

The Impact of Time to Reperfusion on Recanalization Rates and Outcome After Mechanical Thrombectomy: A Single Center Experience

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Abstract

Background: Timely and effective recanalization to salvage the penumbra is the main determinant of outcome in acute ischemic strokes. Randomized controlled trials on late window mechanical thrombectomy (MT) have proved its safety and efficacy upto 24 h after stroke onset. We looked at the impact of time to reperfusion on vessel recanalization rates and short-term outcome in patients undergoing MT for large vessel occlusion. **Methods:** The clinical, imaging, and outcome of all patients undergoing MT upto 24 h from last seen normal was extracted from a prospectively maintained ischemic stroke database from January 2012 till September 2019. **Results:** There were 145 patients with a mean (SD) age of 58.2 (\pm 14) years. Of them, 28 had wake up/unknown time of onset stroke and 9 presented beyond >360 min. There were 23 vertebrobasilar strokes. Median National Institute of Health Stroke scale score (NIHSS) at admission was 16.4 (Inter quartile range (IQR) 12–21). CT-Alberta Stroke program early CT score (CT-ASPECTS) was excellent (8–10) in 39 (31.6%) and fair (5–7) in 77 (63.6%) patients in anterior circulation strokes. About 25% underwent bridging therapy. Recanalization rates did not differ between those presenting early (<6 h) versus wake up strokes and late presenting patients (81.79% vs 71.9%). Symptomatic Intracerebral hemorrhage (ICH) occurred in 5%. At 3 months, excellent outcome (modified rankin scale <2) was observed in 28.9%. While Admission NIHSS remained strong predictor of poor outcome at 3 months, delay in presentation did not impact MT outcome (37.5% vs 45.79% and $P = 0.460$). **Conclusions:** The recanalization rates were similar in patients irrespective of the time to reperfusion from stroke onset. The functional outcome was not inferior in late presenters selected by advanced imaging.

Keywords: Mechanical thrombectomy, multimodality imaging, outcome, recanalization, strokes of unknown time of onset, wake up strokes

INTRODUCTION

The incidence of acute ischemic strokes secondary to large vessel occlusions (LVO) ranges from 11% to 13% across studies.^[1,2] Among these patients with severe strokes, less than half often present within 6 h time window and a quarter may have favorable imaging features for reperfusion therapies, beyond the conventional time window. Imaging studies have also demonstrated the persistence of penumbra upto 24 h in proximal large artery occlusions,^[3] which has been translated into clinical practice with favorable results from late thrombectomy trials.^[4,5]

Acute stroke management in low-middle income countries pose more challenges, with delay in presentation to hospital, limited availability of multimodal neurovascular imaging, and access to endovascular therapy.^[6] With these limitations, actual benefit of revascularization in late time window patients outside the setting of a clinical trial needs to be studied further. We looked at the impact of time to reperfusion on vessel recanalization rates and short-term outcome in our hospital cohort of patients undergoing mechanical thrombectomy (MT) for LVO.

MATERIALS AND METHODS

The study was performed at Comprehensive Stroke care centre, Department of Neurology, Sree Chitra Tirunal Institute for

Medical Sciences and Technology, Trivandrum, a tertiary center for Neurological and Cardiovascular disorders. Methodology was retrospective data collection from a prospectively maintained MT database, maintained in the Stroke unit from January 2012 till date. Patients enrolled in the database from January 2012 till September 2019 with a 3-month completed follow-up were recruited. All the clinical details were collected from the medical records, including time of onset or when last seen normal and presenting time to our hospital. Imaging details were extracted by reviewing PACS. Ours is a CT-based imaging protocol for Acute ischemic stroke (AIS), with all

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patients undergoing noncontrast CT (NCCT), followed by CT angiography, unless there is a known contraindication for contrast where Magnetic resonance imaging (MR) is performed. CT perfusion is done for delayed presentation/wake up stroke patients routinely from 2015, unless Vertebrobasilar (VB) stroke is suspected where MR-based protocol is performed. Outcome at discharge and 3 months follow-up was measured using modified Rankin scale (mRS), with scores 0 and 1 taken as excellent outcome and 0, 1, and 2 as fair outcome. Follow-up details were extracted from stroke clinic out patient records wherever available or telephonically. The study was approved by Institutional ethics committee.

Statistical analysis was performed using SPSS software version 24 (SPSS Inc, Illinois, Chicago). Baseline variables were expressed in means and percentages. Chi-square test was used for testing significance of association between variables.

RESULTS

We had 145 patients during the study period who underwent MT (M:F 105:40) with mean age 58.57 (\pm 13.57) years. Of them, 28 presented with deficits on wake up/had unknown time of onset and 9 presented after 6 h of onset. Eighty five (58.22%) presented during office hours (8 AM to 6 PM). The clinical and imaging characteristics are given in Table 1. Mean onset to door time was 210 min (IQR 120–250). Twenty three had posterior circulation strokes. The mean National Institute of Health Stroke scale score (NIHSS) was 16.4 (IQR 12–21).

Of them 37 (25%) underwent bridging therapy. Mean door to needle time, groin puncture time, and groin puncture to recanalization time were 43, 64, and 47 min, respectively. At 24 h, hemorrhagic transformation was seen in 33 patients with symptomatic ICH in 8 subjects. Mean admission ASPECTS was 6.54 (IQR 5.2–8.3).

Most common etiology of stroke was cardioembolism. There were 17 in hospital mortality. The, admission NIHSS and baseline CT ASPECTS were predictive of excellent discharge outcome (mRS 0,1). Onset time (known vs unknown), stroke etiology, use of bridging therapy, and recanalization status did not have an impact on discharge outcome.

At 3 months, excellent outcome (mRS 0,1) was observed in 37 patients (28.9%), good outcome (mRS 0–2) in 58 patients (50.88%), and there were 8 deaths. Fourteen patients were lost to follow-up Table 2. Bivariate analysis of outcome predictors are given in Table 3. While admission NIHSS remained independent predictor of outcome, diabetes showed borderline significance on multivariate analysis and delay in presentation did not influence the 3-month outcome [Table 4].

DISCUSSION

With advances in acute stroke imaging, time-based eligibility criteria for deciding on reperfusion strategies is getting replaced with tissue based selection.^[7] This strategy is now

backed by robust scientific evidence also with favorable outcome reported in all the recent endovascular trials of delayed time window patients.

In low- and middle-income countries like India, challenges in delivering acute stroke reperfusion therapies are manifold. Prehospital delay remains the single most important reason for exclusion of patients from acute reperfusion strategies across the world, which holds true in low-income countries as well.^[8] Patients presenting within 3 h of AIS ranges from 25% to 29% in hospital-based studies from tertiary care centers of northern part of India.^[9,10] The utilization of reperfusion therapies remains low, with only 13% reported from tertiary academic hospitals across India.^[11] Due to these considerations, any therapy which can be administered to AIS patients presenting late which can improve outcome needs to be carefully studied weighing risks, cost, and benefit. Here, we studied the actual benefit of MT in real world settings, specially looking at the wake up and unknown time of onset strokes.

Among our cohort, mean time from onset till hospital arrival was a little over 3 h and 20% were wake up strokes. In a series of patients undergoing MT from western India, mean delay was comparable, with posterior circulation strokes presenting even later.^[12] Despite the prehospital delay, we could consistently achieve good quality measures in hospital with mean door to needle time of 43 min and door to groin puncture of around 1 h.

Around 20% of our patients had posterior circulation strokes, which has been observed in other hospital-based series as well.^[12] The fraction of patients receiving bridging therapy was lower in our population, in comparison to those reported from India and abroad. This could have been due to many presenting beyond the window and also major proportion being cardioembolic strokes, many being on anticoagulation.

With endovascular therapy, 75.8% of our AIS patients achieved excellent recanalization of Thrombolysis in cerebral infarction (TICI) Grade 2b/3, comparable to the recanalization rates reported in MT trials ranging from 58.7% to 88%, highest with use of solitaire device.^[13] The groin puncture to recanalization time, recanalization rates, and Symptomatic intracerebral hemorrhage (SICH) in our cohort was also similar to previous trials and did not differ between late versus early arrival patients.

We found that admission NIHSS was an independent predictor of excellent and fair outcome at 3 months, while patients with prior stroke and diabetes tended to have a less favorable outcome. We did not find age as a negative predictor of outcome. This observation has been reported earlier, that older people had more effect size due to endovascular therapy, in comparison with age matched controls.^[13]

Effect of time on outcome has been most remarkable in intravenous thrombolysis trials, with the benefit steeply declining after 4 ½ h. In MT trials, the treatment effect was significant even in patients randomized late >300 min after symptom onset, thus laying the background for late window MT trials in 2010s. The pooled analysis of late thrombectomy

Table 1: The clinical and imaging characteristics of the study population

Parameters	Numbers (n=145)	Percentage
Mode of presentation		
Known <360 min	108	74.48
Known >360 min	9	06.20
Unknown/wake up	28	19.31
Time of presentation to hospital		
Office hours 8 am-6 pm	85	58.62
Non-office hours 6 pm-8 am	60	41.38
Risk factors		
Hypertension	80	55.17
Diabetes mellitus	56	38.62
Dyslipidemia	37	25.52
Tobacco smoking	28	19.31
Coronary artery disease	32	22.06
Valvular heart disease	30	20.69
Atrial fibrillation	35	24.14
Prior stroke	18	12.41
Stroke territory		
Anterior circulation	122	84.14
Posterior circulation	23	15.86
Stroke severity at admission (NIHSS)		
Mild (1-4)	6	4.14
Moderate (5-15)	54	37.24
Severe (16 and above)	85	58.62
Stroke etiology		
Large artery atherosclerosis	37	25.69
Cardioembolic	57	39.58
Undetermined	51	35.37
Imaging parameters		
CT ASPECTS at admission (122 anterior circulation strokes)	39/122	31.97
Excellent 8-10	77/122	63.11
Fair 5-7	6/122	04.92
Poor 0-4	6/51	11.76
MR DWI ASPECTS at admission (51 patients)	41/51	80.39
Excellent	4/51	07.95
Fair		
Poor		
Site of occlusion		
MCA-M1	74	51.03
ICA-extracranial + M1	9	6.2
ICA-intracranial + M1	10	6.89
Basilar	18	12.41
Vertebrobasilar	2	1.37
Basilar + P1	3	2.06
CT Perfusion (28 patients)		
Core-penumbra mismatch >20%	26	
No mismatch	2	
Collateral score –Modified Tan (76 patients)		
Excellent	38	50%
Moderate	23	30%
Poor	15	20%
Recanalization status 140 patients		
TICI grade 0	14	78.57
1	4	
2a	12	
2b	50	
3	60	
Excellent (2b+3)	110	

MCA-middle cerebral artery; NIHSS-National Institute for Health Stroke Scale Score

trials have also reported the same observations.^[14] However, clinical benefit declines with increasing delay due to infarct growth.^[15] But studies comparing the outcome between conventional time window patients and wake up/unknown time of onset strokes are few. In the secondary analysis of DAWN trial, mode of onset had no impact on short-term outcome.^[16] We also found that time from onset to treatment had no effect on recanalization rates, complication rates, and short-term outcomes, when patients were selected based on tissue imaging. Similar observations have been reported, where time to treatment did not affect the functional outcome at 3 months.^[17] Our results reaffirm the fact that when selected based on tissue characteristics, delayed window patients perform as well as those presenting early in real world setting.

CT-ASPECTS at admission was predictive of excellent early outcome, at discharge in our series, but failed to remain significant at 3 months. Stroke severity (NIHSS) continued to remain significant in deciding short-term functional outcome. The impact of baseline imaging characteristics on outcome has been well studied. In late window trials of MT, patient selection based on clinical-core mismatch or large perfusion

deficit resulted in good short-term outcome.^[4,5] However, the performance of NCCT-ASPECTS in predicting treatment benefit with MT has not been consistent with pooled analysis of 5 RCTs on conventional time window revascularization showing no effect when subjects with ASPECTS above 5 were selected.^[13] Number of patients with poor ASPECTS were low to study its differential effect on outcome. This is similar to our observation, where patients with favorable ASPECTS mainly were selected. A quarter of our patients only had CT perfusion imaging. But we could achieve comparable results using NCCT with angiography data/and/or MRI-Diffusion weighted imaging (MRI-DWI) in those without perfusion imaging in the patients within 6 h and using advanced imaging modalities judiciously in late presenters and wake up strokes for clinical decision making. This is of particular importance in resource limited settings, where all the components of multimodality imaging as used in clinical trials may not be available or non affordable.

Although around 40% of our MT patients had stroke secondary to cardioembolism, etiology did not show an impact on recanalization rates and short-term outcome. This have been reported before also, where cardioembolic strokes despite having higher NIHSS at admission and increased hemorrhagic transformation continued to show comparable benefit with timely reperfusion strategies.^[18] Recanalization rates, however, have shown mixed results when correlated with short-term functional outcomes. While some have shown that achieving good TIC1 grades translated to good outcomes,^[19] others have reported contrary results as well.^[20] The reason is that recanalization may not always translate into reperfusion and those with target mismatch may only benefit.^[21] We also found that though numbers were small, suboptimal recanalization did not automatically translate to poor outcome.

Our study has its limitations. As the study had patients before the publishing of late window MT trials, number of patients with wake up/delayed presentation were insufficient to study the association between risk factors, etiological subtypes and recanalization rates in the late presenting patients. Although the number of patients in late time window presentation were less,

Table 2: Outcomes at discharge and 3 months

Parameter	Number	Percentage
Discharge mRS		
Excellent 0,1	26	18
Fair 2,3	42	29.17
Poor 4,5,6	76	52.78
Deaths in hospital	17	11.72
Cause of death-neurological	5	
Cardiac	10	
Others	2	
3 month mRS (128 subjects)		
Excellent 0,1	37	28.9
Fair 2,3	46	35.93
Poor 4,5,6	29	35.15
Deaths	8	17.2
Lost to follow-up	14	

mRS- modified Rankin scale

Table 3: Bivariate analysis of predictors of good outcome (modified Rankin score 0-2) at 3 months

Parameter	Good outcome (m RS 0,1,2) n(%)		P
Stroke onset-Unknown vs known	9 (37.5%)	49 (45.79)	0.46
Presentation to hospital-within or out of office hours	31 (40.26)	27 (50)	0.269
Presentation beyond 6 h	50 (43.48)	5 (45.45)	0.765
Diabetes mellitus	42 (50.6)	16 (33.3)	0.055
Hypertension	29 (50.88)	29 (39.19)	0.182
Dyslipidemia	46 (46.46)	12 (37.5)	0.375
Smoking	45 (42.86)	4 (40)	0.581
Atrial fibrillation	44 (44.9)	14 (42.42)	0.805
Prior stroke	54 (46.96)	4 (25)	0.098
NIHSS at presentation	31 (55.77)	27 (36)	0.085
CT-ASPECTS	21 (52.5)	32 (44.12)	0.667
TICI grade of recanalization	39 (39.39)	16 (57.14)	0.094
Hemorrhagic transformation	8 (32)	29 (29)	0.769

Table 4: Predictors of good outcome at 3 months multivariate analysis

Parameter	P	Odds ratio	95% CI	Adjusted OR
Diabetes	0.055	2	0.97-4.28	1.96
Prior stroke	0.107	2	0.8-8.72	2.4
NIHSS at admission	0.028	2.19	1.36-4.47	1.6

their characteristics were comparable with the rest of patients. Perfusion imaging was rarely performed for endovascular patients before 2015.

Nonetheless, we believe our observations are of importance to treating physician in a real world setting. Safety of MT in the extended time window, based on CT-based selection should encourage more stroke physicians and neurologists to pro-actively treat patients with LVO, presenting late, with the help of multimodal imaging techniques, with low risk and good functional outcome, thus justifying this expensive treatment in resource limited settings.

Ethical approval

This study was approved by the Institutional Ethics Committee (IEC) of Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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Conflicts of interest

There are no conflicts of interest.

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