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ORIGINAL COMMUNICATION

Effect of mechanical thrombectomy alone or in combination with intravenous thrombolysis for acute ischemic stroke

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Abstract

Objective and design Whether combining intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) is superior to mechanical thrombectomy alone for large vessel occlusion acute ischemic stroke is still uncertain. Our aim was to compare the safety and the efficacy of these two therapeutic strategies.

Materials Patients with acute ischemic stroke secondary to anterior circulation large vessel occlusion.

Methods A retrospective analysis was conducted. IVT was performed with full dose recombinant tissue plasminogen activator. MT alone was performed only if intravenous thrombolysis was contraindicated. Primary outcomes were successful reperfusion, 3-month functional independence, symptomatic intracranial hemorrhage (sICH), and 3-month mortality.

Results 325 patients were analyzed: 193 treated with combined IVT and MT, 132 with MT alone. The combined treatment group showed higher systolic blood pressure (140 [80–230] vs 150 [90–220]; $p=0.036$), rate of good collaterals (55.9% vs 67%; $p=0.03$), use of aspiration devices (68.2% vs 79.3%; $p=0.003$) and shorter onset-to-reperfusion time (300 [90–845] vs 288 [141–435]; $p=0.008$). No differences were found in the efficacy and safety outcomes except for mortality which was lower in the combined treatment group (36.4% vs 25.4%; $p=0.02$). However, after multivariable analysis combined treatment was not associated with lower mortality (OR 1.47; 95% CI 0.73–2.96; $p=0.3$).

Conclusions Our study suggests that mechanical thrombectomy alone is effective and safe in patients with contraindications to intravenous thrombolysis. Preceding use of IVT in eligible patients was not associated with increased harm or benefit. Randomized controlled trials are needed to clarify whether intravenous thrombolysis before mechanical thrombectomy is associated with additional benefit.

Keywords Large vessel stroke · Intravenous thrombolysis · Mechanical thrombectomy · Combined treatment

Introduction

Randomized endovascular stroke trials have clearly shown the efficacy of mechanical thrombectomy (MT) combined to intravenous thrombolysis (IVT) compared to IVT alone for the treatment of acute ischemic stroke (AIS) secondary to large vessel occlusion (LVO) [1–5]. These trials have opened new perspectives of AIS management in the next future. A recent meta-analysis showed that the number needed to treat with MT to reduce disability by at least one level on modified Rankin scale (mRS) is 2.6 and that the effect size favoring MT over control persists also in patients ineligible for IVT [6]. In line with these findings, a recent randomized controlled trial, the diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting

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strokes undergoing neurointervention with Trevo (DAWN) trial, demonstrated the efficacy and safety of MT between 6 and 24 h after stroke onset [7]. Whether treatment with IVT before MT is necessary in LVO stroke is highly controversial. We compared the safety and efficacy outcomes between patients treated with IVT and MT (IVMT) and those treated with MT alone (MT).

Materials and methods

A retrospective analysis of patients with anterior circulation AIS consecutively collected from our prospective endovascular stroke registry (August 2009–June 2017) was performed. Patients were selected based on following current treatment guidelines criteria: (1) proximal occlusion of MCA or anterior cerebral artery (ACA) or terminal ICA (tICA), or proximal ICA in combination to an intracranial vessel on CT-angiography (CTA) confirmed on conventional angiography; (2) groin puncture within 6 h from symptom onset or Alberta Stroke Program Early CT score (ASPECTS) ≥ 6; (3) pre-stroke modified Rankin Scale (mRS) ≤ 2; (4) available 3-month follow-up [8–10]. IVT was administered within 4.5 h after stroke onset at a full dose (recombinant tissue plasminogen activator 0.9 mg/kg, 10% as a bolus and the remaining in 1-h infusion) without delay in the beginning of endovascular procedure [8–10]. MT alone was employed only if IVT was contraindicated, as listed in Table 1. Patients treated with pharmacological intra-arterial thrombolysis used in addition to mechanical thrombectomy were included in the analysis. Via transfemoral access, intracranial thrombectomy was performed with a coaxial system. An intermediate aspiration catheter was then advanced till the target vessel and aspiration was performed manually or with dedicated aspiration pump. The choice of device (stentriever or aspiration) was at discretion of the neurointerventionalist.

Baseline characteristics including age, sex, NIHSS, vascular risk factors, type of intracranial occlusion, procedural details, ASPECTS on non-contrast CT [11], collaterals on pre-treatment CTA. Collaterals were independently assessed by two investigators (E.P. and S.F.) using a scale from 0 to 3 derived from the prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (0: no collaterals; 1: collaterals to the periphery of ischemia; 2: collaterals filling 50%-100% of ischemic area; 3: collaterals filling 100% of ischemic area) [12], blinded to the treatment arm and clinical outcome. Thereafter, collateral score was dichotomized in poor (0–1) and good (2–3). The validity of this dichotomization has been already shown [13]. Successful reperfusion was defined as TICI ≥ 2b [14] and complete reperfusion as TICI 3, according to the thrombolysis in cerebral infarction (TICI) grading. Hemorrhagic complications were defined according to the European Cooperative Acute Stroke Study criteria (no hemorrhage, hemorrhagic infarction-1, hemorrhagic infarction-2, parenchymal hematoma-1, parenchymal hematoma-2) [15] and symptomatic ICH (sICH) as a hemorrhage associated with an increase of at least 4 points in the NIHSS. HT on follow-up NCCT was assessed independently and retrospectively by two investigators (G. K. and F. A.) blinded to the treatment arm and clinical outcome. Other outcome measures included 24-h clinical improvement defined as a reduction of at least 4 points in the NIHSS or an NIHSS of 0, 3-month functional independence defined as mRS ≤ 2 and 3-month mortality. The study was approved by the local ethics committee. Informed consent was obtained from all patients or their relatives for treatment and for the study.

Statistical analysis

All data were initially entered into an EXCEL database (Microsoft, Redmond, Washington, USA) and the analysis was performed using the Stata/IC version 13 (StataCorp 2013, College Station, TX, USA). Descriptive statistics consisted of means ± standard deviation (SD) or medians with range for parameters with Gaussian distributions (after confirmation with histograms and the Kolmogorov–Smirnov test) or frequencies (%) as appropriate. Comparison of continuous variables was performed by means of Student's *t* test or Mann–Whitney *U* test. Comparison of categorical variables was performed by means of Fisher's exact test. Variables with a p value < 0.2 in univariate analysis were further

Table 1 Contraindications for IVT

Contraindications	No (%) of patients undergoing mechanical thrombectomy without IVT ($n = 132$)
INR > 1.7 or New oral anticoagulants	50 (37.8)
Symptom onset to door time > 4 h	44 (33.3)
Recent major surgery (within 14 days)	7 (5.3)
Recent stroke (within 3 months)	13 (9.8)
Recent gastroenteric bleeding (within 21 days)	9 (6.8)
History or diagnosis of aneurysm	7 (5.3)
Platelets < 100×10^3/μl	2 (1.7)

tested in a multivariable analysis using logistic regression analysis. A p value of <0.05 was considered statistically significant.

Results

Among 414 patients with LVO ischemic stroke, 89 were excluded and 325 patients were included in our analysis (Fig. 1). Of those, 193 were treated with IVMT and 132 were treated with MT. Supplementary table 1 shows the distribution of treated patients over the study period. Baseline and demographic characteristics are shown in Table 2. The two groups differed for lower rate of diabetes (21.5% vs 11.5%; $p=0.01$), higher systolic blood pressure (140 [80–230] vs 150 [90–220]; $p=0.036$) and higher rate of good collaterals (55.9% vs 67%; $p=0.03$) in the IVMT group. Table 3 summarizes the procedural characteristics. The two groups differed for the higher use of thromboaspiration devices (68.2 vs 79.3; $p=0.003$) and shorter onset-to-reperfusion time (300 [90–845] vs 288 [141–435]; $p=0.008$) in the IVMT group. 1 patient in the IVMT and 5 patients in the MT group were treated beyond 6 h after symptom onset because of favorable imaging (ASPECTS ≥ 6).

The analysis of safety and efficacy outcomes revealed no significant difference in the rate of successful reperfusion, sICH and 3-month functional independence. Mortality at 3 months was lower in the IVMT group (36.4% vs 25.4%; $p=0.02$) (Table 4). Complete reperfusion was higher in the IVMT group (44% vs 56%; $p=0.02$). After logistic regression analysis adjusted for age and NIHSS, IVMT remained associated with lower mortality (OR

Table 2 Demographics & baseline characteristics

	MT (132)	MT + IVT (193)	p
Age, years (mean ± SD)	70.3 ± 12.9	71.8 ± 14.2	0.33
Gender (male) (%)	58 (44)	82 (42.5)	0.80
Hypertension (%)	89 (67)	145 (75)	0.32
Diabetes (%)	28 (21.5)	22 (11.5)	0.01
Atrial fibrillation (%)	68 (52)	84 (44)	0.1
Smoking (%)	24 (18.5)	26 (13.5)	0.15
Glycemia median (range)	120 (50–427)	118 (73–350)	0.34
NIHSS[a] median (range)	19 (3–25)	19 (2–26)	0.44
SBP[b] median (range)	140 (80–230)	150 (90–220)	0.036
DBP[c] median (range)	80 (50–125)	80 (50–130)	0.8
ASPECTS[d] median(range)	8 (2–10)	8 (2–10)	0.32
Site of occlusion			
MCA (%)	79 (60)	122 (63)	0.55
Tandem (%)	46 (35)	62 (32)	
Terminal ICA (%)	1 (0.8)	4 (2)	
T (%)	6 (4.5)	5 (2.5)	
Good collaterals (%)	71 (55.9)	128 (67)	0.03

[a]*NIHSS* National Institute of Health Stroke Scale

[b]*SBP* systolic blood pressure

[c]*DBP* Diastolic blood pressure

[d]*ASPECTS* Alberta Stroke Program Early CT Score

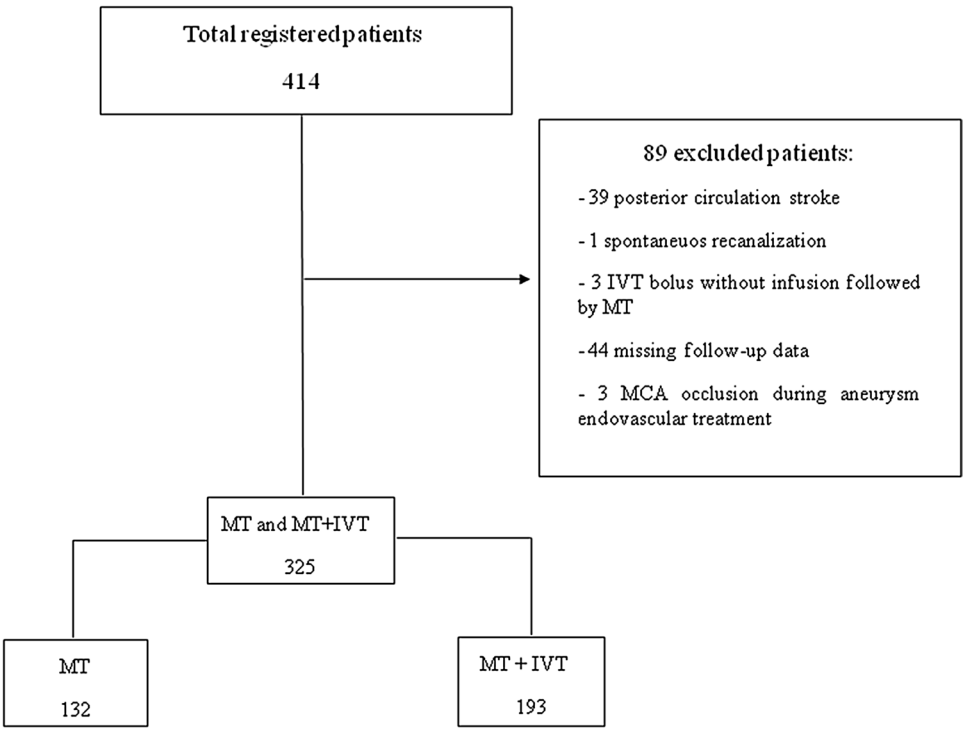

Fig. 1 Flow chart of analyzed patients

Table 3 Procedural characteristics

	MT ($n=132$)	MT + IVT ($n=193$)	p
Intra-arterial thrombolysis	4 (3)	1 (0.5)	0.09
Intra-arterial heparin (%)	79 (60.3)	108 (56)	0.25
General anesthesia (%)	57 (43)	76 (39)	0.53
Type of device			
Stent retriever (%)	35 (26.5)	26 (13.5)	
Thromboaspiration device (%)	90 (68.2)	153 (79.3)	0.003
Combined device (%)	31 (23.5)	62 (32.1)	0.06
Onset-groin puncture time median (range)	222.5 (70–809)	225 (77–380)	0.25
Onset-reperfusion time median (range)	300 (90–845)	288 (141–435)	0.008
Groin-reperfusion time median (range)	60 (7–356)	58 (5–180)	0.42
Device attempts median (range)	2 (1–10)	2 (0–11)	0.61

Table 4 Safety and efficacy outcomes

	MT ($n=132$)	MT + IVT ($n=193$)	p
Successful reperfusion (TICI 2b-3) (%)	90 (68)	146 (75.5)	0.09
Complete reperfusion (TICI 3) (%)	58 (44)	108 (56)	0.02
Overall reperfusion (TICI ≥ 2a) (%)	113 (85.5)	176 (91)	0.08
24-h clinical improvement (%)	52 (39.4)	90 (46.6)	0.22
24-h NIHSS difference median(range)			0.25
Any intracranial hemorrhage (%)	49 (38)	69 (37)	0.48
Type of hemorrhagic infarction (%)			
Subarachnoid hemorrhage	1 (0,8)	3 (1.6)	0.69
Hemorrhagic infarction-1	5 (3.8)	4 (2.1)	
Hemorrhagic infarction-2	10 (7.6)	9 (4.7)	
Parenchymal hematoma-1	11 (8.3)	20 (10.4)	
Parenchymal hematoma-2	18 (13.6)	29 (15)	
Symptomatic intracranial hemorrhage (%)	23 (17)	24 (12.5)	0.14
3-month mRS ≤ 2 (%)	45 (34.1)	78 (40.4)	0.15
3-month mRS ≤ 3 (%)	57 (43.2)	95 (49.2)	0.17
3-month mortality (%)	48 (36.4)	49 (25.4)	0.02

TICI thrombolysis in cerebral infarction, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin Scale

2, 95% 1.1–3.4, $p=0.009$). However, this association did not remain significant when we included collateral status and successful reperfusion in the multivariable model ($p=0.07$). When we included all variables with a p value < 0.2 in univariate analysis, age (OR 1.00; 95% CI 092-0.98; $p=0.001$), successful reperfusion (OR 0.38; 95% CI 0.19–0.77; $p=0.007$), 24-h clinical improvement (OR 0.31; 95% CI 0.15–0.65; $p=0.002$), sICH (OR 5.0; 95% CI 2.0–12.7; $p=0.001$), atrial fibrillation (OR 2.18; 95% CI 1.11–4.29; $p=0.024$), collateral status (OR 0.39; 95% CI 0.20–0.75; $p=0.005$) and baseline glycemia (OR 1.0; 95% CI 0.98–1.0; $p=0.018$) were associated with higher mortality, whereas, treatment strategy (OR 0.76; 95% CI 0.4–1.48; $p=0.4$) was not.

Discussion

In this retrospective analysis of a large prospective registry of LVO ischemic stroke, the safety and efficacy of MT were not significantly different in patients treated with MT alone or combined IVT and MT. Mechanical thrombectomy alone appeared to be a valid option for AIS patients ineligible for IVT. The apparent safer profile with lower mortality found in the IVMT group was not confirmed after adjustment for confounding factors. However, our data showed that combining IVT to MT did not result in an increased risk of sICH. Recent studies comparing MT and IVMT have shown contrasting results in terms of safety and efficacy [16–18]. In a recent metanalysis showing

better safety and efficacy outcomes for combined treatment, IVMT represented 60% of all treatments [18]. The lower use of MT alone in randomized and non-randomized studies could be explained as a result of the current 6-h time window with the first 4.5 h for IVMT and the last 1.5 h for direct MT [8–10]. This proportion is likely going to change after the results of the DAWN and DEFUSE 3 trials [7, 19]. Of note, our results are in line with those from the study by Coutinho et al. which is the only based on randomized controlled data to date [16]. Differently from this study, we found shorter onset-to-reperfusion time in the IVMT group. This finding was not affected by the site of the occlusion since no differences were found between groups, including in the rate of tandem occlusions which are known to an independent predictor of poor outcome [20, 21]. Despite shorter reperfusion time (12 min earlier) and higher rate of complete reperfusion (absolute difference = 12%) in the IVMT group, this did not translate in different outcomes. Our data revealed a higher use of aspiration catheters compared to stent-retrievers. This could be explained by the availability of different devices throughout the study period and by the cost-effectiveness of aspiration catheters.

Although we cannot exclude that the higher mortality rate found in the MT group may be related to the pre-existing IVT contraindications with possible severe comorbidities and poorer prognosis [22], our results also suggested an association with the higher rate of recanalization and good collaterals in the IVMT group.

The unanswered question of whether IVT prior to endovascular clot retrieval is beneficial for LVO stroke is currently of high interest in clinical practice. The reasons are numerous: (1) IVT increases the risk of ICH and systemic bleeding without definite increase chances of recanalization; (2) IVT might limit the use of antiplatelets or anticoagulants, especially in the hyperacute phase; MT without IVT has no contraindications when delivered in the appropriate time window for LVO stroke.

Our "real-world" results suggest that combining IVT with MT for AIS is not harmful and that MT alone for AIS patients with contraindication to IVT is effective and safe. In addition, if early post-treatment antithrombotic prevention is required, MT alone could be a safe and effective alternative option.

Our study has several limitations. First, its retrospective design and relatively small sample size. Second, assignment to MT group was based on contraindications to IVT which might have affected our results. These contraindications included: late presentation, use of oral anticoagulants, recent major surgery and recent gastrointestinal bleeding, which could have made patients more fragile. In a recent study comparing bridging thrombolysis and direct MT in eligible-IVT patients, the final decision on treatment approach was individualized on a case-by-case basis at the discretion of the team of neurologists and neuroradiologists [23]. This approach may lead to significant delays in pre-treatment workflow and biased assignment group with a likely increase in cohort heterogeneity. Third, this was a single-center study, and therefore, generalizability of results should be cautious. Nonetheless, our analyses are not affected by treatment protocol heterogeneity deriving from multicenter experience. Fourth, the two groups differed for lower rate of diabetes, higher SBP and rate of good collaterals in the IVMT group. However, admission glycemia, which has been shown to be a strong predictive factor of outcome [24], was not different between groups. Furthermore, a recent post hoc analysis from the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) showed that blood pressure did not affect the benefit or safety of MT in AIS patients [25]. Concerning collaterals, it is of note that such a favorable condition in the IVMT group did not translate into a better clinical outcome. Fifth, as shown in Fig. 1, 44 patients were excluded from our analysis because of missing 3-month follow-up data. This could have affected our results. One of the strengths of our study is that all patients in the combined group were treated with full dose recombinant tissue plasminogen activator and thus results were unlikely affected by IVT dose. There are several ongoing randomized controlled clinical trials which are aiming to compare combined IVT and MT vs MT alone (MR CLEAN-NO IV, DIRECT-SAFE and SWIFT-DIRECT) in patients eligible for intravenous thrombolysis. Pending these results, our findings demonstrated that MT alone is effective and safe in patients with contraindications to intravenous thrombolysis. Preceding use of IVT in eligible patients was not associated with increased harm or benefit.

In conclusions, we found no differences in 3-month functional independence and rate of any or symptomatic ICH between combined IVT and MT and MT alone in patients with LVO anterior circulation ischemic stroke. Quicker reperfusion time observed in the combined treatment group needs further research. Results from the ongoing clinical trials may clarify whether IVT is associated with an additional benefit in MT patients eligible for intravenous thrombolysis.

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Compliance with ethical standards

Conflicts of interest None of the authors has conflict of interest to declare.

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