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ORIGINAL ARTICLE

Reperfusion strategies in stroke with medium-to-distal vessel occlusion: a prospective observational study

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Abstract

Introduction Medium vessel occlusion (MeVO) accounts for 30% of acute ischemic stroke cases. The risk/benefit profile of endovascular thrombectomy (EVT) and intravenous thrombolysis (IVT) or the combination of the two (bridging therapy (BT)) is still unclear in MeVO. Here, we compare reperfusion strategies in MeVO for clinical and radiological outcomes.

Methods This prospective single center study enrolled consecutive patients with AIS due to primary MeVO undergoing IVT, EVT, or BT at a comprehensive stroke center. Primary outcome was good functional status, defined as modified Rankin Scale (mRS) 0–2 at 3-month follow-up. Additional outcomes included mortality, successful recanalization, defined as mTICI ≥ 2b, stroke severity at discharge, and symptomatic intracerebral hemorrhage (sICH) according to SITS-MOST criteria. Logistic regression was modeled to define independent predictors of the primary outcome.

Results Overall, 180 consecutive people were enrolled (IVT = 59, EVT = 38, BT = 83), mean age 75. BT emerged as independent predictor of primary outcome (OR = 2.76, 95% CI = 1.08–7.07) together with age (OR = 0.94, 95% CI = 0.9–0.97) and baseline NIHSS (OR = 0.88, 95% CI = 0.81–0.95). BT associated with a 20% relative increase in successful recanalization compared to EVT (74.4 vs 56.4%, $p = 0.049$). Rates of sICH (1.1%) and procedural complications (vasospasm 4.1%, SAH in 1.7%) were very low, with no difference across groups.

Discussion BT may carry a higher chance of good functional outcome compared to EVT/IVT only in people with AIS due to MeVO, with marginally higher rates of successful recanalization. Randomized trials are needed to define optimal treatment tailoring for MeVO.

Keywords Medium vessel occlusion · Endovascular thrombectomy · Bridging therapy

Introduction

Up to 40% of acute ischemic stroke cases occur due to medium vessel occlusions (MeVOs) [1]. Despite optimal management, AIS due to MeVO seems to have similar functional outcome to that due to large vessel occlusion (LVO) stroke [2, 3]. Endovascular treatment (EVT) for LVO stroke

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has gained extensive evidence as a critical procedure to reach good functional outcome [4, 5]. However, the more distal the occlusion site, the more difficult is to weigh benefit and risk of treatment. In MeVO stroke, the benefit-risk profile is influenced by small at-risk tissue volumes, lower NIHSS scores, restricted potential reperfusion benefit, and by the higher risk of procedure-related complications [1, 6]. Indeed, medium vessels have lumen diameters between 0.75 and 2.0 mm, longer distances and more tortuous pathways than proximal vessels, and loops around anatomical structures that increase the risk of navigation and alter the forces deliverable by a retrieval device [1].

Another key point is that the distinction between LVOs and MVOs is often challenging, given the variability in anatomy and in clinical symptoms. A multidimensional definition based on morphological features and clinical deficits has been proposed [7], but clinical practice faces significant imbalance between NIHSS and occlusion site in relation to collateral flow, lateralization, and eloquence. The benefit of EVT in MeVOs is therefore still under investigation. For middle cerebral artery M2 segment occlusion, a sub-analysis of the HERMES collaboration [8] and the ASTER trial [9] suggested safety and efficacy of EVT. However, such evidence is limited to M2 segment, and data for other occlusion sites comes primarily from case series [10, 11], with no specific recommendations given in international guidelines [12].

Here, we report an observational prospective study comparing reperfusion strategies (IVT, EVT, IVT + EVT defined as bridging therapy, BT) in primary MeVO AIS people, to define clinical and procedural outcomes.

Methods

Cohort

Consecutive patients with AIS due to MeVO were enrolled between January 2019 and July 2021. Demographical, clinical, and radiological data features were prospectively collected through a standardized dataframe. Patients were treated according to local protocol, adhering to national and international guidelines. MeVO included M3 or distal M2 segment in the MCA territory, A2 or A3 segment in anterior cerebral artery (ACA) territory, or P2 or P3 segment in posterior cerebral artery (PCA) territory [1]. Vessel occlusion was adjudicated by two experienced neuroradiologists on baseline CTA. We collected demographic, clinical, and neuroradiological data, including follow-up NCCT at 24 h, NIHSS scores at baseline and discharge, and functional status according to modified Rankin scale (mRS) at baseline and 3 months. Patients were grouped according to revascularization procedure performed (IVT, EVT, or BT), which was based on clinical decision. Primary outcome was good functional status, defined as mRS 0–2 at 3-month follow-up.

Additional outcomes included mortality, successful recanalization, defined as mTICI 2b or higher [13], NIHSS at discharge, and symptomatic intracerebral hemorrhage (sICH), defined according to SITS-MOST definition as an increase of 4 or more points in the score on the NIHSS and evidence of PH1 or PH2 on emergent NCCT [14]. We also collected safety events other than intracranial hemorrhage, including procedural subarachnoid hemorrhage (SAH), vessel dissection, or perforation.

Imaging protocol

Institutional stroke imaging protocol included non-contrast computed tomography (NCCT), multiphase CT angiography (mCTA), and perfusion CT (PCT) at admission. NCCT protocol was conducted on a 64-detector row clinical system (Revolution Evo 128, GE Healthcare, Milwaukee, WI). NECT helical scans were performed from the skull base to the vertex (120 kV, 400 mA, 5-mm section thickness with 2.5-mm reconstructions). mCTA was conducted from the aortic arch to the frontal vertex for arterial phase, and then with two following scans from C2 to vertex for venous and delayed phases (120 kV; 320–400 mA; section thickness 0.625 mm), after intravenous administration of 60–70 mL iodinated contrast medium injected at 4 mL/s and followed by 50 mL saline flush, and scan start 4 s after bolus tracking up to threshold level (80 HU) of a region of interest (ROI) placed at the level of the distal aortic arch. PCT scans (80 kV, 300 mA) consisted of a continuous acquisition, with a total duration of about 200 s and a scanning volume of 8 cm, that started after administration of 50 mL of iodinated contrast medium injected into an antecubital vein at 4 mL/s and followed by 50 mL saline flush. PCT data were initially processed by commercially available delay-insensitive deconvolution software CT Perfusion 4D, PCT 4D (GE Healthcare, Waukesha, Milwaukee, WI).

For this study, baseline NCCT, mCTA, ColorViz, PCT, and follow-up NCCT were reviewed in all patients. The Alberta Stroke Program Early CT Score (ASPECTS) and hyperdense or dot sign were determined on baseline NCCT. Sagittal and coronal reformations and maximum-intensity projections of all 3 planes and all 3 phases were used to evaluate the occlusion site. PCT qualitative maps were used to detect the hypoperfusion area without collecting quantitive data. We collected sensitivity of hyperdense/dot sign on baseline CT scan, mCTA, and ColorViz technique in detecting MeVOs, with digital subtraction angiography taken as the gold standard to confirm MeVO site.

Statistical analysis

Continuous variables are presented as means and SD and categorical variables as number and percentage. The primary outcome was functional independence at 3 months, defined as a modified Rankin Scale score of 0 to 2. Three groups were identified and analyzed (IVT, EVT, and BT). Comparisons of clinical characteristics between subjects with and without primary outcome (mRS 0–2 at follow-up) were performed with the *t*-test, the Mann–Whitney *U* test, and the χ^2 test (Fisher exact test). To identify potential predictors for a good functional outcome, we performed univariate analysis, including demographic, clinical, and treatment-related variables. For model development, we included significant ($p < 0.05$) predictors from univariate analysis. All candidate variables were entered into binary logistic regression analysis for primary outcome, with a backward stepwise elimination approach set to simplify the model. Age was imputed as a forced entry in the model to take into account the composition of our cohort. For outcomes measured with ordinal variables, a logistic regression model was fitted, with predictors imported from univariate analysis. R v.3.3.1 was used for all analyses.

Results

Among 917 patients receiving reperfusion treatment for acute ischemic stroke between January 2019 and July 2021, 180 consecutive patients (19.6%) had MeVO occlusion. Fifty-nine patients received IVT only, 38 EVT-only, and 83 BT. Mean age ranged 72–80 across groups, with patients in the IVT group being older than their pairs in EVT and BT groups (80.2 vs 76.1 in EVT-only and 72 in the BT group) and with slightly lower rates of functional independence at baseline (mRS 0–2: 83.1% IVT vs 94.7% EVT vs 97.6% BT, $p = 0.002$, Table 1). MeVO occlusion was identified by mCTA in 96% of cases (170/177), by ColorViz in 95% (98/103), and in all cases by the combination of the two (Supplemental material—Fig. 1S). CTP deficit was found in all patients except one undergoing EVT-only. MCA MeVO was the most prevalent type of occlusion (Table 1). Time metrics were similar across groups, with particular regard to onset-to-needle and onset-to-groin (Table 2).

Good functional outcome was significantly more frequent among those receiving BT compared to those EVT-only (63.9% vs 31.6%, $p < 0.005$, Table 4), while rates were superimposable between BT and IVT. Mortality was very low across groups, with a non-significant increase in the IVT-only group compared to BT and EVT (Table 3).

BT was associated with a 20% relative increase in successful recanalization compared to EVT (74.4 vs 56.4%, $p = 0.049$, Table 3). Mean NIHSS score at discharge was significantly higher in the EVT group (8.7 vs 3 for IVT, 4.4 for BT, $p < 0.001$, Table 3). No difference in hemorrhagic complication was observed between groups. Overall, sICH rates were very low in our study (2/180; 1.1%), with no differences across groups. Procedural complications of EVT were uncommon. Vasospasm was reported in 4.1% (5/121) and SAH in 1.7% (2/121). No neurological deterioration due to complications was observed (Table 4).

In the logistic regression model for good functional outcome, age (OR = 0.94, 95% CI = 0.9–0.97), baseline NIHSS (OR = 0.88, 95% CI = 0.81–0.95), and BT (OR = 2.76, 95% CI = 1.08–7.07) emerged as independent predictors. Regression modeling for NIHSS at discharge revealed that baseline NIHSS (OR = 1.21, 95% CI = 1.14–1.28) and systolic blood pressure (OR = 1.02, 95% CI = 1.01–1.03) were independent predictors of final stroke severity (Supplemental material Table 1S). Regression modeling for successful reperfusion showed only NIHSS and gender were independent predictors of the outcome (Table 2S). In the latter models, BT resulted in a non-significant trend towards better outcomes (OR = 0.65, 95% CI = 0.33–1.31 for higher NIHSS at discharge, OR = 1.67, 95% CI = 0.8–4.79 for successful reperfusion, Tables 1S,2S).

Discussion

Despite undergoing reperfusion treatments, one in four people with AIS due to MeVO will not achieve functional independence, and only half will reach excellent clinical outcome (mRS ≤ 1) [2, 8]. In this prospective observational study, BT was associated with higher rates of good functional outcome compared to other treatments, suggesting a potential benefit of pursuing a combined approach in MeVO. This finding seems to be supported by the higher rates of successful reperfusion achieved with BT over EVT-only, which highlights a potential non-marginal gain in functional status achieving an optimal revascularization among people with MeVO. The rate of successful recanalization in previous studies seems to some extent heterogeneous [3], reaching 58% in HERMES M2 segment occlusion sub-analysis [8], 65% in ASTER trial [9], and up to 93% in the Trevo Registry [6]. Our rates of recanalization with BT and EVT seem overall in line with those reported in literature, although consistently in the upper limit for BT. As successful recanalization was defined according to mTICI score for MeVOs [13], which might therefore have been applied in a more stringent fashion than TICI, these findings reinforce the concept that high rates of successful recanalization can be pursued also in real-world settings. Safety outcomes further support this approach. No difference in hemorrhagic complication was observed between groups, and the overall rate of sICH was very low (1%). Also, procedure-related adverse events of EVT were

Table 1 Demographic and stroke clinical features

	IVT	EVT	BT	*p*-value		
				IVT vs BT	IVT vs EVT	BT vs EVT
Age at onset	80.2 ± 9.4	76.1 ± 11.5	72 ± 14.9	< 0.001	ns	ns
Female	36 (61)	21 (55.3)	47 (56.6)	ns	ns	ns
mRS ≤ 2 at baseline	49 (83.1)	36 (94.7)	81 (97.6)	0.002	ns	ns
Cardiovascular risk factors						
Atrial fibrillation	22 (37.3)	21 (55.3)	29 (34.9)	ns	ns	0.035
Diabetes mellitus	11 (18.6)	9 (23.7)	13 (15.7)	ns	ns	ns
Hypertension	50 (84.7)	30 (81.1)	57 (68.7)	0.029	ns	ns
Hypercholesterolemia	28 (47.5)	10 (26.3)	27 (32.9)	ns	0.037	ns
Smoke	10 (16.9)	4 (10.5)	11 (13.3)	ns	ns	ns
Previous stroke	8 (13.8)	2 (5.3)	8 (9.9)	ns	ns	ns
Etiology						
Cardioembolic	24 (40.7)	23 (60.5)	30 (36.1)	ns	0.04	ns
Atherosclerosis	3 (5.1)	2 (5.3)	3 (3.6)	ns	ns	ns
Small vessel	0 (0)	1 (2.6)	2 (2.4)	ns	ns	ns
Other	0 (0)	0 (0)	1 (1.2)	ns	ns	ns
More than one cause	2 (3.4)	1 (2.6)	3 (3.6)	ns	ns	ns
Undefined	30 (50.8)	11 (28.9)	44 (53)	ns	ns	ns
NIHSS at admission	6 ± 3.7	12.1 ± 6.4	9.1 ± 5.8	0.001	< 0.001	0.013
Systolic blood pressure (mmHg)	157.6 ± 24.3	145.8 ± 21.1	150 ± 24.5	ns	0.017	ns
Blood glucose (mg/dL)	131.6 ± 45.7	147 ± 61	128.7 ± 54	ns	ns	ns
ASPECTS baseline	9.6 ± 0.7	8.7 ± 1.3	9.3 ± 1	0.019	< 0.001	0.003
CTP deficit, *n* (%)	58 (100)	34 (97.1)	81 (100)	ns	ns	ns
Leukoaraiosis	50 (84.7)	26 (70.3)	55 (67.1)	ns	ns	ns
Occlusion site						
M2	14 (23.8)	37 (100)	72 (87.8)	< 0.001	< 0.001	ns
M3	35 (59.3)	0 (0)	5 (6.1)	ns	ns	ns
P2	5 (8.5)	0 (0)	4 (4.9)	ns	ns	ns
P3	2 (3.4)	0 (0)	0 (0)	ns	ns	ns
A2	2 (3.4)	0 (0)	0 (0)	ns	ns	ns
A3	1 (1.7)	0 (0)	1 (1.2)	ns	ns	ns

BT bridging therapy, *EVT* endovascular treatment, *IVT* intravenous thrombolysis

Table 2 Metrics and angiographic procedural outcomes

	IVT	EVT	BT	*p*-value BT vs EVT
Onset-to-imaging time	123 (51–986)	203 (20–1335)	128 (33–1080)	ns
Stroke-to-needle time	164 (78–876)	-	161.5 (65–1640)	ns
Onset-to-groin time	-	250 (102–840)	225 (120–1185)	ns
mTICI for MeVOs				
0	-	4 (10.8)	0 (0)	0.014
1	-	3 (8.1)	9 (11.3)	
2a	-	10 (27)	13 (16.3)	
2b	-	13 (35.1)	44 (53)	
2c	-	7 (18.9)	14 (16.9)	

Time metrics are reported in minutes, as medians and ranges

BT bridging therapy, *EVT* endovascular treatment, *IVT* intravenous thrombolysis, *mTICI* modified thrombolysis in cerebral infarction

Table 3 Distribution of outcomes across treatment groups

	IVT	EVT	BT	*p*-value		
				IVT vs BT	IVT vs EVT	BT vs EVT
mRS 0–2 at 3 months	36 (61)	12 (31.6)	53 (63.9)	ns	0.005	0.001
Mortality	2 (3.4)	1 (2.6)	1 (1.2)	ns	ns	ns
NIHSS score at discharge	3 ± 4.3	8.7 ± 7.6	4.4 ± 5.2	ns	< 0.001	< 0.001
Successful recanalization°	/	22 (56.4)	58 (74.4)	/	/	0.049
Haemorrhagic complications						
HI1	2 (3.4)	2 (5.3)	5 (6.1)	ns	ns	ns
HI2	0 (0)	1 (2.6)	2 (2.4)			
PH1	0 (0)	0 (0)	0 (0)			
PH2	1 (1,7)	1 (2.6)	0 (0)			
rPH	0 (0)	0 (0)	0 (0)			

Successful reperfusion: mTICI score 2b or higher (available for patients in BT and EVT groups only)

BT bridging therapy, *HT* hemorrhagic transformation, *EVT* endovascular treatment, *IVT* intravenous thrombolysis, *mRS* modified Rankin Scale, *PH* parenchymal hematoma, *rPH* remote parenchymal hematoma

Table 4 Logistic regression modeling for primary outcome (good functional outcome, mRS 0–2)

Factor	OR (95% CI)	*p*-value	Elimination step
Age	0.94 (0.9–0.97)	0.001	/
NIHSS at admission	0.88 (0.81–0.95)	0.002	/
Bridging	2.76 (1.08–7.07)	0.034	/
Leukoaraiosis	0.79 (0.12–5.04)	0.799	1
mRS 0–2 at baseline	1.96 (0.13–28.73)	0.677	2
ASPECTS	0.82 (0.52–1.29)	0.389	3
Smoking	0.44 (0.07–2.77)	0.379	4
Successful reperfusion	0.54 (0.2–1.41)	0.208	5
Systolic blood pressure (per mmHg)	0.98 (0.96–1)	0.117	6
Blood glucose (per mg/dL)	0.99 (0.99–1)	0.106	7

very low (5.2%), with vasospasm and SAH occurring in less than 5 and 2% of people, respectively. Such rates seem particularly reassuring of the safety of BT and EVT in MeVO in real world, despite the general assumption that local distortion and shear-stress are more problematic the more distal the EVT is performed, with higher risk of vasospasm, vessel perforation, and SAH. Current literature reports a 8–10% rate of sICH [11, 17], slightly higher compared to that expected for LVOs (4.4%) [4]. In ASTER study sub-analysis, total adverse events occurred in 14.6% patients with contact aspiration and 9.7% patients treated with stent-retriever [9], therefore with higher prevalence compared to our cohort.

Our study also suggests that we should aim for recanalization independently from clinical severity. Indeed, the median NIHSS score of our cohort was lower than that expected for LVO [4], highlighting that this cannot be regarded as a consistent item to hesitate in pursuing revascularization in MeVOs [7]. As a further point, ASPECT score does not seem to support any meaningful decision in MeVO, as scores are usually high and seem to have little impact on functional outcome on long term. Therefore, advanced imaging, with assessment of collaterals and perfusion deficit, might find large application in these patients. In this study, all patients received multimodal imaging including CT, CTA, and CTP, independently from timing of onset, allowing to cover potential marginal gaps in the identification of MeVO due to single neuroimaging technique.

Our findings should be interpreted in light of some limitations. First, the most represented MeVO was distal M2, with clinical features well represented in the NIHSS score and an anatomical region that could be easily investigated with multimodal imaging. Other occlusive patterns were present, but their global prevalence prevented from drawing firm conclusions. Therefore, further studies are needed to investigate the potential advantage of bridging in more distal sites, with the aim of reaching a tailored treatment. A second limitation also derives from real-world setting and our singe-center design, with EVT-only patients suffering from IVT-ineligibility criteria, which carries potential bias for worse outcome. To this extent, however, the EVT-only group had higher rates of baseline good functional status compared to the IVT-only group, had slightly lower rates of previous stroke, and had similar onset-to-groin timing to the BT group, adding some robustness to our findings. Since our center is a high volume EVT center, our data, although limited by the small sample, may suggest that, at least, common practice seems to have very little hazards in MeVO treatment. Third, we defined successful recanalization according to mTICI, which, despite being now suggested as a reasonable rating for MeVO, still may incur in strict scoring given the peculiar denominator, represented by the supply downstream to the occlusion rather than the entire vascular territory. Finally, the nature of this study,

observational and non-funded, reverberates the standard of practice at our comprehensive stroke center, with advanced imaging performed in all patients independently from timing of presentation, aiming at tailored emergent treatment. Therefore, generalizability may be limited to context with available advanced imaging.

Overall, our results suggest that in AIS due to MeVO, BT may carry higher rates of functional independence on long term, with marginal gains in successful reperfusion and with very low risk of sICH. Results from randomized controlled trials are awaited (DISTAL trial, the American DISTAL, Canadian ESCAPE-MeVO—NCT05151172—and FRONTIER trial) to weigh the benefit of a combined approach to treat distal occlusions.

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Author contribution FR: study design, data collection, and manuscript drafting. MR: study design, manuscript drafting, and statistical analysis. MP, GL, and AZ: study design supervision, and revised manuscript for intellectual content. MG, SF, LP, FN, MP, SG, FT, CP, and LM: revised manuscript for intellectual content.

Declarations

Ethical approval Ethical approval was not sought for the present study because the study was nested within the local stroke registry.

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