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"Mechanical thrombectomy beyond 6 hours for acute ischemic strokes due to M2 occlusions"

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ABSTRACT

Background: The time frame for mechanical thrombectomy (MT) in acute ischemic stroke (AIS) is enlarging. Guidelines recommend MT until 6 h of symptom onset in M2 segment occlusions (grade IIB). In practice, it is frequently performed later.

Aims: To assess the functional prognosis of AIS patients subjected to M2 segment's MT beyond 6 h, compared to standard intervention.

Methods: Retrospective cohort study including all consecutive AIS patients subjected to MT of M2 occlusions between 1st January 2018 and 31st December 2020 in St Joseph's Local Health Unit, Lisbon, Portugal. Allocation to standard or extended groups was done according to the symptom-to-puncture time, whether within or beyond 6 h after symptom onset, respectively. The primary outcome was the modified Rankin Scale (mRS) at three months. Secondary outcomes were symptomatic intracranial hemorrhage (sICH) at 24 h and three-month mortality.

Results: We included 155 patients, 51.0 % men, median age 76.0 years (P_{25}:69.0;P_{75}:86.0), baseline mRS "0-2" in 84.5 %, mean NIHSS 13.6(6.5). Initial Computed Tomography showed early ischemic changes in 27.1 %. Most patients belonged to the standard group (71.0 %). Groups had similar baseline features. The standard group underwent more frequent (68.2 % vs 44.4 %, $p = 0.006$) and earlier (2 h02 min, 3 h02 min, $p < 0.001$) fibrinolysis. Symptom-to-puncture times were 7 h13 min (extended) and 4h01 min (standard), $p < 0.001$. Outcomes were similar between groups (three months' mRS [$p = 0.578$]; sICH [$p = 0.720$]; three-month mortality [$p = 0.422$]).

Conclusions: Our study suggests similar outcomes in M2 occlusions performing MT before and beyond 6 h of symptom onset, consistent with previous studies. Patients might benefit from widening inclusion criteria for MT in AIS.

Introduction

The time frame for mechanical thrombectomy (MT) in the setting of acute ischemic stroke (AIS) has been progressively extended. The DAWN and DEFUSE-3 trials led ultimately to the recommendation of MT from 6 to 24 h after symptom onset in selected patients with intracranial large vessel occlusion (LVO), namely intracranial internal carotid artery or the proximal segment of the medium cerebral artery (MCA M1 segment)[1-3]. MT for M2 occlusions in the first 6 h after symptom onset has a grade IIB recommendation in the American Heart Association's 2019 Guidelines for Acute Ischemic Stroke[3]. Patients presenting with M2 occlusions beyond 6 h of symptom onset have been excluded from clinical trials. Nonetheless, in clinical practice MT is frequently performed in these cases, depending on a case-by-case evaluation.

Aims

We aimed to evaluate the functional prognosis of AIS in patients

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subjected to MT of the M2 segment beyond 6 h of symptom onset, comparing them to patients intervened before 6 h after symptom onset, hypothesizing that the therapeutic benefit extends over a longer time window.

Methods

This is an observational cohort study including all consecutive patients subjected to MT of an M2 occlusion in the setting of AIS in a tertiary center in Lisbon, Portugal, in the three-year period between January 1st, 2018, and December 31st, 2020. Data was collected through the registry SITS (Safe Implementation Of Treatments in Stroke), including demographic baseline features (sex, age, functional status, cerebrovascular risk factors, relevant medication), initial clinical and imaging features (baseline NIHSS, early ischemic Computed Tomography (CT) changes, MCA hyperdensity, side of the occluded M2 segment), information on the acute phase treatment (performance of fibrinolysis, MT recanalization outcome [TICI score], timing of symptom onset, of fibrinolysis and of the puncture, primary/secondary referral to our center), and effectiveness and safety outcomes (functional status and mortality at three months, and the occurrence of symptomatic intracranial hemorrhage at 24 h [sICH], defined as an increase in at least four points in the NIHSS and evidence of bleeding on the repeat brain CT).

Two groups were defined according to the symptom-to-puncture time: the "standard" and the "extended" groups, for patients with a symptom-to-puncture time below and superior to 6 h, respectively.

The primary outcome was the functional status at three months given as the modified Rankin Scale (mRS), and secondary outcomes were the occurrence of symptomatic intracranial hemorrhage (sICH) at 24 h and three-month mortality.

Additionally, two other variables were dichotomized, namely the recanalization – defined as "successful" for a TICI score of 2b and 3 and "not successful" for a TICI score of 0, 1 and 2a –, and the functional outcome at three months – defined as "autonomous" for an mRS between 0 and 2 and "not autonomous" for an mRS > 2.

Statistical analysis used Mann-Whitney test for age and ordinal variables, and chi-squared and Fisher's exact tests for categorical variables, as appropriate. Adjusted odds ratios were estimated (adjOR) with corresponding 95 % confidence intervals using multivariable logistic regression models. A level of significance α=0.05 was considered. Data were analyzed using the Statistical Package for the Social Sciences for Windows (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

The study received approval from the Center's Ethics Committee.

Results

A total of 1257 MT were performed at our center during the study period in the setting of AIS. We excluded from the analysis 1099 cases because they were related to occlusion of other vessels or segments – in isolation or concurrently to an M2 occlusion –, and three additional patients due to missing data preventing the allocation to a subgroup or the assessment of the primary outcome. (Fig. 1)

A total of 155 patients were included, with a slight male predominance (51.0 %), median age 76 years (P_{25}:69.0;P_{75}:86), mostly functionally independent (84.5 % baseline mRS 0-2). The sample's mean baseline NIHSS was 13.6 (6.5). Early ischemic changes occurred in 27.1 % of the baseline CTs, MCA hyperdensity in 46.7 %, and right M2 segment occlusion in 46.5 %.

Most patients belonged to the standard group (n = 110, 71.0 %). There were no significant differences between the standard and the extended group in the above-mentioned demographic, clinical and imaging features (Tables 1 and 2).

Intravenous thrombolysis was more frequent in the standard group (68.2 % vs 44.4 %, $p = 0.006$) and was administered earlier (median 2 h02 min [P_{25}:1 h31 min; P_{75}:2 h42 min] vs 3 h02 min [P_{25}:2 h35 min; P_{75}:4 h05 min], $p < 0.001$). As expected, the extended group was more frequently referred from other hospitals as a "drip and ship" model (82.2 % vs 45.5 %, $p < 0.001$) and had a significantly longer symptom-to-puncture time: median 7 h13 min (P_{25}:6 h33 min; P_{75}:8 h09 min) (extended) and 4h01 min (P25:3 h01 min; P_{75}:4h56 min) (standard), $p <$ 0.001. Successful recanalization (TICI score 2b or 3) was achieved in a similar frequency in both groups (82.7 % standard vs 80.0 % extended, p

Table 1
Baseline demographic, clinical and imaging features.

	Standard (n = 110)	Extended (n = 45)	p value
Sex, male – n (%)	55 (50.0)	24 (53.3)	0.706
Age – median (P_{25}-P_{75})	77.5 (70.0-86.0)	75.0 (64.5-86.5)	0.385
Baseline mRS – median (P_{25}-P_{75})	0.0 (0-4)	0.0 (0-3)	0.297
Baseline mRS, 0-2 – n (%)	90 (81.8)	41 (91.1)	0.147
Arterial hypertension – n (%)	79 (71.8)	35 (77.8)	0.445
Dyslipidemia – n (%)	49 (44.5)	18 (40.9)	0.604
Diabetes Mellitus – n (%)	35 (31.8)	12 (26.7)	0.527
Smoking history – n (%)	9 (8.2)	5 (11.4)	0.554
Previous stroke/TIA – n (%)	14 (12.7)	8 (17.8)	0.413
Atrial fibrillation – n (%)	33 (30.0)	14 (31.1)	0.891
Heart failure – n (%)	24 (21.8)	10 (22.2)	0.956
Arterial disease in other territory – n (%)	15 (13.6)	6 (13.3)	0.960
Antiaggregation – n (%)	34 (30.9)	14 (31.1)	0.980
Anticoagulation – n (%)	21 (19.1)	7 (15.6)	0.604
Statin – n (%)	42 (38.2)	19 (42.2)	0.640
Baseline NIHSS – mean (SD)	13.66 (6.48)	13.30 (6.53)	0.836
Early ischemic changes on head CT – n (%)	32 (29.1)	10 (22.2)	0.382
MCA hyperdensity – n (%)	51 (47.2)	20 (45.5)	0.843
Right MCA M2 occlusion – n (%)	46 (41.8)	26 (57.8)	0.071

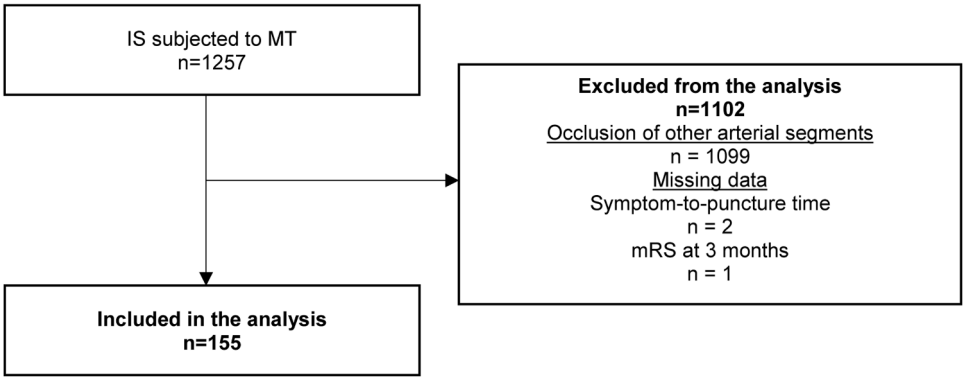

Fig. 1. Flowchart of the included patients. IS: ischemic stroke, MT: mechanical thrombectomy, mRS: modified Rankin scale.

Table 2
Functional status at baseline.

mRS basal n (%)	Total (n = 155)	Standard (n = 110)	Extended (n = 45)
0	120 (77.4)	82 (74.5)	38 (84.4)
1	6 (3.9)	5 (4.5)	1 (2.2)
2	5 (3.2)	3 (2.7)	2 (4.4)
3	15 (9.7)	12 (10.9)	3 (6.7)
4	8 (5.2)	7 (6.4)	1 (2.2)
5	1 (0.6)	1 (0.9)	0 (0.0)

= 0.689) (Table 3).

Using the dichotomized three months' mRS, autonomy (mRS "0-2") was reached in 40.9 % of the standard group and in 42.2 % of the extended group.

Multivariable analysis results showed that, after adjusting for baseline mRS (adjOR 2.610, 95 %CI 1.491-4.567, $p < 0.001$), the primary outcome did not differ significantly between both groups (adjOR 1.305, 95 %CI 0.511-3.333, $p = 0.578$), meaning functional status was similar regardless of the timing of the MT.

The other variables of this multivariable model significantly associated with the mRS at three months were age (adjOR 1.063, 95 % CI: 1.020-1.108, $p = 0.004$), the presence of cerebral oedema at the 24 h repeat imaging (adjOR 3.255, 95 % CI: 1.144-9.261, $p = 0.027$), and NIHSS score at discharge (adjOR 1.151, 95 % CI: 1.073-1.235, $p < 0.001$).

Secondary outcomes were also similar between groups. Regarding sICH, an incidence of 10.0 % was observed in the standard group and of 6.7 % in the extended group. In the multivariable analysis, an adjusted OR of 0.774 (95 % CI: 0.191-3.141) was obtained, but not reaching statistical significance ($p = 0.720$). Only therapy with antiplatelet agents (adjOR 4.050, 95 % CI: 1.227-13.361, $p = 0.022$) and the presence of early ischemic changes in the initial CT scan (adjOR 6.659, 95 % CI: 1.979-22.405, $p = 0.002$) were significantly associated with the occurrence of sICH.

Mortality at three months was 19.1 and 8.9 % in the standard and extended groups, respectively (Fig. 2, mRS 6). In the multivariable model, this difference did not reach statistical significance after adjusting for additional independent variables (adjOR 0.548, 95 % CI: 0.127-2.375, $p = 0.422$). The variables associated with this outcome were age (adjOR 1.130, 95 % CI: 1.036-1.231, $p = 0.006$), NIHSS score at discharge (adjOR 1.162, 95 % CI: 1.062-1.271, $p = 0.001$), and local hemorrhage at the 24 h repeat imaging (adjOR 4.233, 95 % CI: 1.197-14.972, $p = 0.025$).

Discussion

This study evaluated the outcomes of the acute MTs performed in a tertiary center for stroke in a three-year period. The fact that data were collected from a database and the similarity between the groups' baseline features reduced substantially the risk of bias in our sample.

As expected, groups differed in the relative frequency of intravenous thrombolysis and of secondary referrals to our hospital center, as well as in the symptom-to-puncture median times, reflecting a tendency for later admission in the extended group. Still, as said, functional statuses and NIHSS scores did not differ.

Table 3
Referral and acute phase therapy.

	Standard (n = 110)	Extended (n = 45)	p value
Fibrinolysis – n (%)	75 (68.2)	20 (44.4)	0.006
TICI score n (%)			
0	13 (11.8)	6 (13.3)	0.388
1	0 (0)	1 (2.2)	
2a	6 (5.4)	2 (4.4)	
2b	30 (27.3)	17 (37.8)	
3	61 (55.5)	19 (42.2)	
Symptom-to-needle time - median (P_{25}-P_{75})	2 h02 min (1 h31 min-2 h42 min)	3 h02 min (2 h35 min-4 h05 min)	<0.001
Symptom-to-puncture time – median (P_{25}-P_{75})	4 h01 min (3 h01 min-4 h56 min)	7h13 (6 h33 min-8 h09 min)	<0.001
Secondary referral – n (%)	50 (45.5)	37 (82.2)	<0.001

At the three months' evaluation, patients treated before and after 6 h of symptom onset showed similar functional status' scores, favoring our initial hypothesis that patients with later presentations of AIS due to M2 occlusions might still benefit from acute endovascular treatment. Grossly, and not having performed direct comparisons, this outcome seems at least noninferior to the three months' functional status of the treated group in DEFUSE-3 trial, where patients with large vessel occlusion subjected to MT beyond 6 h of symptom onset obtained an mRS score of 0-2 in 44.6 %[2], as well in the DAWN trial, in which the intervention group obtained functional independence in 49.0 %[1].

The outcomes of functional prognosis (both mRS and mortality at three months) and of sICH showed a significant association with some already established factors: functionality was worse in older patients, in those with visible complications in the 24-hours CT scan, and in those with a higher NIHSS at discharge. Moreover, the incidence of sICH was associated with therapy with antiplatelet agents and with the presence of early ischemic changes in the first CT scan. This reinforces the importance of weighing the risks and benefits for each individual patient, specifically pondering age, drugs and initial imaging changes, but possibly not excluding patients solely based on the timing.

Interestingly, and although not statistically significant, we observed a tendency towards better mRS at three months in the extended group. Secondary outcomes – the occurrence of sICH and the three-month mortality – also showed a tendency towards lower frequencies in the extended group. This may point to the relative safety of MT beyond 6 h in M2 occlusions. The relatively benign evolution of the cases in the extended group is hypothesized to lie on biologically different diseases, with some patients having slower progressions of their acute ischemic strokes and being better responders to acute stroke therapy.[4] However, this still lacks substantiation by larger studies.

Limitations of our study include its retrospective design and a reduced statistic power due to the small size of the extended group. As it is not specified in the SITS registry, we do not elaborate on concrete CT scores such as ASPECTS (Alberta Stroke Program Early CT Score). We also did not report data on advanced imaging methods for patient selection, because we do not routinely use them for decision at our center. This practice is consistent with recent and growing evidence questioning the utility of perfusion CT for extended time window patient selection and reinforcing that this decision can be safely performed without advanced imaging data[5].

Overall, this study reports similar effectiveness and safety outcomes in AIS with M2 occlusions performing MT before and after 6 h of symptom onset. It goes in line with recently published results supporting the benefit of MT in patients with M2 occlusions in the late time window.[6] In the cited multicentric study, the comparison was made between M1 and M2 occlusions, both in the late time window, with even better clinical outcomes of late-treated M2 occlusions than those of late-treated M1 occlusions. Our study adds to these results the comparison between early and later MT both in M2 occlusions, and is, to the best of our knowledge, the first work directly addressing this question. It underscores the benefit and the relative safety of MT beyond six hours in AIS due to M2 occlusions.

We consider that patients might benefit from the widening of inclusion criteria for MT in acute stroke. Larger studies are needed to validate our findings and to establish selection criteria.

Data availability

The data supporting these findings are available on request from the corresponding author.

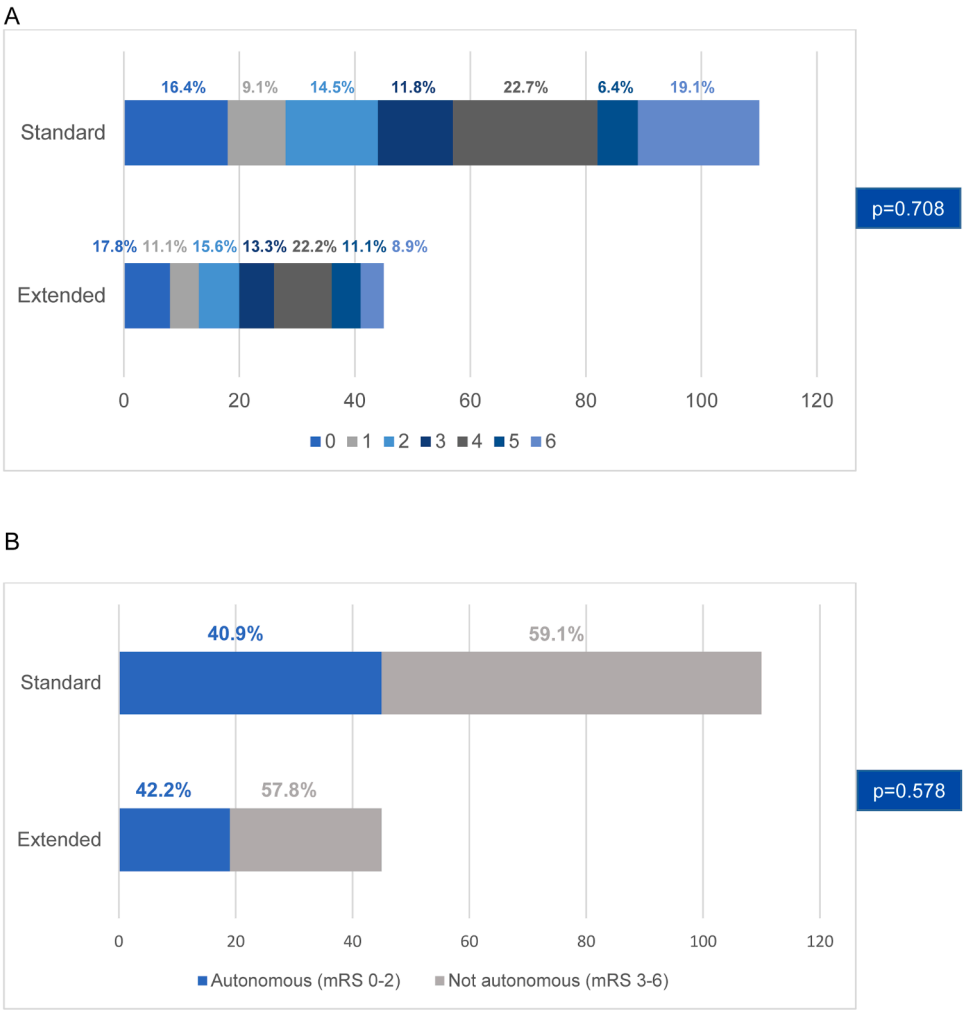

Fig. 2. Functional status at three months given as the seven degrees of mRS (A) and as the dichotomized functional status (B). mRS: modified Rankin scale.

CRediT authorship contribution statement

Maria Pereira Coutinho: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Sofia Galego:** Validation, Methodology, Investigation, Conceptualization. **Marta Alves:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Ana Papoila:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Isabel Fragata:** Writing – review & editing, Validation, Investigation, Conceptualization. **Ana Paiva Nunes:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors have nothing to disclose.

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N/A.

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