Intra-Arterial Alteplase Thrombolysis during Mechanical Thrombectomy for Acute Ischemic Stroke

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Background: Intra-arterial alteplase (IA tPA) is commonly used during mechanical thrombectomy for acute ischemic stroke in patients with large-vessel occlusion, but specific indications and applications for its use remain undefined. *Methods:* We analyzed 40 patients who underwent stent-retriever mechanical thrombectomy, 28 of whom received adjunctive IA tPA. To our knowledge, this is the largest cohort with this concomitant treatment reported in the literature in the post-mechanical thrombectomy trial era. *Results:* Between patients with and without IA tPA, rates of hemorrhagic conversion, neurologic outcome, and mortality were equivalent, with a trend toward improved angiographic revascularization observed in the IA tPA group. *Conclusions:* IA tPA is a safe adjunct to mechanical thrombectomy, and more investigation is warranted to understand ideal indications and dosage methodologies. **Key Words:** Ischemic stroke—large-vessel occlusion—endovascular therapy—mechanical thrombectomy—tPA—alteplase—intra-arterial thrombolysis—stentriever.

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Introduction

First described in 1983, intra-arterial (IA) thrombolysis was used as a stand-alone treatment of acute ischemic stroke in the early years of neuroendovascular intervention.[1] After almost 2 decades without consensus, the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study became the first randomized controlled trial of IA chemical thrombolysis as a primary intervention; however, it did not lead to FDA approval of the treatment modality.[2] Additionally, with the preceding publication of the National Institute of Neurological Disorders and Stroke (NINDS) tPA study, many believed that IA therapy may not play a meaningful role in the effective treatment of ischemic stroke.[3]

Despite growing research efforts into endovascular stroke treatment since the landmark mechanical thrombectomy (MT) trials demonstrated efficacy of this modality in selected patients, the role of concomitant IA alteplase (tPA) treatment has not been clearly defined in the literature in the MT era.[4-8] Furthermore, when discussed, significant variations in administration strategies and dosages have been reported. To address these questions, we analyzed patients who underwent stent retriever MT for acute ischemic stroke who also received adjunctive

IA tPA. To our knowledge, this study involved the largest cohort in the literature.

Methods

Patients/Procedure

All patients who underwent MT for large-vessel occlusion (LVO) by senior authors (WWA and AT) between January 2015 and March 2016 were included in the analysis. Procedures for treatment of anterior circulation LVO were initiated with the goal of obtaining revascularization within 6 hours of symptom onset. Intravenous (IV) tPA was administered when indicated, and when IV tPA was not given, procedural heparinization was targeted to an activated clotting time (ACT) >200. The Solitaire (Medtronic Inc., Dublin, Ireland) stent retriever device (stentriever) with Penumbra (Penumbra, Inc., Alameda, CA) aspiration was used in all cases. IA tPA was used in a standardized fashion in one senior author's practice (5 mg at 3 time points during the procedure: (1) upon catheterization of the cervical internal carotid artery, (2) at stentriever clot engagement, and (3) postrecanalization). The other senior author used IA tPA at his discretion, commonly for patients who had not received IV tPA or who had a hard clot.

Radiographic Assessments

Pre- and postprocedural angiographic revascularization was assessed by the operating neurointerventionalist in real-time using the standard thrombolysis in cerebral infarction (TICI) grading system.[9] An immediate postprocedural computed tomography brain scan was obtained. When not contraindicated, a magnetic resonance imaging brain study was obtained within 24 hours of the procedure. Computed tomography and magnetic resonance imaging were reviewed by the operating neurointerventionalist and an independent radiologist to determine the presence of intracranial hemorrhage. Symptomatic hemorrhages were noted when patients had a decline in neurologic examination related to the postprocedural intracranial hemorrhage based on size and location, per the Heidelberg bleeding classification.[10]

Study Design

The study was conducted with approval of the university's institutional review board (LU No. 208269). Nonrandomized data, prospectively collected in the Loyola Neuroscience Stroke Database, were retrospectively analyzed by univariable comparisons between cases with and without IA tPA, using Fisher's exact test for gender and receipt of IV tPA. An exact version of the Wilcoxon rank sum test was used to compare age, differences in National Institutes of Health Stroke Scale (NIHSS) scores, minutes from ictus to revascularization, and minutes from groin to revascularization. An ordinal logistic regression model was used to assess whether those without IA tPA were more likely to receive an unsuccessful postprocedure TICI score (defined as = 0, 1, or 2a) when compared with those patients who received IA tPA.

Results

Forty patients with LVO that caused ischemic stroke who met endovascular intervention criteria underwent MT with or without IA tPA infusion. The median presenting NIHSS score was 19, without a difference between the 2 groups. All patients had presenting TICI grades of 0 on pre-thrombectomy angiogram. Of 40 patients, 28 received IA tPA during MT. Twenty-four of the 40 received IV tPA before MT, and 15 of those patients received both IV and IA tPA. Of note, all 3 patients with posterior circulation LVO received IA tPA. Of 37 successfully revascularized patients, the median ictus-to-revascularization time was 290 minutes, and the median groin-to-revascularization time was 56 minutes. Gender, age, initial NIHSS score, receipt of IV tPA, and revascularization time (all $P > .20$) were comparable between the 2 groups (Tables 1 and 2).

Approximately 96% of the IA tPA group and 84% of the non–IA tPA group were TICI 2b or 3 post-thrombectomy, representing successful revascularization. A marginal association, although not statistically significant, was noted between postprocedure TICI grade and receipt of IA tPA (Table 2).

Six postprocedural intracranial hemorrhages were visualized on follow-up imaging, with 3 in the IA tPA group. All of these hemorrhages occurred within an area of infarction. Three of the 6 post-thrombectomy hemorrhages were hematomas with Heidelberg bleeding classification scores of 2. Two of those 3 had radiographic evidence of associated mass effect and were symptomatic, with decline in neurologic examination. One of 2 patients with symptomatic hemorrhage received IA tPA (Table 3). Three inpatient mortalities occurred; 2 patients were unable to be revascularized, and care was withdrawn from the third patient to comply with family wishes. At discharge, the average NIHSS score was 6, with average improvement in NIHSS score of 8 points across both groups. No statistically significant differences were observed between groups regarding postprocedural hemorrhage, clinically significant hemorrhage, mortality, or improvement in NIHSS scores (Table 2).

Discussion

Over the past 4 decades, the landscape of stroke treatment has changed dramatically. Although many believed IA treatment would drive clinical practice, the NINDS tPA trial indicated that IV tPA was the gold standard in stroke care.[3] Published in 2013, the Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) trial was designed to directly compare IV tPA and endovascular intervention, consisting of MT when an LVO was noted