IA therapy might improve outcomes for such patients with greater National Institutes of Health Stroke Scale (NIHSS) scores (11).

This study was designed to compare outcomes of bridging therapy with IV tPA

in conjunction with endovascular therapy versus an endovascular approach alone in the management of patients presenting within 3 hours of symptom onset with large vessel occlusion of the anterior or posterior circulation. In a recent study authors compared IV tPA only versus bridging therapy (12); however, to our knowledge, this is the first study to compare bridging therapy with endovascular therapy alone in which treatment in the endovascular-only group was initiated within the first 3 hours of symptom onset in acute large vessel occlusions and the endovascular therapy was not limited to IA tPA, as was the case in an early bridging trial (9).

METHODS

We conducted a retrospective review of charts at the Stroke Care Center at Millard Fillmore Gates Circle Hospital from the years 2005 through 2010 to identify all cases of acute ischemic stroke with large vessel occlusion, defined as occlusion of the internal carotid, vertebral, basilar, or proximal first or second branch (MCA, anterior cerebral artery, or posterior cerebral artery) arteries, documented on admission by computed tomographic angiography. Only patients presenting within 3 hours of symptom onset were included in the analysis. Records of those patients meeting these inclusion criteria were retrieved. None of those patients participated in other investigational trials. The patients were then divided into two groups. The endovascular-only group received endovascular therapy with IA tPA and/or thrombectomy with the Merci retrieval system (Concentric Medical, Mountain View, California, USA) or the Penumbra system (Penumbra Inc., Alameda, California, USA) within the first 3 hours of symptom onset, without IV thrombolysis. Because data defining IV thrombolysis failure are still lacking, our study bridging group received either full-dose (0.9 mg/kg) or two-thirds-dose (0.6 mg/kg) IV tPA thrombolysis within 3 hours of symptom onset followed shortly afterwards by IA therapy with tPA and/or the Merci retrieval system or the Penumbra system.

Patients who presented to our center with strokes because of large-vessel occlusion by high-burden clot were evaluated by a team of neurologists and interventional neurosurgeons. The team's decision to proceed with endovascular therapy versus bridging therapy was individualized on a case-by-case basis depending on the proximity of the clot, the severity of the stroke (NIHSS score of 8 or greater) and contraindication to thrombolysis treatment. Moreover, endovascular therapy was administered in patients in whom IV thrombolysis failed.

The primary outcome of interest was the modified Rankin Scale (mRS) score at 90 days in each group. The secondary outcomes of interest in the two groups included revascularization rates measured by comparing Thrombolysis In Myocardial Infarction (TIMI) scores immediately post treatment, NIHSS scores at discharge, mRS scores at discharge, procedure-related symptomatic intracranial hemorrhage (sICH) rates (defined by the European Cooperative Acute Stroke Study III criteria (6) as any intracranial hemorrhage with 4-point worsening of the NIHSS score), and mortality.

SAS software version 9.2 (SAS Institute, Inc., Cary, North Caroline, USA) was used to perform the desired statistical analysis. The NIHSS score was treated as a continuous variable. A simple two-sample *t*-test was performed to compare the NIHSS score between the two groups. The mRS score was categorized as favorable if the score was 0 (no disability), 1, or 2 and poor if the score was 3, 4, 5, or 6 (death). The χ^2 test of independence was used to compare the total improvement in each group after treatment. The χ^2 test was also used to test the improvement in the recanalization rate between the two groups and compare the mortality rate between the two groups. Subjects were then stratified into three groups depending on the dose of tPA received: none, two-thirds dose, and full dose. One-way analysis of variance was used to compare the means of the recanalization time among the three groups. Because 25% of the values in the tables of comparison of sICH were expected to have counts of <5, the Fisher exact test was used for that analysis. The Institutional Review Board at the University at Buffalo approved this retrospective study (Project #NEU318011E), and a standard Health Insurance Portability and Accountability Act-compliant protocol was followed. Work was conducted at the former Millard Fillmore Gates Circle Hospital/Kaleida Health in Buffalo, New York, USA.

RESULTS

Clinical and Treatment Characteristics

A total of 104 patients were included in the study. The occlusion sites were: anterior cerebral artery, 1; ICA, 30; MCA, 45; and posterior circulation, 28. Among the study patients, 62 patients in the endovascular-only group received acute therapy with IA tPA and/or the Merci retrieval system or the Penumbra system. In the bridging group, consisting of 42 patients, 11 patients received two-thirds-dose IV tPA and the rest received full-dose IV tPA before endovascular therapy (i.e., IA tPA and/or Merci or Penumbra). The mean patient age in the endovascular-only group was 69.26 years (±15.76 years), which was similar to the mean age in the bridging group, 67.64 years (±14.85 years; $P = 0.601$). The percentage of women was also similar in the two groups (53.23% vs. 52.38%; $P = 0.932$). Stroke risk factors between the two groups were similar (**Table 1**).

The NIHSS score upon admission did not differ statistically between groups (16 ± 5.37 endovascular-only vs. 14.78 ± 4.7 bridging, $P = 0.23$). The degree of occlusion upon presentation in the two groups, estimated by the TIMI score, was also very similar in the two groups. The mean time from symptom onset to catheterization for angiography was significantly longer in the bridging arm because of the time elapsed from the initiation of IV thrombolytic therapy until the patient was taken to the angiography suite for endovascular therapy (121.9 ± 36.78 endovascular-only vs. 227.8 ± 88 bridging, $P < 0.0001$). Applying the combined therapy delayed the onset of the IA therapy by approximately 100 minutes.

Primary and Secondary Clinical Outcome

Six patients (two in the endovascular group and four in the bridging group) were lost to follow-up; thus, they were not included in the 90-day outcome analysis. There was a tendency for a better mRS score at 90 days in the bridging group with 37.5% of those patients ($n = 40$) achieving good outcome versus 32.76% in the endovascular-only group ($n = 58$). However, this result was not statistically significant ($P = 0.64$). In the bridging group, there was also a tendency for a lower mortality rate at discharge (8 deaths among 42 patients [19.04%] vs. 18 among 62 patients [29.03%] in the endovascular-only group). However,