Functional Outcome After Mechanical Thrombectomy with or without Previous Thrombolysis

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Introduction: Combined intravenous therapy (IVT) and mechanical thrombectomy (MT) is the standard treatment for acute ischemic stroke (AIS) with large vessel occlusion (LVO). However, the use of IVT before MT is recently being questioned. **Objectives:** To compare patients treated with IVT before MT with those treated with MT alone, in a real-world scenario. **Methods:** Retrospective analysis of AIS patients with LVO of the anterior circulation who underwent MT, with or without previous IVT, between 2016 and 2018. **Results:** A total of 524 patients were included (347 submitted to IVT+MT; 177 to MT alone). No differences between groups were found except for a higher time from stroke onset to CT and to groin puncture in the MT group (297.5 min vs 115.0 min and 394.0 min vs 250.0 min respectively, $p < 0.001$). Multivariable analysis showed that age < 75 years (OR 2.65, 95% CI 1.71–4.07, $p < 0.001$), not using antiplatelet therapy (OR 1.93, 95% CI 1.21–3.08, $p = 0.006$), low prestroke mRS (OR 4.33, 95% CI 1.89–9.89, $p < 0.001$), initial NIHSS (OR 0.89, 95% CI 0.86–0.93, $p < 0.001$), absent cerebral edema (OR 7.83, 95% CI 3.31–18.51, $p < 0.001$), and mTICI 2b/3 (OR 4.56, 95% CI 2.17–9.59, $p < 0.001$) were independently associated with good outcome (mRS 0–2). **Conclusions:** Our findings support the idea that IVT before MT does not influence prognosis, in a real-world setting.

Key Words: Stroke—Thrombectomy—Thrombolysis—Functional Outcome

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Introduction

Mechanical thrombectomy (MT) has deeply changed the therapeutic approach to acute ischemic stroke in large vessel occlusions (LVO).^{1–6} Combined therapy of intravenous rtPA and MT is currently the standard treatment for patients with LVO in acute ischemic stroke,⁷ however, in all clinical trials only highly selected patients were enrolled, with the great majority of cases in both arms treated with intravenous rtPA.

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In a meta-analysis of several randomized trials, the effect of MT was not influenced by intravenous therapy (IVT), raising the question of whether IVT is beneficial in patients with large vessel occlusion.⁸

It is known that IVT has low effectiveness in the recanalization of large vessels.⁹ Additionally, other potential drawbacks of IVT before MT include delayed initiation of MT, major bleeding, neurotoxicity, and disruption of the blood–brain barrier.^{10–12} Nevertheless, administration of IVT can have advantages. Tissue plasminogen activator promotes the breakdown of fibrin polymers. This way, it could favor the success of MT, not only by softening and reducing the clot size, but also by lysing possible distal small emboli and improving overall microvascular reperfusion, optimizing cerebral perfusion distal to the occlusion.^{12,13}

Our main goal was to evaluate if patients treated with IVT before MT had a better functional outcome at 90 days after stroke than those treated with MT alone in a real-world scenario. Moreover, we aimed to evaluate if other variables such as age, baseline functional status, neurologic deficits and recanalization rates influence the functional outcome.

Methods

All clinical information was retrospectively collected from our prospective acute stroke database. The study protocol was approved by the Ethics Committee of the [Centro Hospitalar Universitário Lisboa Central].

All patients over 18 years old with acute ischemic stroke and LVO of the anterior circulation who underwent MT, with or without previous treatment with IVT, between January 2016 and December 2018, were included. Patients were either referred directly to our hospital (mothership), or transferred from primary stroke centers for MT. Patients with LVO were selected to MT according to international guidelines: time from symptom onset ≤ 6 h, Alberta Stroke Program Early CT (ASPECT) score ≥ 6 and National Institutes of Health Stroke Scale (NIHSS) on admission ≥ 4 , baseline modified Rankin Scale (mRS) score >2 . In particular cases, the decision to treat with MT resulted from a consensus between the stroke physician and the interventional neuroradiologist, using advanced imaging to evaluate collateral circulation and core-perfusion or core-clinical mismatch.

Primary outcome was mRS score at 90 days after stroke onset. A good outcome was defined as mRS 0–2 at 90 days, and poor outcome was defined as mRS 3–6 at 90 days.

Pre-stroke, stroke, procedural and acute post-stroke characteristics were analyzed to assess their effects on functional outcome. Pre-stroke characteristics were age, sex, medical history (cerebral infarction/transient ischemic attack, hypertension, antiplatelets and anticoagulants treatment, diabetes mellitus, dyslipidemia, current smoker, and atrial fibrillation), prestroke mRS, time from stroke onset to Computed Tomography (CT) Scan and from onset to groin puncture.

Stroke characteristics were NIHSS score, stroke etiology and vessel occlusion location (ICA, MCA and ACA).

Procedural characteristics were type of acute intervention (Endovascular Stroke Treatment alone or IVT+Endovascular Stroke Treatment), and modified Thrombolysis in Cerebral Infarction (mTICI) score.

Acute post-stroke characteristics were cerebral hemorrhage, edema according to the European Cooperative Acute Stroke Study (ECASS II)¹⁴ and successful revascularization with mTICI score 2b and 3.

The location of vessel occlusion was determined by CT angiogram performed immediately after non contrast head CT. Cerebral hemorrhage and edema were evaluated by CT scan 24h after thrombectomy. For cerebral edema, COED 2 (Focal brain swelling up to one third of the hemisphere) or COED 3 (Focal brain swelling greater than one third of the hemisphere Brain swelling with midline shift) were considered. For cerebral hemorrhage PH2 (hemorrhage exceeding 30% of the infarct area with significant space occupying effect) and PHr2 (Large confluent hemorrhage in an area remote from the actual infarct; significant space occupying effect may be present) were considered.¹⁵

Thrombectomy was performed using aspiration (ADAPT) (Penumbra, Alameda, CA) as the first choice, by an experienced interventional neuroradiologist. We performed percutaneous transluminal angioplasty, intra-arterial injection of alteplase, or other procedures depending on the case. The selection of devices/technique was according to the discretion of each operator. Thrombolysis was performed according to standard international guidelines.

Statistical analysis

Continuous variables were described with median and inter-quantile range (IQR: P_{25} – P_{75}), and categorical variables as frequencies (percentages).

Nonparametric Chi-Square, Fisher's exact and Mann-Whitney tests were used, as appropriate.

Univariable and multivariable analyses were performed using logistic regression models. In the multivariable regression analysis, all the variables that had a p -value <0.25 in the univariable analysis were considered. Crude and adjusted odds ratios were estimated (OR) with corresponding 95% confidence intervals (95%CI). A sensitivity analysis with propensity scores techniques was performed. The level of significance was $\alpha=0.05$. Data analysis was performed using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

There were 524 patients in our cohort. Median age was 76 (IQR: 64–83), and 47.1% were male. Three hundred and forty-seven patients (66.2%) were submitted to IVT previous to MT, and 177 to MT alone (33.8%). There were no statistically significant differences between the two groups at baseline (Table 1) with exception of time from stroke onset to CT scan and to groin puncture, that were higher in the MT only group (297.5 min vs 115.0 min for time to CT scan, and 394.0 min vs 250.0 min for time to groin puncture, $p < 0.001$ for both), and previous vascular disease, more prevalent in the MT only group (20.9% vs 11.5%, $p = 0.004$).

There was no statistically significant difference in mRS at 90 days between the two groups ($p = 0.759$) (Fig. 1).

In the analysis of the excellent outcome (mRS 0–1), 31% of the patients of the IVT + MT had an excellent outcome at 90 days, when compared to 32% on the MT only group ($p = 0.345$). There were also no significant differences in death rate at 90 days between the two groups (17.9% of patients in IVT+MT vs 23.2% of patients in MT alone, $p = 0.149$) (Fig 1).

Table 2 shows the baseline characteristics of patients according to mRS at 90 days. Two hundred and eighteen patients (41.6%) had a good outcome (mRS 0–2) and 306 (58.4%) had a poor outcome (mRS 3–6), of which with 103 deaths (33.7%). The univariable analysis showed that

Table 1. Comparison of treatment groups

	MT group (n=177)	IVT+MT group (n=347)	p-value
Age, years, median (P ₂₅ -P ₇₅)	75 (53–81)	76 (65–83)	0.330
Male, n (%)	89 (50.3%)	158 (45.5%)	0.303
Co-morbidities, n (%)			
AF	61 (34.5%)	139 (40.1%)	0.212
Antiplatelet therapy	60 (33.9%)	103 (29.7%)	0.285
DM	37 (20.9%)	74 (21.3%)	0.916
HTA	135 (76.3%)	260 (74.9%)	0.729
Dyslipidemia	90 (50.8%)	147 (42.4%)	0.065
Previous stroke	22 (12.4%)	31 (8.9%)	0.112
TIA	2 (1.1%)	8 (2.3%)	0.270
Anticoagulation	9 (5.1%)	22 (6.3%)	0.564
Vascular Disease	37 (20.9%)	40 (11.5%)	0.004
Previous mRS 0-2, n (%)	151 (85.3%)	312 (89.9%)	0.091
NIHSS at entrance, median (P ₂₅ -P ₇₅)	16 (11–22)	17 (12–22)	0.566
Time from onset			
to CT scan, min, median (P ₂₅ -P ₇₅)	297.5 (140.5–466.5)	115.0 (90.0–171.5)	<0.001
to groin puncture, min, median (P ₂₅ -P ₇₅)	394.0 (255.5-605.0)	250.0 (180.0-328.0)	<0.001
Transfer, n (%)	93 (52.5%)	153 (44.1%)	0.066
mTICI score 2b-3, n (%)	155 (87.6%)	295 (85.0%)	0.434
Haemorrhage (PH2 or PHr2), n (%)	10 (5.6%)	11 (3.2%)	0.097
Oedema (COED 2 or 3), n (%)	30 (16.9%)	44 (12.7%)	0.143
NIHSS 24H, median (P ₂₅ -P ₇₅)	13 (4–21)	11 (4–20)	0.686
mRS 0-2 at 90 days, n (%)	72 (40.7%)	146 (42.1%)	0.759

AF - Atrial fibrillation; CT - Computed tomography; DM - Diabetes Mellitus; HTA - hypertension; IVT - Intravenous therapy; mRS - modified Rankin Scale; MT - Mechanical thrombectomy; mTICI - modified Thrombolysis in Cerebral Infarction; NIHSS - National Institutes of Health Stroke Scale; TIA - Transient Ischemic Attack.

Fig. 1. Distribution of modified Ranking Scale (mRS) at 90 days depending on treatment modality.

lower age (median 72 versus 78 years, $p < 0.001$), male sex (52.8% versus 43.1%, $p = 0.030$), low (0–2) prestroke mRS (95.4% versus 83.3%, $p < 0.001$), lower initial NIHSS score (median 14 versus 19, $p < 0.001$), occlusion site M1 (59.2% versus 53.6%, $p = 0.031$), and occlusion site M2+M3+ACA (19.7% versus 16.0%, $p = 0.038$), mTICI score 2b or 3

(91.3% versus 77.8%, $p < 0.001$) and NIHSS score at 24h after stroke (median 4 versus 18, $p < 0.001$) were associated with a good outcome. On the other hand, medical history of atrial fibrillation (29.4% versus 42.5%, $p = 0.002$), antiplatelet therapy (24.8% versus 35.6%, $p = 0.008$), hypertension (68.3% versus 79.7%, $p = 0.003$),

Table 2. Baseline clinical characteristics of patients and mRS at 90 days.

	All (n=524)	mRS 0-2 (n=218)	mRS ≥ 3 (n=306)	p-value
Age, years, median (P ₂₅ -P ₇₅)	76 (64-83)	72 (57-79)	78 (69-84)	<0.001
Male, n (%)	247 (47.1%)	115 (52.8%)	132 (43.1%)	0.030
Medical record, n (%)				
AF	194 (37.0%)	64 (29.4%)	130 (42.5%)	0.002
Antiplatelet therapy	163 (31.1%)	54 (24.8%)	109 (35.6%)	0.008
DM	111 (21.2%)	41 (18.8%)	70 (22.9%)	0.262
HTA	393 (75.0%)	149 (68.3%)	244 (79.7%)	0.003
Dyslipidemia	237 (45.2%)	90 (41.3%)	147 (48.0%)	0.126
Previous stroke	53 (10.1%)	16 (7.3%)	37 (12.0%)	0.078
TIA	10 (1.9%)	1 (0.4%)	9 (3.0%)	0.075
Anticoagulation	31 (5.9%)	11 (5.0%)	20 (6.5%)	0.477
Vascular Disease	77 (14.7%)	28 (12.9%)	49 (16.0%)	0.313
Previous mRS 0-2, n (%)	463 (88.4%)	208 (95.4%)	255 (83.3%)	<0.001
Etiology, n (%)				
Large vessel	67 (12.7%)	31 (14.2%)	36 (11.8%)	0.450
Embolic	237 (45.2%)	78 (35.8%)	159 (52.0%)	<0.001
Not	188 (35.9%)	86 (39.5%)	102 (33.3%)	
Unusual	32 (6.1%)	23 (10.5%)	9 (2.9%)	0.639
NIHSS at entrance, median (P ₂₅ -P ₇₅)	16 (12–22)	14 (8–19)	19 (15-23)	<0.001
Patients with previous IVT, n (%)	347 (66.2%)	146 (67.0%)	201 (65.7%)	0.759
Time from onset				
to CT scan, min, median (P ₂₅ -P ₇₅)	139.5 (92.0-233.3)	146.5 (90.0-248.8)	137.0 (97.5-222.5)	0.475
to groin puncture, min, median (P ₂₅ -P ₇₅)	282.0 (197.0-384.5)	265.0 (189.0-384.0)	290.5 (201.8-375.0)	0.731
Occlusion site, n (%)				
ICA	139 (26.5%)	46 (21.1%)	93 (30.4%)	0.550
M1	293 (55.9%)	129 (59.2%)	164 (53.6%)	0.031
M2 + M3 + ACA	92 (17.6%)	43 (19.7%)	49 (16.0%)	0.038
Patients with no bridging, n (%)	246 (47.0%)	108 (49.5%)	138 (45.1%)	0.315
mTICI score 2b-3, n (%)	437 (83.4%)	199 (91.3%)	238 (77.8%)	<0.001
Haemorrhage (PH2 or PHr2), n (%)	21 (4.0%)	2 (0.9%)	19 (6.2%)	0.009
Oedema (COED 2 or 3), n (%)	74 (14.1%)	7 (3.2%)	67 (21.9%)	<0.001
NIHSS 24H, median (P ₂₅ -P ₇₅)	11 (4–20)	4 (1–8)	18 (12–23)	<0.001

ACA - anterior cerebral artery; AF - Atrial fibrillation; CT - Computed tomography; DM - diabetes mellitus; HTA - hypertension; ICA - Internal Carotid Artery; IVT - intravenous therapy; mRS - modified Rankin Scale; MT - Mechanical thrombectomy; mTICI - modified Thrombolysis In Cerebral Infarction; NIHSS - National Institutes of Health Stroke Scale; TIA - Transient Ischemic Attack. p-values were obtained by univariable logistic regression models.

embolic stroke etiology (35.8% versus 52.0%, $p < 0.001$), large hemorrhage complication (0.9% versus 6.2%, $p=0.009$) and significant edema (3.2% versus 21.9%, $p < 0.001$) were associated with a poor outcome.

The multivariable analysis showed that age under 75 years (OR 2.65, 95% CI 1.71–4.07, $p < 0.001$), not using antiplatelet therapy (OR 1.93, 95% CI 1.21–3.08, $p=0.006$), low prestroke mRS (0-2) (OR 4.33, 95% CI 1.89–9.89, $p < 0.001$), initial NIHSS score (OR 0.89, 95% CI 0.86–0.93, $p < 0.001$), no significant edema (OR 7.83, 95% CI 3.31–18.51, $p < 0.001$), and mTICI 2b or 3 (OR 4.56, 95% CI 2.17–9.59, $p < 0.001$) was independently associated with a good outcome.

From the univariable analysis, all the above variables were selected for the multivariable study, but only younger age, previous antiplatelet therapy, low prestroke mRS, low initial NIHSS score, no significant edema, and mTICI $\geq 2b$ remained independently associated with a good outcome.

Accordingly, age under 75 years old had almost a three-fold increase in the odds of a good outcome (OR 2.65, 95% CI 1.71–4.07, $p < 0.001$). Patients not using antiplatelet therapy and not having significant edema had approximately a two-fold (OR 1.93, 95% CI 1.21–3.08, $p=0.006$) and an eight-fold (OR 7.83, 95% CI 3.31–18.51, $p < 0.001$) increase in the odds of a good outcome, respectively. For each increase of 1 unit on the initial NIHSS score, there was an 11% reduction in the odds of having a good outcome (OR 0.89, 95% CI 0.86–0.93, $p < 0.001$). Also, a prestroke mRS (0-2) and patients with TICI 2b or 3 had approximately a four-fold (OR 4.33, 95% CI 1.89–9.89, $p < 0.001$, and OR 4.56, 95% CI 2.17–9.59, $p < 0.001$, respectively) increase in the odds of a good outcome. Treatment group was not chosen to be part of the final regression model.

The results obtained by the propensity scores methods were similar as no difference between the two treatment groups was observed.

Discussion

We compared patients with acute stroke due to anterior circulation LVO, submitted either to IVT followed by MT or MT alone in a real-world setting, to evaluate differences in the functional outcome. We found similar results for the two groups in terms of the outcome at 90 days.

The wide adoption of IVT has changed the therapeutic approach of acute ischemic stroke. Although IVT is safe and effective in reducing disability in patients with acute ischemic stroke, it has poor efficacy in the recanalization of large vessels.⁹ More recently, MT has been proven a safe and effective therapy for patients with LVO. The usefulness of endovascular MT for acute ischemic stroke in LVO has shown in several randomized controlled trials to improve the functional outcome and for this reason, combined therapy with MT and IVT is currently the standard of care treatment for patients with acute ischemic stroke with LVO in the anterior circulation.^{3–8}

The administration of IV tPA before MT is thought to facilitate clot detachment from the vessel wall as a result of tPA-induced fibrin degradation, and downstream microvascular thrombosis reduction.¹⁶ Nevertheless, considering that 1) LVO are characterized by a low recanalization rate after IVT; 2) MT has high recanalization rates, and 3) there are concerns of increased intracranial and extracranial bleeding risk with IVT pretreatment, the utility of IVT before MT in LVO has recently been questioned.

It is still unclear whether pretreatment with IVT provides any additional benefits to patients with LVO undergoing MT.¹⁷ Although there are some studies which showed that combined therapy (IVT+MT) has better outcomes compared with MT alone,^{18–21} there are others in contradiction suggesting no benefit of IVT pretreatment to MT.^{22–24}

In our study, the use of IVT previous to MT was not associated with better outcome at 90 days or better NIHSS at 24H after stroke, when compared to the use of MT alone. These results are in line with previous meta-analyses that found no significant differences in functional outcome after mechanical thrombectomy alone versus combined therapy with previous IVT.^{25,26} Also, a recently published trial comparing endovascular thrombectomy with or without intravenous Alteplase in acute stroke showed no benefit in the use of thrombolysis previous to MT regarding functional outcome.²⁷ Other recent papers also found that MT alone or IVT+MT did not differ significantly in functional independence rate at 90 days or median discharge National Institutes of Health Stroke Scale (NIHSS) score.^{28–31}

The association between reperfusion success and rate of good outcome was clearly demonstrated in our population, and as with previous studies, our results suggest mTICI to be an important independent predictor of outcome.^{32–35} Our results showed a high reperfusion success rate (83,4%) compared with other studies.^{36–38} One of the variables known to influence the recanalization success is

the clot composition. Rich red blood cell (RBC) thrombi were positively associated with successful reperfusion after thrombectomy, as opposed to thrombi with low RBC content and high fibrin content.^{39,40} We did not analyse the composition of clots in our sample, which constitutes a limitation. The fact that we used newer aspiration devices might also contribute to our better recanalization rates.⁴¹

Since the previous administration of IVT can theoretically influence the recanalization rate, we would expect to see a higher recanalization rate in patients that underwent combined treatment with IVT and MT. However we found no differences between groups (IVT+MT and MT alone) in recanalization rates. Although there is some suggestion that the use of IVT may actually reduce the clot size,⁴² the evidence that IVT previous to MT actually leads to better recanalization rates is still weak.^{26,37,42,43}

In our cohort, we had longer total times from onset to groin puncture in MT alone group when compared to other observational studies.⁴³ The time from onset to CT or to groin puncture were the variables with the most relevant differences between groups. We are aware that the longer CT to groin puncture times in the MT alone group was in many cases probably the reason for not using IVT, and that this fact constitutes a bias in the interpretation of the present data. We could think that the longer CT to groin puncture times in the MT alone group could represent a theoretical advantage in the outcome for the IVT +MT group, however, our analysis does not confirm this. Moreover, the time variable does not seem to be an independent predictor of outcome in these patients. These findings are in line with the evolving idea that shifts from the “time window paradigm” to the “tissue window paradigm”.⁴⁴ Two clinical trials^{45,46} (DAWN and DEFUSE-3) showed benefit in patients treated up to 24 hours from symptom onset, disrupting the “time window paradigm”. It is now demonstrated that other factors contribute to the degree of ischemic injury at any point in time.^{47,48} The growth of ischemic lesions is of vital importance and this growth varies substantially among patients. Thus, the role of collateral circulation in selecting patients for MT should not be underestimated.

Although the time to endovascular treatment and the use of previous IVT does not seem to influence the outcome, other variables were independently associated with a better outcome at 90 days in our cohort. Favorable pre-stroke mRS (0-2), lower NIHSS scores at admission, and age under 75 years old were strongly associated with good outcome, suggesting that these variables have a strong influence on the prognosis of patients after MT regardless of the effect of treatment. This is in line with the literature, showing a complex interaction between several other variables, besides time, such as infarct volume, infarct location laterality, age and baseline functional status of the outcome prognosis.⁴⁹

Our study has several limitations, mainly its retrospective nature, being a single-center study, with lack of external validation. Also, variables such as ASPECTS were not considered since they were unavailable in our prospective database. This variable seems to play an important role in the outcome in patients with ischemic stroke. Not analyzing it represents a major limitation to the study. Nevertheless, the results are representative of a tertiary stroke center, and of a real world scenario of acute stroke due to LVO.

Conclusion

In our cohort of patients with LVO that were submitted to MT, younger age, low mRS at baseline, lower NIHSS at presentation, and good reperfusion status after MT were independent predictors of good clinical outcome. The use of previous IVT and time from onset to treatment did not influence outcome. These findings in a real-world scenario support the existing data that IVT does not influence prognosis in patients with anterior circulation LVO, submitted to MT.

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