

Mechanical Thrombectomy for Large Vessel Occlusion in Patients Presenting in Late Time Window

Ahmed Elbassiouny MD, PhD,¹ Mahmoud H Mohammaden, MD, MSc,^{2,3} Abeer Tony, MD, PhD,⁴ Radwa K Soliman MD, PhD,⁵ Ahmed Nasreldien MD, PhD,⁶ Abdallah K Mohamed MD, MSc,⁴ Eman Khedr, MD, PhD^{6,*}

¹Ain Shams University Faculty of Medicine, Department of Neurology, Cairo, Egypt

²Emory University School of Medicine, Department of Neurology, Marcus Stroke & Neuroscience Center, Grady Memorial Hospital Atlanta, GA, USA

³South Valley University Qena, Faculty of Medicine, Department of Neurology, Qena, Egypt

⁴Aswan University, Faculty of medicine, Department of Neurology, Sahary City, Egypt

⁵Assiut University, Faculty of Medicine, Department of Radiology, Assiut, Egypt

⁶Assiut University, Faculty of Medicine, Department of Neurology, Assiut, Egypt

Abstract

Background and Purpose— We sought to evaluate safety and efficacy of mechanical thrombectomy in patients with anterior circulation large vessel occlusion strokes presented after 6 hours of last known well and selected based on Diffusion Weighted Imaging (DWI)-Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on Magnetic Resonance Image (MRI).

Methods— Consecutive patients presented with large vessel occlusion strokes were enrolled from January 2019-August 2019 in two-stroke centers if they had anterior circulation ischemic stroke due to intracranial internal carotid artery (ICA) or proximal middle cerebral artery (MCA) occlusion and had a baseline DWI-ASPECTS >5. Patients underwent mechanical thrombectomy plus best medical management or best medical management alone depending upon the hospital of presentation. The primary outcome was the shift in the degree of disability at 90-day as measured by the modified Rankin scale (mRS). Secondary outcome was functional independence at 90-day (mRS 0-2). Safety measures were the rates of symptomatic intracranial hemorrhage (sICH) and 90-day mortality.

Results— Fifty-seven patients were eligible for the analysis. Demographics, and baseline clinical characteristics were similar between the patients who underwent mechanical thrombectomy (n=32) and control groups (n=25). Mechanical thrombectomy was associated with a favorable shift in the overall distribution of 90-day mRS (P<0.001, adjusted odds ratio; 7.985, 95% confidence interval (CI) [2.759-25.031], p<0.001). Similarly, patients who underwent mechanical thrombectomy had higher rates of functional independence (56.3% vs. 12%, p=0.001, adjusted odds ratio; 16.760, 95% CI [2.822-99.548], p=0.002) at 90 days. The rates of sICH and 90-day mortality were similar between the two groups.

Conclusions— We found that patients presenting after 6 hours of last well-known normal benefit from mechanical thrombectomy when selected based on Diffusion Weighted Imaging-ASPECTS.

Key words— Acute ischemic stroke, thrombectomy, diffusion-weighted imaging, ASPECTS, late time window, clinical trial

INTRODUCTION

Stroke burden in Egypt is high with an overall prevalence of 963/100 000 inhabitants.[1-3] Due to small number of comprehensive stroke centers and prominent delays in pre-hos-

pital and intra-hospital management of patients with acute ischemic stroke, a large proportion of patients present after 6 hours of symptom onset resulted in decreasing the chances of achieving mechanical thrombectomy in the early time window (within 6 hours of presentation). Two randomized

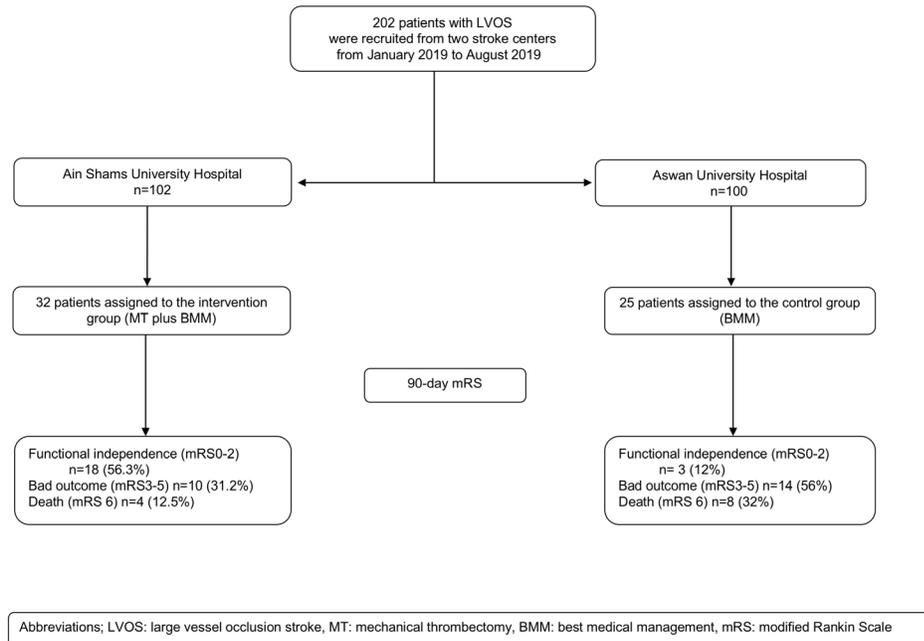


FIGURE 1: Patients flow chart.

controlled trials (RCTs) have demonstrated the safety and efficacy of mechanical thrombectomy in patients with anterior circulation large vessel occlusion strokes presented beyond 6 hours of last known well.[4,5] However, those trials included patients based on a mismatch between the severity of the clinical deficit and the infarct core volume that was assessed by automated software (RAPID, iSchemaView). The advanced imaging processing software is not readily available in developing countries due to the high cost. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was a previously validated tool to estimate early ischemic changes on non-contrast computed tomography (NCCT).[6] The diffusion-weighted imaging (DWI) magnetic resonance (MR) sequence is more sensitive than CT for the early detection of ischemic changes [7] which can be scored using DWI-ASPECTS. [8] and may offer a potential alternative for patient selection.

In this prospective study, we investigated for the first time in Egypt whether it is possible to safely expand the time window for mechanical thrombectomy and hence might improve clinical outcomes of patients presented with large vessel occlusion strokes in late time window using a selection criteria based on DWI-ASPECTS.

METHODS

Study Design

This is a prospective case-control clinical trial conducted in two-stroke centers in Egypt from January 2019 to August 2019 where mechanical thrombectomy was available in one center (Ain shams university hospital) at which patients were enrolled for mechanical thrombectomy if eligible and not available in the other center (Aswan university hospital) where eligible patients assigned for best medical management. The trial protocol was approved by the Medical Research Ethical

Committee at each participating site. Enrolled patients or their surrogates provided written informed consent.

Patients

Patients were included in the study if they were 18 years or older, had large vessel occlusion strokes due to intracranial internal carotid artery (ICA) and proximal middle cerebral artery (MCA), National Institutes of Health Stroke Scale (NIHSS) score of 10 or more, DWI-ASPECT score >5 and an interval between the time that the patient was last known well and presentation of 6-24 hours. Patients with a pre-stroke score of ≥ 2 on the modified Rankin scale (mRS)-a 7-point scale ranging from 0 (fully independent) to 6 (dead)-were excluded.

Mechanical thrombectomy and medical managements

Patients were assigned to mechanical thrombectomy plus best medical management (the thrombectomy group) or best medical management alone (the control group) as mentioned before. Patients underwent mechanical thrombectomy with stent-retrievers using either Trevo (Stryker Neurovascular, California, USA) or Solitaire (Medtronic Neurovascular, Minnesota, USA) according to device availability. Procedures were performed under monitored anesthesia care by experienced neurointerventionalist. For patients with stenosis or occlusion of the cervical ICA, carotid angioplasty with or without stenting was permitted as part of the intervention. Successful reperfusion was defined as the achievement of modified Thrombolysis In Cerebral Infarction (mTICI) score of 2b-3 at the end of the procedure. Patients in the control group received antiplatelet (150 mg, acetylsalicylic acid) and statin (atorvastatin 40 mg).

TABLE 1: Demographic, clinical characteristics and outcomes between the two groups.

	Mechanical thrombectomy group (n=32)	Control group (n=25)	P value
Age years median [IQR]	63 [48.8-70]	67 [56.5-73.5]	0.22
Female	17 (53.1)	12 (48)	0.70
Diabetes mellitus	14 (43.8)	11 (44)	0.99
Hypertension	14 (43.8)	13 (52)	0.54
Dyslipidemia	16 (50)	13 (52)	0.88
Current smokers	8 (25)	8 (32)	0.56
LKW-imaging (min) median [IQR]	510 [360-600]	480 [360-600]	0.91
Baseline NIHSS score mean \pm SD	20.2 \pm 4.5	21.2 \pm 4.7	0.41
DWI-ASPECTS mean \pm SD	8.9 \pm 1.2	9.1 \pm 0.8	0.78
Site of occlusion:			
Internal carotid artery	9 (28.1)	5 (20)	
Middle cerebral artery	23 (71.9)	20 (80)	0.48
Left sided lesion	14 (43.8)	9 (36)	0.55
Successful reperfusion (mTICI2b-3)	26 (81.3)	NA	NA
Outcome n (%)			
sICH	7 (21.9)	5 (20)	0.86
NIHSS score at discharge mean \pm SD	11.3 \pm 5.5	18 \pm 4.5	<0.001
90-day mRS	18 (56.3)	3 (12)	0.001
90-day mortality	4 (12.5)	8 (32)	0.10
Abbreviations used:			
IQR	Interquartile range		
LKW	Last Known Well		
NIHSS	National Institute of Health Stroke Scale		
IV-tPA	Intravenous tissue plasminogen activator		
DWI-ASPECTS	Diffusion Weighted Imaging-Alberta Stroke Program Early CT		
mTICI	modified thrombolysis in cerebral infarction		
sICH	symptomatic intracranial hemorrhage		
mRS	modified Rankin Scale		

Outcomes

The primary outcome was the shift in the degree of disability at 90-day as measured by mRS. A vascular neurologist who was blinded to the treatment arms evaluated patients. Secondary outcomes included NIHSS score at discharge and 90-day functional independence (defined as mRS 0-2). Safety measures included rates of symptomatic intracranial hemorrhage (sICH) defined as parenchymal hematoma leading to neurologic deterioration, as reflected by NIHSS score worsening of ≥ 4 points, and 90-day mortality.

Sample size calculation

Based on the rates of good outcome, functional independence (90-day mRS0-2) in the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial [5] (49% in the MT group vs. 13% in the control

TABLE 2: Results of multivariable regression analysis identifying predictors of functional independence (90-day mRS of 0-2).

	Odds Ratio	95% Confidence Interval	P value
Mechanical thrombectomy	16.760	2.822-99.548	0.002
Hypertension	0.069	0.011-0.435	0.004
Age	1.017	0.943-1.098	0.66
Baseline NIHSS score	0.877	0.744-1.033	0.12
Abbreviations used:			
NIHSS	National Institute of Health Stroke Scale		
mRS	modified Rankin Scale		

group) a calculated sample size of 25 participants in each group could give reliable results with type I error equal 0.05 and statistical power of 80%. [9]

Statistical analysis

The normality of distributions was assessed by the Shapiro-Wilk test, continuous variables were reported as mean \pm SD for parametric and median [interquartile range] for non-parametric variables. Categorical variables were reported as frequencies and percentages. Comparisons of continuous and ordinal variables were made with the Mann-Whitney U test or paired t-test as appropriate. Categorical variables were compared using Pearson χ^2 or Fisher exact test as appropriate. The shift in disability levels in mRS scores at 90-day was compared between cases and controls using the Wilcoxon signed-rank test. Multivariable regression analyses were performed to evaluate the association of different variables with functional independence. Variables with $P < 0.1$ in the univariate analysis were added to the analysis. Ordinal regression was computed for odds ratios (ORs) to assess the association between the intervention and mRS score after adjustment for the same confounding variables mentioned in table 2. Significance was set at $P < 0.05$, and all P values were 2-sided. Statistical analyses were performed using SPSS 26 software (IBM® Armonk, NY, USA).

Results

Among 202 patients who presented with large vessel occlusion strokes after 6 hours of last known well during the study period, 57 were eligible for inclusion in the study. (**Figure 1. Patients flow chart**).

Median [IQR] age (63 [48.8-70] vs. 67 [56.5-73.5] years, $p=0.22$) and last known well-imaging time (510 [360-600] vs. 480 [360-600] minutes, $p=0.91$) were comparable between patients in the mechanical thrombectomy group ($n=32$) and those in the control group ($n=25$). Similarly, there were no significant differences in mean baseline NIHSS score (20.2 \pm 4.5 vs. 21.2 \pm 4.7, $p=0.41$) and DWI-ASPECTS (8.9 \pm 1.2 vs. 9.1 \pm 0.8, $p=0.78$) between both groups. Also, other patients' demographics, stroke-related risk factors, and clinical characteristics were balanced between the patients who underwent thrombectomy and in control group (**Table 1**).

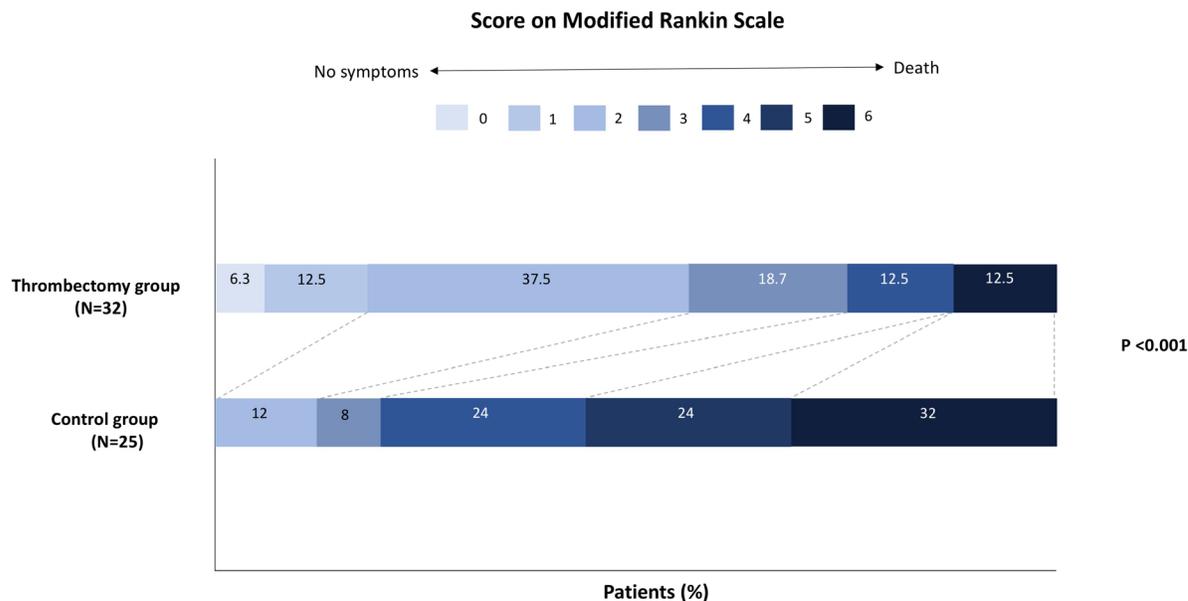


FIGURE 2: Distribution of modified Rankin scores at 90-Days.

Shown are scores on the modified Rankin scale for thrombectomy group and control group. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help, but able to walk unassisted; 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. A significant difference between both groups (Shift analysis by Wilcoxon signed-rank test).

Primary and secondary outcomes

Mechanical thrombectomy was associated with a favorable shift in the overall distribution of 90-day mRS ($P < 0.001$) (**Figure 2**). Multivariable ordinal regression analysis showed that mechanical thrombectomy was an independent predictor of a favorable shift in the overall distribution of 90-day mRS after adjustment for age, baseline NIHSS score, and hypertension (OR; 7.985, 95% CI [2.759-25.031], $p < 0.001$). Similarly, patients in the thrombectomy group had higher rates of functional independence (56.3% vs. 12%, $p = 0.001$, adjusted OR; 16.760, 95% CI [2.822-99.548], $p = 0.002$). Also, the mean NIHSS score at discharge was significantly lower in those who underwent mechanical thrombectomy (11.3 ± 5.5 vs. 18 ± 4.5 , $p < 0.001$) than the control group (**Tables 1 & 2**).

Safety measures

There were no significant differences in rates of sICH (21.9% vs 30%, $p = 0.86$) and 90-day mortality (12.5% vs. 32%, $p = 0.10$) across two groups (**Table 1**).

DISCUSSION

The present study demonstrated the safety and efficacy of MT in patients with anterior circulation large vessel occlusion strokes presented in late time window beyond 6 hours of last known well in whom the selection of patients was based on clinical/imaging mismatch assessed by DWI-ASPECTS.

Our study showed higher rates of functional independence (56.3%) compared to DIFFUSE3 [4] (45%) and DAWN [5] (49%) trials which could be explained by the shorter time from last known well to inclusion.

The hyperintense signal in DWI is evident within minutes of the onset of ischemic injury and occurs as the result of a reduction in the apparent diffusion coefficient of water and the development of cytotoxic edema.[10] Unlike hypodense lesions in CT, acute DWI lesions can be clearly delineated from surrounding normal brain tissue and areas of old infarction.[11] Moreover, it has been reported the significant correlation between DWI-ASPECTS and lesion volume DWI in the prediction of malignant core profile.[12] The fundamental concept underlying the eligibility of mechanical thrombectomy in the late time window is demonstration of viable brain tissue where good collaterals can maintain a salvageable brain tissue for extended time. Previous studies described the correlation between hyperintense lesion on DWI and degree of leptomeningeal collaterals where large DWI lesion size predicts malignant collateral profile and vice versa.[13, 14] The studied population had high DWI-ASPECTS with a mean value of 8.9 in the thrombectomy group and 9.1 in the control group.

We reported the safety of mechanical thrombectomy in the treatment arm where there were no significant differences in the rates of sICH (21.9% vs 30%, $p = 0.86$) and 90-day mortality (12.5% vs. 32%, $p = 0.10$) between the thrombectomy and control groups. The present study showed higher rates of sICH both in thrombectomy and control groups compared to DAWN (6% vs 3%) and DIFFUSE3 (7% vs. 4%) trials. However the rates of 90-day mortality were comparable to the two RCTs, 19% and 14%, respectively.[4, 5]

Our study has several limitations. First, the small sample size which limits studying the effect size of the treatment across different subgroups. Second, the selection bias of non-randomization where the thrombectomy group was enrolled from one center and the control group from another center

however, the baseline demographics and clinical characteristics were similar between both groups. Also, there may be other differences in overall care between the two hospitals that may affect the rates of functional independence at 90 days post treatment. Finally, there was no core laboratory adjudication of final reperfusion grades and DWI-ASPECTS.

CONCLUSION

Our results confirm that mechanical thrombectomy is a safe and effective treatment among patients with anterior circulation large vessel occlusion strokes who presented after 6 hours of last known well when selected using clinical/imaging mismatch (DWI-ASPECTS >5 and baseline NIHSS score ≥ 10). Moreover, we provide evidence of the successful applicability of mechanical thrombectomy in a developing country with a lack of resources and shortage of neurointerventionalists.

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CONFLICT OF INTERESTS

Authors report no conflict of interest.

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DATA SHARING

The unpublished data from this dataset is held by the corresponding author and available on reasonable request.