Comparing Bridging Thrombolysis with Direct Thrombectomy in Stroke due to Large Vessel Occlusion- Indian Experience (LVO-Direct)

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Abstract

Objectives: Intravenous thrombolysis alone has poor recanalization rates in large vessel occlusion strokes. Bridging thrombolysis has evolved as a standard treatment approach in emergent large vessel occlusions. Patients who undergo thrombectomy have a higher probability of favorable outcomes irrespective of the use of prior intravenous thrombolysis. Our aim was to compare bridging thrombolysis with direct thrombectomy in ischemic stroke due to large vessel occlusion. **Methods:** We included patients from our stroke registry, with large vessel occlusion strokes, presenting <4.5 hr from onset. Bridging thrombolysis was the standard approach. Direct thrombectomy was done in patients with contraindications to intravenous thrombolysis. The primary outcome was the modified Rankin scale at 3 months. Secondary outcomes were National Institute of Health Stroke Scale at 24 hr post-procedure, door to puncture time, puncture to recanalization time, the extent of recanalization, and the number of passes required. Safety outcomes were any occurrence of intracranial hemorrhage or other complications related to procedure or death. Logistic regression analysis was used to find the factors affecting the outcome. **Results:** Total 76 patients were included, 29 underwent bridging thrombolysis and 47 underwent direct thrombectomy. A favorable outcome (mRS 0-2) was achieved in 19 (65.5%) patients in the bridging group and 25 (58.1%) patients in the direct group ($P = 0.4$, Chi-square test). There was no significant difference in any of the secondary outcomes as well. Symptomatic intracranial hemorrhage occurred in 2 (2.6%) patients and a total of 10 (13.9%) were dead at 3-month follow-up, comparable in both groups. **Conclusion:** Direct thrombectomy has comparable outcomes to bridging thrombolysis in emergent large vessel occlusions.

Keywords: Ischemic stroke, mechanical thrombolysis, thrombectomy, thrombolytic therapy

Introduction

For over 25 years, intravenous thrombolysis (IVT) with tissue plasminogen activator (tPA) was the only established therapy for reperfusion in acute ischemic stroke. But in 2015, after the publication of five independent randomized trials, it was proven that mechanical thrombectomy (MT) in addition to best medical management has a substantial treatment effect in stroke with large vessel occlusion in the anterior circulation.[1–5] It was also seen that in patients who had undergone MT, clinical outcomes did not differ significantly in patients who had not received IVT.[6,7] This questions the necessity of IVT in addition to MT, when both are available immediately. There are several advantages and disadvantages of IVT and they might differ according to systems and availability of healthcare. IVT bridges the gap where MT is not available immediately (drip and ship) and in many centers in India that might be the only available option for reperfusion. In thrombectomy ready centers also, IVT might lead to a better degree of recanalization or complete recanalization without MT in some cases, it can improve collaterals because of lysis of small distal thrombi and might prevent infarctions in new territory which can result as a complication of MT. Disadvantages might include delaying initiation of thrombectomy, increased risk of intracranial or systemic hemorrhage, precluding the use of antithrombotics in acute settings, or lysis of the proximal clot causing distal emboli inaccessible to catheters.[8] India as well as other low and lower-middle-income countries face different challenges in this setting. Cost is often the limiting factor for reperfusion therapies as most of the time families are needed to pay from their pocket. IVT significantly adds cost to the therapy which itself is very costly.

We aimed to compare the safety and efficacy of direct mechanical thrombectomy to bridging thrombolysis in the Indian population.

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Subjects and Methods

The institutional ethics committee approved the study. Patient data were taken from the stroke registry maintained prospectively by the department of interventional neurology. The need for individual patient consent was waived off due to the nature of the study. We included adult patients from January 2016 to January 2020 with ischemic stroke due to large vessel occlusion and onset to the arrival time of less than 270 min or patients with in-hospital stroke. Patients who were thrombolysed elsewhere and referred for MT (drip and ship) were also included. Patients with the unclear time of onset and with wake-up stroke were excluded. Patients with recent stroke and new-onset worsening were also excluded. All patients' characteristics including demographic details, risk factors for stroke, neurological deficits as measured by the National Institute of Health Stroke Scale (NIHSS) were recorded. The patient underwent either computed tomography (CT) or magnetic resonance imaging (MRI) to rule out intracranial hemorrhage as well as to estimate the infarct/core. Computed tomography contrast angiography (CTA) or magnetic resonance time of flight angiography (MRA) were then performed to look for the site of vessel occlusion. All patients with involvement of the internal carotid artery, middle cerebral artery M1 or M2 segment, anterior cerebral artery, basilar artery as well as posterior cerebral artery were included. Patients with tandem proximal and intracranial occlusions were not excluded. Mechanical thrombectomy was contemplated if NIHSS was ≥6, or isolated aphasia or hemianopia was there and in patients with anterior circulation stroke in whom the infarct was not more than 1/3rd of involved arterial territory. Bridging thrombolysis with alteplase or tenecteplase was the norm in patients presenting within 4.5 hr and mechanical thrombectomy alone was done in patients with contraindications to intravenous thrombolysis. Mechanical thrombectomy procedure was done under general anesthesia in patients who were not communicative or were restless. Yet, whether to perform the procedure under general anesthesia or local anesthesia as well as conversion from local to general anesthesia was at the discretion of the operator. Femoral arterial access was used in all cases. An angiogram of the vessel involved was performed in all cases at the start of the procedure. The use of balloon guide catheters was preferred wherever vascular anatomy was feasible. Thrombectomy was done with the use of stent-retrievers, aspiration catheters, or a combination thereof and use of rescue stenting was also at the discretion of the operator. Stent-retrievers were deployed across the occlusion site and were retrieved after 5 min under aspiration through the guide catheter. Aspiration catheters when used as A Direct Aspiration First Pass Technique or in combination with stent-retrievers, were taken to the proximal face of the clot and retrieved with combined manual aspiration through a guide catheter with a 50cc syringe. In patients who underwent bridging thrombolysis, completion of the tissue plasminogen activator dose was again at the discretion of the operator. An attempt was made to achieve recanalization with an mTICI (modified thrombolysis in cerebral infarction) score of 2b-3 in the shortest possible time and with the lowest number of passes in all cases.[9,10] After the procedure, control of blood pressure, blood sugars, and temperature were provided as per stroke unit protocol in all patients. Non-contrast computed tomography scans were repeated on the next day of the procedure or at any time if there was a decline in neurological status. NIHSS on the next day of the procedure as well as any occurrence of adverse events including intracranial hemorrhage or deaths were recorded. Intracranial hemorrhage was considered symptomatic if there was a worsening of ≥4 points in NIHSS.[11,12] Stroke mechanisms were recorded as per TOAST classification after detailed evaluation and patients were started on secondary prophylaxis according to etiology.[13] Neurorehabilitation was started in-hospital and all patients were encouraged to make lifestyle modifications. Modified Rankin Scale (mRS) at 3 months was assessed telephonically or in person with a structured questionnaire.[14]

The primary outcome to be compared was the Modified Rankin scale (range 0-6) at 3 months; mRS score of 0-2 was considered a favorable outcome. Secondary outcomes were NIHSS at 24 hours post-procedure, door to puncture time, puncture to recanalization time, the extent of recanalization achieved (TICI), and the number of passes required. Safety outcomes were any occurrence of intracranial hemorrhage or other complications related to the procedure.

Statistical analysis

Data were analyzed using R software version 4.0.3. Continuous variables were expressed as Mean ± SD/Median [Q3- Q1] whereas categorical variables were described using frequency and percentage. Comparison of neurological parameters like time from onset minutes, door to puncture, etc., were analyzed by an independent sample t-test/Mann Whitney U test depending upon the distribution. The Chi-square test was used to compare complications between two groups. Paired t-test was used to find the change of NIHSS before and after the procedure. Logistics regression was used to find the factors affecting the outcome. *P* value <0.05 was considered statistically significant.

Results

A total of 134 patients underwent thrombectomy in our institute from January 2016 to January 2020. [Figure 1] Seventy-six patients were included in the study; 36 presented >4.5 hr after the onset of stroke, 10 had the unclear time of onset or had a wake-up stroke, 4 were of <18 years age, 8 had a recent stroke, and new-onset worsening. Out of the 76 included patients, 47 underwent direct thrombectomy and 29 underwent bridging thrombolysis. Baseline characteristics did not differ between both groups. [Table 1] The mean age was 50.5 years and 67.1% were males. The mean time from stroke onset to presentation was 102.4 ± 52.4 minutes in the bridging group and 105.4 ± 70.4 minutes in the direct thrombectomy group. The majority of patients were deemed to have cardioembolic strokes in both groups, 41.4% patients in the bridging thrombolysis group and 61.7% patients in the direct thrombectomy group. Median NIHSS was 16 in both groups. In the bridging group, 24 patients had undergone CT with CTA (one patient underwent perfusion imaging) and 5 patients had undergone MRI with MRA. In the direct thrombectomy group, 36 patients had undergone CT with CTA (two patients underwent perfusion imaging) and 11 patients had undergone MRI with MRA. Median ASPECTS in the direct thrombectomy group was 8 and 7.5 in the bridging thrombolysis group. Two patients in bridging group had undergone thrombolysis with tenecteplase and rest of the patients received alteplase. Most of the patients in both groups had either occlusion involving the internal carotid or M1 segment of the middle cerebral artery. General anesthesia was used in 51% of patients in the direct thrombectomy group and 69% in the bridging thrombolysis group. There was partial recanalization in one and complete recanalization in another patient in the bridging thrombolysis group noted at the time of digital subtraction angiography before thrombectomy.

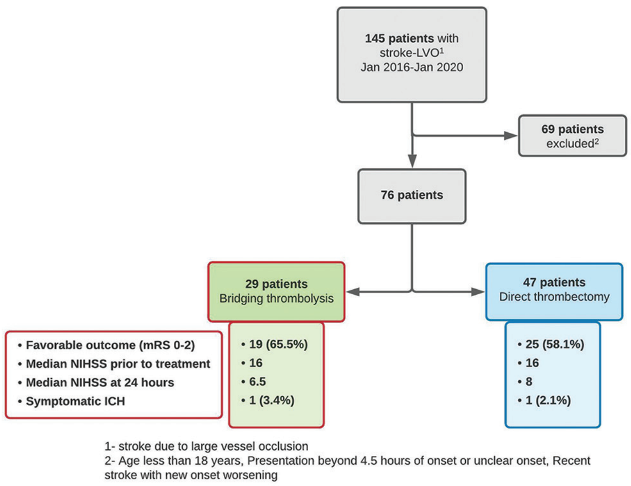

Figure 1: Overview of included patients and outcomes

Modified Rankin Scale at 3 months was available in 72 patients (data NA in four patients in the direct thrombectomy group-three of these patients had decrement of NIHSS from 14,16 and 22 to 11, 1 and 8 at 24 hr, respectively). A favorable outcome (mRS 0-2) was achieved in 65.5% of the patients

Table 1: Baseline characteristics

Characteristic	Bridging thrombolysis (*n*=29)	Direct Thrombectomy (*n*=47)	*P*
Age, Mean	52.6 years	49.2 years	0.375*
Sex	20 (69%) male	31 (66%) male	0.81**
Diabetes mellitus	4 (13.8%)	15 (31.9%)	0.1**
Hypertension	10 (34.5%)	18 (38.3%)	0.81**
Ischemic heart disease	6 (20.7%)	14 (29.8%)	0.43**
Rheumatic heart disease	5 (17.2%)	10 (21.3%)	0.77**
Atrial fibrillation	5 (17.2%)	8 (17%)	1**
Previous stroke	3 (10.3%)	2 (4.3%)	0.36**
Stroke mechanism			
Large artery atherosclerosis	7 (24.1%)	8 (17%)	0.35**
Cardioembolic	12 (41.4%)	29 (61.7%)	
Other determined	2 (6.9%)	2 (4.2%)	
Undetermined	8 (27.6%)	8 (17%)	
Time from onset (Median, minutes) [Q1-Q3] (*n*=61)	120 [60-135] (*n*=23); 1 In hospital stroke; 5 thrombolysed elsewhere	90 [43.7-180] (*n*=38); 9 In hospital stroke	0.98*
NIHSS, median [Q1-Q3] (*n*=73)	16 [14-19.5]	16 [14-18.7] (*n*=44)	0.82*
ASPECTS, median [Q1-Q3] (*n*=69)	7.5 [7-8.7] (*n*=28)	8 [6-9] (*n*=41)	0.73*
Vessel involved			
ICA	12 (41.4%)	18 (38.7%)	0.76**
M1 MCA	13 (44.8%)	19 (40.4%)	
M2 MCA	3 (10.3%)	4 (8.5%)	
Basilar	0	2 (4.3%)	
Other	1 (3.4%)	4 (8.5%)	
Side of involvement in anterior circulation stroke (*n*=73)			
Left	12 (41.4%)	20 (45.5%)	0.81**
Right	17 (58.6%)	24 (54.5%)	
Anesthesia			
GA	19 (65.5%)	24 (51.1%)	0.15*
LA	9 (31%)	23 (48.9%)	
LA to GA	1 (3.4%)	0	

*Independent sample *t*-test/Mann Whitney U test. **Chi-square test/Fishers exact test in the bridging group and 58.1% (25 of 43 in whom data was available) in the direct thrombectomy group. Successful recanalization (mTICI 2b or higher) was achieved in > 90% of patients in both groups. NIHSS at 24 hr was not available in five patients (one in the bridging group) as they were sedated and were on mechanical ventilation. There was a median reduction of 8.5 NIHSS points in the bridging group and 6.5 NIHSS points in the direct thrombectomy group 24 hr post-procedure. Mean puncture to recanalization time was 50.9 ± 23.7 min in bridging group and 50.6 ± 29.9 min in direct thrombectomy group [Table 2]. There was no difference in both groups regarding the occurrence of intracranial hemorrhage or other complications. [Table 3] There were a total of 15 intracranial hemorrhages; two were symptomatic (one in each group). Four patients in the direct thrombectomy group underwent decompressive craniectomy; two of these patients also had asymptomatic reperfusion hemorrhage. There was a total of 10 deaths at 3 months (2 in the bridging group, 8 in the direct thrombectomy group), 4 occurred in-hospital (1 in the bridging group, 3 in the direct thrombectomy group). Following variables were used in logistic regression to find if they could have affected outcome-Age >65 years, NIHSS >15, ASPECTS ≤7, Time from onset ≤3 hr. None of these variables affected significantly either of the groups for the outcome. [Table 4]

Table 2: Outcomes

Outcome	Bridging thrombolysis	Direct thrombectomy	P
mRS at 3 months (*n*=72)			
Favorable (0-2)	19 (65.5%)	25 (58.1%)	0.4**
Dependent (3-5)	8 (27.6%)	10 (23.3%)	
Dead (6)	2 (6.9%)	8 (18.6%)	
24 hour NIHSS, median (Q1-Q3) (*n*=71)	6.5 (4.2-14)	8 (2-14)	0.94*
NIHSS drop post procedure, median (Q1-Q3) (*n*=71)	8.5 (1.25-13.75)	6 (0-12)	0.63*
Door to puncture time, minutes, median (Q1-Q3)	45.0 (40.0-70.0)	60.0 (45.0-90.0)	0.19*
Puncture to recanalization, minutes, median (Q1-Q3) (*n*=74)	45 (30-60)	40 (30-60)	0.65*
Extent of recanalization, mTICI			
2a or lesser	2 (6.9%)	2 (4.3%)	0.63**
2b or higher	27 (93.1%)	45 (95.7%)	
Number of passes required, median (Q1-Q3)	2 (1-3)	2 (1-3)	0.79*

*Independent sample *t*-test/Mann Whitney U test. **Chi-square test/ Fishers exact test

Table 3: Complications

Complication	Bridging thrombolysis	Direct thrombectomy	P
ICH			
Nil	23 (79.3%)	38 (80.9%)	1.00**
Symptomatic	1 (3.4%)	1 (2.1%)	
Asymptomatic	5 (17.2%)	8 (17%)	
Others			
Nil	28 (96.6%)	41 (87.2%)	0.26**
Decompression	0	4 (8.5%)	
Dissection	1 (3.4%)	0	
Access site complication	0	1 (2.1%)	
Infarct in new territory	0	1 (2.1%)	

**Chi-square test/Fishers exact test

Table 4 (Supplementary material): Logistic regression to find factors affecting the outcomes

Variable	Bridging thrombolysis			Direct thrombectomy		
	P	Odds ratio	95% CI	P	Odds ratio	95% CI
Age	0.39	2.3	0.34-15.44	0.83	1.2	0.22-6.5
NIHSS	0.34	1.85	0.53-6.48	0.7	1.35	0.29-6.38
ASPECTS	0.26	0.47	0.12-1.76	0.69	1.39	0.28-6.83
Time from onset	0.18	2.54	0.65-9.95	0.71	0.7	0.11-4.48

Reference categories- Age >65 years, NIHSS >15, ASPECTS ≤7, Time from onset ≤3 hours

Discussion

We have presented the real-world comparison from India between bridging thrombolysis and direct thrombectomy without IVT in patients with ischemic stroke due to large vessel occlusions. Overall, we did not find significant differences in various outcomes between both the treatment modalities.

Ever since mechanical thrombectomy has emerged as a standard treatment strategy in anterior circulation large vessel occlusions, there has been increasing literature addressing the question of whether bridging with intravenous thrombolysis is needed or not. Yet, there have been no previous studies from India till the time of writing this report.

There is significant variability among conclusions of initial observational studies as well as meta-analysis. Goyal *et al.*[15] compared 104 patients undergoing direct thrombectomy to 208 patients receiving bridging therapy after propensity score matching. They reported higher odds of functional improvement and decreased mortality with bridging therapy. Ferrigno *et al.*[16] showed better reperfusion rates, improved functional outcomes, and decreased mortality in patients receiving IVT before thrombectomy. Anne Broeg-Morvay *et al.*[17] included 40 patients who were eligible for IVT but underwent direct thrombectomy as decided on a case-by-case basis by the treating team and compared them with 40 patients receiving bridging thrombolysis after propensity score matching. They reported lower asymptomatic ICH and mortality in the direct thrombectomy group. Weber *et al.*[18] also included patients eligible as well as ineligible for IVT and concluded that preceding use of IVT was not an independent predictor of a favorable outcome and complication rates were similar in both groups. In the direct thrombectomy group, favorable outcomes were achieved in 48.2% and 32% in patients who were eligible and ineligible for IVT. Wang *et al.*[19] reported a lower rate of asymptomatic ICH and a higher rate of successful reperfusion in patients who underwent direct thrombectomy. Overall, observational studies which included IVT eligible as well as ineligible patients tended to favor bridging thrombolysis, and studies that excluded IVT ineligible patients did not show a difference in outcomes.[20]

Recent randomized control trials also seem to have incongruity. The first, DIRECT-MT trial showed that thrombectomy alone was non-inferior to bridging in Chinese patients.[21] While, SKIP trial failed to demonstrate non-inferiority of direct thrombectomy in Japanese patients with a prespecified margin of 0.74.[22] These trials were criticized for their wide non-inferiority margins, suboptimal door-to-needle times in presence of comparatively better door-to-puncture times in the DIRECT-MT trial, a significant number of patients (9.4%) in bridging arm not undergoing thrombectomy in DIRECT-MT and use of 0.6 mg/kg dose of alteplase in SKIP trial.[23] DEVT trial was terminated early because prespecified efficacy boundary was crossed and it showed non-inferiority of direct thrombectomy. Although, direct thrombectomy group had lower rates of asymptomatic ICH[24] A meta-analysis including three randomized trials showed no significant difference in functional outcome, probability of successful recanalization or randomization to puncture times. Patients receiving direct thrombectomy had lower intracranial bleeding rates, but symptomatic ICH, any serious adverse event, as well as mortality at 3 months were not different between both the groups.[25] A recent randomized trial (MR CLEAN NO IV) showed that direct thrombectomy alone was neither superior nor inferior to bridging therapy in European patients.

There are several limitations to our observation. First, apart from the inherent limitations due to retrospective observational nature of the study, patients in both the groups are not directly comparable because in the direct thrombectomy group majority patients had contraindications to IVT and 31.9% did not receive thrombolysis because families did not give consent. Second, there were several imbalances in baseline although not statistically significant- the proportion of patients with diabetes and cardiac conditions was higher in the direct thrombectomy group, and the door to puncture time was paradoxically higher in the direct thrombectomy group. This is likely because of the inclusion of patients with acute conditions (e.g., with recent surgery or myocardial infarction) which could have prevented quick consent from the family. Although patients in both the groups did not differ significantly as far as stroke severity and time from onset are concerned, radiological parameters like collateral score, clot burden were not analyzed. Third, our observation is from a single center and included a relatively small number of patients; results might not be generalizable to larger more heterogeneous populations. For example, the proportion of patients with cardioembolic stroke is higher in our study compared to other reports from India because of the association of a high volume cardiac institute with our center.[26]

Now with the growing data with equivocal answers, it seems prudent to individualize the therapy based on patient characteristics, till time larger randomized trials including heterogeneous populations give definitive answers, as both modalities are safe and effective.[25] Direct thrombectomy seems the favored approach in patients presenting to thrombectomy ready centers with more proximal occlusions, large clots, having high bleeding risk (large infarcts, basal ganglia infarcts, very old age, current antithrombotic use). While bridging thrombolysis seems to be a favored approach in patients with small clots, more distal occlusions, less severe stroke, when thrombectomy is not immediately available.[23] Though the majority of the above-mentioned data is involving alteplase, the EXTEND-IA TNK trial had shown a higher incidence of reperfusion and better functional outcomes with tenecteplase compared to alteplase before thrombectomy.[27] Then the question that remains to be answered is- what if tenecteplase is used for bridging?

In conclusion, direct thrombectomy has comparable outcomes in Indian settings as well and can be offered to patients presenting directly to thrombectomy-ready centers. Though, the decision should be driven by individual patient characteristics.

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Conflicts of interest

There are no conflicts of interest.

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