Original Paper

Clinical and Imaging Outcomes of Endovascular Therapy in Patients with Acute Large Vessel Occlusion Stroke and Mild Clinical Symptoms

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Keywords

Acute ischemic stroke · Endovascular stroke therapy · Outcomes · Reperfusion · Safety

Abstract

Background: The minimal stroke severity justifying endovascular intervention remains elusive. However, a significant proportion of patients presenting with large vessel occlusion stroke (LVOS) and mild symptoms go untreated and face poor outcomes. We aimed to evaluate the clinical outcomes of patients presenting with LVOS and low symptom scores (National Institutes of Health Stroke Scale [NIHSS] score ≤ 8) undergoing endovascular therapy (ET).

Methods: We performed a retrospective analysis of a prospectively collected ET database between September 2010 and March 2016. Endovascularly treated patients with LVOS and a baseline NIHSS score ≤ 8 were included. Baseline patient characteristics, procedural details, and outcome parameters were collected. Efficacy outcomes were the rate of good outcome (90-day modified Rankin Scale score 0–2) and of successful reperfusion (modified Treatment in Cerebral Infarction [mTICI] score 2b–3). Safety was assessed by the rate of parenchymal hematoma (parenchymal hematoma type 1 [PH-1] and parenchymal hematoma type 2 [PH-2]) and 90-day mortality. Logistic regression was used to identify predictors of good clinical outcomes. **Results:** A total of 935 patients were considered; 72 patients with an NIHSS score ≤ 8 were included. Median [IQR] age was 61.5 years [56.2–73.0]; 39 patients (54%) were men. Mean (SD) baseline NIHSS score, computed tomography perfusion core volume, and ASPECTS were 6.3 (1.5), 7.5 mL (16.1), and 8.5 (1.3), respectively. Twenty-eight patients (39%) received intra-

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venous tissue plasminogen activator. Occlusions locations were as follows: 29 (40%) proximal MCA-M1, 20 (28%) MCA-M2, 6 (8%) ICA terminus, and 9 (13%) vertebrobasilar. Tandem occlusion was documented in 7 patients (10%). Sixty-seven patients (93%) achieved successful reperfusion (mTICI score 2b–3); 52 (72%) had good 90-day outcomes. Mean final infarct volume was 32.2 ± 59.9 mL. Parenchymal hematoma occurred in 4 patients (6%). Ninety-day mortality was 10% ($n = 7$). Logistic regression showed that only successful reperfusion (OR 27.7, 95% CI 1.1–655.5, $p = 0.04$) was an independent predictor of good outcomes. **Conclusion:** Our findings demonstrate that ET is safe and feasible for LVOS patients presenting with mild clinical syndromes. Future controlled studies are warranted.

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Introduction

Endovascular therapy (ET) has recently become the standard of care for patients presenting early in the therapeutic window with anterior circulation large vessel occlusion stroke (LVOS) [1]. Despite this, the minimal stroke severity justifying the risks inherent to this invasive procedure remain elusive. A 2016 meta-analysis of the five major randomized controlled ET trials found no significant treatment benefit amongst patients presenting with a National Institutes of Health Stroke Scale (NIHSS) score ≤ 10 [2].

Treatment of patients suffering from mild stroke symptoms with intravenous tissue plasminogen activator (tPA) also remains controversial. Nearly one-third of patients are not treated with intravenous tPA due to mild or rapidly improving symptoms [3, 4]. Previous reports have addressed the potential benefit of intravenous tPA and/or ET for low NIHSS score given the outcomes of untreated patients, with the greatest potential for benefit amongst those patients with lower symptom severity and imaging-proven LVOS; however, the data on treated cohorts are limited by small sample sizes and the inclusion of patients with lacunar disease [5–11]. Thus, we set out to evaluate the clinical and imaging outcomes of a cohort of endovascularly treated LVOS patients presenting with initial mild symptoms (NIHSS score ≤ 8).

Methods

Patient Selection and Outcome Measures

We reviewed a prospectively collected LVOS ET registry ($n = 935$) at the Grady Memorial Hospital Marcus Stroke & Neuroscience Center, a tertiary care academic institution, spanning September 2010 through March 2016 for patients with lower symptom scores, defined as a baseline NIHSS score ≤ 8 . This study was approved by the Emory University Institutional Review Board.

Demographic data as well as procedural and outcome parameters were collected. Computed tomography perfusion (CTP) encompassing 8 cm of brain coverage was evaluated with a fully automated software environment (RAPID version 4.5.0; iSchemaView, Menlo Park, CA, USA). The infarcted tissue volume (ischemic core) was defined by a voxel relative cerebral blood flow of $<30\%$ of the normal tissues. The total hypoperfused volume was defined by >6 s delay in the time to maximum of the tissue residue function, and a penumbral volume of at risk tissue was defined by the difference between total hypoperfused and ischemic core tissue estimates.

The primary outcome was the rate of favorable clinical outcome, defined as a 90-day modified Rankin Scale (mRS) score of 0–2. Secondary outcomes included the rate of successful reperfusion, defined as a modified Treatment in Cerebral Infarction (mTICI) score of 2b–3, and final infarct volume (FIV) [12]. Safety outcomes were defined as the rate of 90-day mortality and the rate of significant hemorrhagic transformation. Significant hemorrhage included any symptomatic parenchymal hematoma and parenchymal hematoma type 2 (PH-2), defined as bleeding occupying $>30\%$ of the infarcted area; parenchymal hematoma

Table 1. Baseline clinical and imaging characteristics of the patients ($n = 72$)

Variable	
Baseline characteristics	
Age, years	63.3 ± 15.9
Male	39 (54.2%)
White	42 (58.3%)
Hypertension	53 (73.6%)
Diabetes	22 (30.6%)
Dyslipidemia	28 (38.9%)
Atrial fibrillation	25 (34.7%)
Admission systolic blood pressure, mm Hg	156.1 ± 40.6
Blood glucose, mg/dL	132.5 ± 55.8
Baseline NIHSS score	6.4 ± 1.5
Intravenous tPA given	28 (38.9%)
Imaging profile	
ASPECTS	8.5 ± 1.3
Core volume, mL	7.6 ± 16.1
Penumbra volume, mL	89.5 ± 70.9
Occlusion location	
MCA-M1	29 (40.3%)
MCA-M2	20 (27.8%)
ICA terminus	6 (8.3%)
Extracranial internal carotid artery	11 (15.3%)
Vertebrobasilar	9 (12.5%)
Procedure characteristics	
Last known normal time to groin puncture, h	10.3 ± 8.4
Procedure length, min	71.0 ± 43.4
Last known normal time to reperfusion, h	10.5 ± 7.6
Stent retriever	49 (68.1%)
Monitored anesthesia care	56 (77.8%)

Values are presented as mean ± SD or n (%). NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

type 1 (PH-1) was defined as bleeding occupying <30% of the infarcted area, as per the European Cooperative Acute Stroke Study criteria [13].

The imaging outcome of FIV was documented on follow-up magnetic resonance imaging, preferentially, or non-contrast computed tomography within 5 days of treatment. FIV was measured using a previously reported, semi-automated approach (<http://imagej.nih.gov/ij/>) [14].

Statistical Analysis

The Shapiro-Wilk test was used to assess normality. Continuous variables were reported as mean (SD) if normally distributed or as median [IQR] if nonparametric. Categorical variables were reported as proportions. Logistic regression models for predictors of good outcomes were developed by backward selection, with presentation NIHSS score, age, pretreatment glucose levels, time from symptom onset to treatment, and reperfusion status as predictors.

Significance was set at $p < 0.05$; all p values were two-sided. Statistical analysis was performed using IBM® SPSS® Statistics 23 (IBM, Armonk, NY, USA).

Results

Over the study period, 72 patients qualified for the study and underwent primary analysis. Baseline characteristics and imaging parameters are described in Table 1. Patients had a median [IQR] age of 61.5 years [56.2–73.0]; 39 (54%) were men. The mean baseline NIHSS

Table 2. Outcomes of the 72 patients with a baseline NIHSS score ≤ 8 treated with endovascular therapy

Variable	
Successful reperfusion (mTICI 2b–3)	67 (93.1%)
Full reperfusion (mTICI 3 only)	31 (43.1%)
Favorable clinical outcomes (90-day mRS score 0–2)	52 (72.2%)
Any parenchymal hematoma	4 (5.6%)
90-day mortality	7 (9.7%)
Final infarct volume, mL	32.2 $\pm$ 59.9

Values are presented as mean $\pm$ SD or *n* (%). mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale.

Fig. 1. Distribution of 90-day clinical outcomes for 72 mild large vessel occlusion stroke patients treated with endovascular therapy. mRS, modified Rankin Scale.

score was 6.3 ± 1.5 , with a mean baseline CTP core volume of 7.5 ± 16.1 mL. Twenty-eight patients (39%) received intravenous tPA.

Successful reperfusion (mTICI score 2b–3) was achieved in 67 patients (93%), with 31 (43%) achieving full mTICI score 3 reperfusion. Ninety-day outcomes were available for 66 patients; of these, favorable clinical outcomes were found in 52 patients (78.8%), and of these, 16 (24.2%) were symptom-free (mRS score 0) (Table 2; Fig. 1).

Four patients (6%) developed parenchymal hematomas (2 each PH-1 and PH-2), none of which were symptomatic. The 90-day mortality was 9.7% (7 patients), including 1 patient who died following acute MI during hospitalization and another secondary to mesenteric ischemia.

Fifty-seven patients had technically adequate discharge and/or 5-day follow-up imaging. The mean FIV was 32.2 ± 59.9 mL. Amongst the 47 patients who underwent CTP prior to treatment, the average volume of salvaged penumbra, defined as the presentation mismatch volume less the FIV, was 65.0 mL. Twenty-five of these 47 patients (53%) with pretreatment CTP and follow-up imaging had infarction expansion, with a median infarct growth of 7.9 mL.

Multivariable regression analysis showed that only successful reperfusion (OR 27.7, 95% CI 1.1–655.5, $p = 0.04$) was an independent predictor of good outcomes (Table 3).

Discussion

To our knowledge, this study represents the largest published series of endovascularly treated low NIHSS score stroke patients, showing that ET can safely and reliably lead to successful reperfusion and minimal infarction expansion in patients with less severe initial LVOS symptoms.

Table 3. Results of multivariable logistic regression predicted favorable clinical outcomes (mRS score 0–2)

Variable	OR	95% CI	<i>p</i>
Age	0.929	0.862–1.001	0.05
Glucose	0.995	0.977–1.013	0.56
Procedure length	1.002	0.988–1.015	0.83
Monitored anesthesia care	6.52	0.830–51.19	0.75
Fully reperfused (mTICI 2b–3)	27.729	1.173–655.53	0.04

mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction.

These findings complement our prior pilot prospective intention-to-treat analysis of thrombectomy versus medical management for patients with an NIHSS score ≤ 5 , which found a statistically significant discharge NIHSS score shift favoring ET-managed patients (-2.5 vs. 0 , $p = 0.01$) and numerically higher rates of good outcomes [15].

Amongst patients presenting within the therapeutic window, the most common reason for not undergoing thrombolysis is mild or rapidly improving symptoms [4, 16]. While historically thought to be a relatively benign condition, more recent data have shown that even these putatively minor strokes, if untreated, lead to higher rates of early neurologic decline, requiring rescue thrombectomy in up to 40% of patients, as well as lower rates of favorable clinical outcomes and independence, compared to patients receiving thrombolysis, ET, or both, with the greatest trend towards poor outcomes amongst untreated patients with an NIHSS score of 5–7 [5, 8, 15, 17].

While our mortality rates were slightly higher than those in previous reports on mild stroke, prior studies often disproportionately evaluated patients with a very low initial NIHSS score or did not evaluate rates of hemorrhagic transformation. One study of 162 untreated patients (123 with a baseline NIHSS score of 1–2) found that 75% of patients had 90-day mRS outcomes of ≤ 1 and a 90-day mortality of 1.3%; however, only 9 low NIHSS score patients had imaging-proven LVOS, which was found to be an independent predictor of worse clinical outcomes [9, 18]. In comparison, our study presents results exclusively from angiographically proven LVOS patients.

One series of 41 untreated mild or rapidly improving patients found that 27% died during initial admission ($n = 2$) or were unable to be discharged home [11]. Another study of 136 untreated patients with an admission NIHSS score ≤ 5 found that 25% had early neurologic deterioration, defined as a 4-point increase in the NIHSS score; 90-day mortality was 4% [18].

On imaging, our cohort's mean FIV was 32.2 mL, with only 16 of the 72 patients with follow-up imaging (22%) having infarction expansion $>10\%$ over their initial presentation core volume, likely due to the very high rates of successful reperfusion in the current study (Fig. 2). While this final volume is larger compared to the mean volume of 11 mL in the 136-patient cohort of Khatri et al. [18], half of that study's population were lacunar stroke patients. Another key finding of this analysis is that reperfusion was the most significant predictor of favorable clinical outcomes, which is in keeping with historical findings that it is persistent occlusion that drives early neurologic deterioration in patients with mild or rapidly improving symptoms [10, 19, 20].

This study has several limitations mostly inherent to its retrospective design, relatively small sample size, and absence of a control group that would have allowed us to directly evaluate treatment effects. Additionally, the relatively high proportion of patients who received intravenous tPA prior to intervention may have influenced our results. However, given that these patients were subsequently endovascularly reperfused and that only reper-

Fig. 2. Case study. A 70-year-old male patient with a history of atrial fibrillation, hypertension, and coronary artery bypass graft presented with acute onset speech difficulty and right facial droop with a baseline NIHSS score of 5. **a** Computed tomography angiography revealed an occlusion in the distal MCA-M1. **b, c** Computed tomography perfusion showed a core of 15.3 mL (**b**) and viable hypoperfused penumbra of 154.5 mL (time to maximum of the tissue residue function >6 s) (**c**) [22, 23]. The patient subsequently underwent mechanical thrombectomy with successful reperfusion (mTICI score 2b). **d** Follow-up computed tomography on day 2 showed a final infarct volume matching the presentation core, with a final infarct volume of 15.8 mL. The hospital course was uncomplicated, and the patient was discharged home on day 3. The 90-day modified Rankin Scale score was 0.

fusion status was found to be associated with favorable clinical outcome in multivariable analysis, we feel this contribution to be minimal, given the recent study by Coutinho et al. [21], which found no significant difference in the rate of favorable 90-day clinical outcomes between those treated with ET and intravenous tPA and those treated with ET alone (OR 1.50, 95% CI 0.94–2.40, vs. OR 1.48, 95% CI 0.80–2.74, respectively).

Conclusions

We believe that the strengths of our analysis, especially its focus on patients with LVOS and low baseline NIHSS score, suggest that ET is acceptably safe in this patient population, with potential to reduce the loss of viable parenchyma and improve clinical outcomes. Future prospective controlled studies of this large subgroup of stroke patients are warranted.

Acknowledgments

This work was supported in part by the National Center for Advancing Transitional Sciences of the National Institutes of Health under award numbers UL1TR00454 and TL1TR000456. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. There was no funding by any other party.

Disclosure Statement

The authors declare no financial or other conflicts of interest.

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