



Short term outcome of reperfusion therapies in acute ischemic stroke of 3-6 hours duration at a tertiary care public hospital in western India

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Abstract

Introduction: Treatment of acute ischemic stroke has seen major revolution in last few years in the resource limited countries with availability of thrombolysis therapy, widespread availability of MRI and vascular intervention set-up for thrombectomy or thrombus aspiration. Best results with IV thrombolysis are achieved if administered within 3 hours of stroke symptom onset. As the time period after onset increases the outcomes are less favourable. In this study we intended to study the outcomes of stroke patients who arrived to our centre at 3-9 hours of symptom onset.

Methods: It is a prospective observational study performed at a tertiary care public teaching hospital in Mumbai, India over period of 18 months. Patients of acute ischemic stroke arriving at 3-9 hours of onset are included in the study. Following patients were excluded from the study: previous stroke with significant permanent deficit, hemorrhagic stroke. The patients received IV thrombolysis or endovascular intervention or conservative therapy as per standard

recommendations. NIHSS and GCS were monitored at regular intervals upto 48 hours.

Results: 50 patients were included in the study. 27 patients came within 3-4.5 hours window from which 22 received IV thrombolysis. In this group, 70% patients had improvement in NIHSS of mean 8.36 units. 12 patients came within 4.5-6 hours window from which 2 underwent endovascular intervention. In this group, 33% patients had NIHSS improvement by mean 3.09 units. 11 patients came after 6 hours. They received conservative treatment. 36% patients showed improvement in this group; but mean improvement in NIHSS was 0.6 units. Significantly greater number of patients achieved GCS 13-15 among patients who received revascularization.

Conclusion: Clinical outcome of acute ischemic stroke is better with shorter time of presentation after onset. Outcome is better in 3-4.5 hours group than 4.5-6 hours group than 6-9 hours group. Thrombolysis in 3-4.5 hours group gives better outcome in terms of NIHSS and GCS at 48 hours.

Keywords: ischemic stroke, thrombolysis, reperfusion therapies.

Introduction

Cerebrovascular accident or stroke is a common disease; having significant mortality, morbidity and residual functional disability. Traditionally the conservative treatment offered only secondary prevention, control of risk factors, physiotherapy and nursing care. IV thrombolysis with rt-PA was approved for treatment of acute ischemic stroke within 3 hours of onset in 1996 (1). The therapeutic window period was extended to 4.5 hours in 2008 (2). In 2016, an endovascular interventional radiology procedure of mechanical endovascular thrombectomy was approved for patients of acute ischemic stroke with presence of accessible thrombus in large arteries like ICA or MCA (3). This procedure is beneficial within 6 hours of onset of stroke symptoms. In 2018 few studies demonstrated the benefits of this intervention in extended window period for 24 hours in carefully selected patients (4).

The clinical benefits of reperfusion therapies (IV thrombolysis or mechanical endovascular thrombectomy) depend on presence of salvageable brain tissue (penumbra) around the infarct core. Various radiological techniques help to estimate the volume of penumbra. The acute cerebral infarct shows abnormal signal on diffusion weighted images of MRI (DWI) very early. However, the FLAIR (fluid attenuated inversion recovery) sequences are normal in ischemic zone in initial 4.5 hours. This area of mismatch helps to estimate the area of penumbra. Similarly, CT perfusion imaging can identify the infarct core and ischemic penumbra and is useful to guide reperfusion therapy. These techniques are also helpful in 'wake-up' strokes where exact onset of stroke symptoms is not known.

In this study we present our experience of reperfusion therapies in patients of acute ischemic stroke presenting in time window of 3-6 hours. As per approved standard of care, the patients within 3-4.5 hour of onset received IV thrombolysis with rt-PA or Tenecteplase. The patients within time window of 4.5-6 hours underwent CT angiography for presence of thrombus in MCA or ICA and MRI diffusion and FLAIR sequences for presence of salvageable brain tissue. The suitable patients were offered endovascular mechanical thrombectomy. The patients who arrived after 6 hours of onset; but within 9 hours were included as control group and they received conservative management that included antiplatelets, statins, IV fluids, drugs to control hypertension, diabetes and in case of atrial fibrillation, the anticoagulants and heart rate control drugs.

Material and methods

The study was conducted at a tertiary care public teaching hospital in Mumbai over period of 18 months Jan 2018- Jun 2019. It was a prospective observational study. All patients coming to EMS with suspected cerebrovascular accident and within 6 hours of symptom onset were identified. A non-contrast CT scan of brain was performed as fast as possible by a coordinated approach by emergency medical team, treating medical unit, neurology unit, radiodiagnosis and vascular interventional radiology department. After ruling out cerebral hemorrhage and after checking Sr. Creatinine CT angiography was also performed. Patients beyond 4.5 hours duration underwent MRI as given above. For patients arriving within window of 4.5 hours, IV thrombolysis was performed in EMS with Alteplase or Tenecteplase after considering standard contraindications. Patients who came between 4.5-6 hours and who were suitable for mechanical

thrombectomy underwent the intervention procedure after written informed consent. After reperfusion therapy the patients were monitored in ICU for BP, GCS, motor function and NIHSS every hourly for 4 hours, then 6 hourly for 24 hours and then at 48 hours. A NCCT was repeated at 24 hours or earlier if clinical worsening was noted. Antiplatelet medications were started after 24 hours if no evidence of hemorrhage on repeat CT. The primary end-points were improvement in NIHSS score >3 points at 48 hours, improvement in GCS at 48 hours and mortality. Improvement or deterioration in NIHSS of > 5 points or disappearance of stroke symptoms and improvement in GCS to >13 was considered significant.

All data was recorded after obtaining permission from the Institutional Ethics Committee. Statistical analysis was performed on SPSS software.

Results

Total 50 patients were included in the study; 35 were males, 15 were females. 22 patients were from age group 41-60 years; 14 patients each were from age groups <40 years and > 60 years. 23 had hypertension; 18 had diabetes; 6 had valvular atrial fibrillation; 5 had previous history of CVA. Severity of stroke varied in patients at admission. Three patients had minor stroke (NIHSS 1-4), 27 patients had moderate stroke (NIHSS 5-15), 10 patients had moderate to severe stroke (NIHSS 16-20) and 10 patients had severe stroke (NIHSS 21-42).

27 patients presented to EMS at 3-4.5 hours after symptom onset (group 1); 12 patients presented at 4.5-6 hours (group 2) and 11 patients arrived at 6-9 hours after onset of symptoms (group 3). IV thrombolysis therapy was administered in 22 patients from group 1. Four patients were found suitable for mechanical thrombectomy from group 2. However, only 2 patients'

relatives gave consent for the procedure. The intervention was performed in them. So total 24 patients received revascularization therapy. Table 1 gives the outcome of patients in terms of improvement in NIHSS score >5 at 48 hours in relation with revascularization therapy. Significantly greater improvement in NIHSS was observed in revascularization group and no. of patients improved was also significantly higher in revascularization group. ($p<0.05$)

Table 2 gives outcome of patients in terms of changes in NIHSS at 48 hours with respect to time of arrival in hospital after onset. Chances of improvement are significantly greater if patients present before 4.5 hours. ($p< 0.05$). Also, the magnitude of improvement was more in group 1 as compared to group 2 and 3. ($p< 0.05$). Earlier the time of presentation to the hospital after onset, more the possibility to receive revascularization therapy and the chances of clinically significant improvement. This proves the saying 'time is brain'.

Table 3 gives trends in NIHSS scores at admission and at 48 hours in the revascularization group and patient group without revascularization therapy. Significantly greater number of patients in revascularization group have lesser NIHSS scores at 48 hours. ($p< 0.05$).

Table 4 gives the changes in GCS in patients after 48 hours. Significantly more no. of patients had good GCS (13-15) after 48 hours after revascularization. ($p< 0.05$). Major intracerebral hemorrhage post-thrombolysis was seen in 2 patients; 1 succumbed. 2 patients underwent mechanical endovascular thrombectomy; 1 improved and one expired.

Outcome (NIHSS score)	Revascularization	No revascularization	Total
Improved	19 (18 thrombolysis, 1 mechanical thrombectomy)	8	27
Remained same	2	14	16
Deteriorated	1	2	4
Death	2 (1 thrombolysis, 1 mechanical thrombectomy)	2	4
Mean change in NIHSS	9.45	1.71	P < 0.05

Table 1: Changes in NIHSS score at 48 hours with respect to revascularization.

Outcome	3-4.5 hour	4.5-6 hour	6-9 hours
Improved	19 (70%) (thrombolysed: 18)	4 (33%) (mechanical thrombectomy: 1)	4 (36%)
Remained same	5 (18.5%) (thrombolysed: 2)	7 (58%)	4 (36%)
Deteriorated	1 (4%) (thrombolysed)	0 (0%)	2 (18%)
Death	2 (7.5%) (thrombolysed: 1)	1 (8%) (mechanical thrombectomy: 1)	1 (9%)
Mean change in NIHSS	8.36	3.09	0.6

Table 2: Outcome of patients in terms of changes in NIHSS score > 5 units at 48 hours with respect to time of presentation to the hospital after onset of symptoms.

NIHSS score	On admission Revascularization group	At 48 hours after revascularization	On admission: no revascularization group	At 48 hours without revascularization
0 (no stroke symptoms)	0	3	0	1
1-4 (minor stroke)	0	12	3	5
5-15 (moderate stroke)	14	6	13	12
16-20 (moderate severe)	6	0	4	1
21-42(severe stroke)	4	1	6	5
Death	0	2	0	2

Table 3: Stroke severity after 48 hours with respect to revascularization.

GCS	On admission Revascularization group	At 48 hours after Revascularization	On admission: no revascularization group	At 48 hours without revascularization
Mild (13-15)	12	19	17	17
Moderate (9-12)	9	2	4	1
Severe (3-8)	3	1	5	6
Death	0	2	0	2

Table 4: Changes in GCS after 48 hours with respect to revascularization.

Discussion

In this study we aimed to study the clinical outcome at 48 hours of patients of acute ischemic stroke who presented to our centre at 3-9 hours of symptom onset. 22/27 patients presenting before 4.5 hours received IV thrombolysis and had significant improvement in NIHSS and GCS at 48 hours (81%). Two patients who arrived at 4.5-6 hours underwent endovascular mechanical thrombectomy. From these, one improved and other had post procedure cerebral hemorrhage and expired.

Delay in hospital arrival is a major factor determining outcome of stroke as the volume of salvageable brain tissue decreases with time. The decision of thrombolysis depends on the time of presentation after onset of symptoms. The therapeutic window for stroke thrombolysis is shorter than that for myocardial infarction. In a study in Kerala, (5) only 25% patients could reach the hospital within 4 hours. Table 2 shows the association of time of presentation after onset with outcome. Earlier the presentation, better is the outcome. 70% (19/27) of patients who presented within 3-4.5 hours had improvement; showing that they had salvageable brain tissue that could be reperfused with IV thrombolysis. Out of 12 cases presenting within 4.5-6 hours only 4 (33%) had improvement (in NIHSS by 4,4,6 units respectively); one had improvement of NIHSS (9 units) after mechanical thrombectomy and 3

with standard therapy. Out of 11 cases presenting within 6-9 hours 4 had improvement (36%) (in NIHSS by 4,4,6,4 units respectively). This improvement was clinically less significant. This finding suggests that very few patients have salvageable brain tissue at 4.5-6 hours; still fewer at 6-9 hours.

In the study by Matsuo et al (6) the odd's ratio for neurological improvement and good clinical outcome increased significantly with shorter onset-to-door time even after adjusting for confounding factors like reperfusion treatment and basal NIHSS score. Study by Srinivasa, Mehta et al (7) shows favorable outcome in 67% patients of acute ischemic stroke of 3-4.5 hours duration when treated with IV thrombolysis. Similar finding is noted in our study.

In conclusion, IV thrombolysis is effective and safe also in patients arriving at 3-4.5 hours of symptom onset. In patients presenting after 4.5 hours the decision for reperfusion therapy should be taken on case-to-case basis depending on presence of salvageable brain tissue on MRI or CT scan.

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