

## Original Paper

# Does Intravenous Thrombolysis Influence the Time of Recanalization and Success of Mechanical Thrombectomy during the Acute Phase of Cerebral Infarction?

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## Keywords

Stroke · Thrombectomy · Revascularization time · Revascularization

## Abstract

**Objectives:** Mechanical thrombectomy (MT) is an effective treatment for acute ischemic stroke (AIS) caused by large vessel occlusion. Recanalization time is a key factor in the treatment of AIS. It has previously been suggested that intravenous thrombolysis (IVT) may be associated with a shorter recanalization time. The aim of our study was to investigate whether IVT or other factors could be associated with shorter or longer MT procedure times. **Methods:** We performed a retrospective analysis of a local cohort of patients treated by MT. We collected procedure time (puncture to recanalization and clot visualization to recanalization), demographic data, localization of the thrombus, antithrombotic treatment at arrival, IVT infusion, and stroke subtype at discharge according to the TOAST classification. We planned to analyze the full cohort and the successful revascularization subgroup. **Results:** There was no difference in procedure times between patients who received IVT and those who did not. In the successful revascularization subgroup, patients presenting with cardioembolic stroke had a significantly shorter time between clot visualizations and revascularization than the other patients (41 vs. 56 min,  $p = 0.024$ ), but this was not the case in the full cohort. Also in the successful revascularization subgroup, the revascularization time was 76 vs. 61 min ( $p = 0.075$ ) in patients presenting with tandem occlusion vs. the others, but there was no difference between these groups in the full cohort. **Conclusions:** There was no difference in terms of procedure times in patients treated by IVT and MT vs. patients treated by MT alone either in the

full cohort or in the successful revascularization subgroup. The data from the successful revascularization subgroup may be useful for studying revascularization times, provided that data from procedures that were stopped prematurely by the operator due to the length of time since symptom onset is removed.

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## Introduction

It has been shown that mechanical thrombectomy (MT) associated with intravenous thrombolysis (IVT) treatment is effective during the acute phase of cerebral infarction with proximal occlusion of the anterior circulation in reducing disability at 3 months [1–6]. Treatment by MT alone versus standard-of-care treatment has only been assessed retrospectively in subgroups of randomized controlled trials, with a significant difference in favor of the treatment. These results have led to a discussion about the benefits of MT without IVT in cases of proximal occlusion [7] or distal ICA occlusion [8]. A recent study and meta-analysis suggested a better prognosis for patients who receive a combined procedure [9, 10]; however another meta-analysis found no association between a combined procedure and improved outcomes [11]. The impact of IVT on MT is widely debated, in particular because the perfusion time could delay MT. On the other hand, IVT could be associated with faster recanalization following the thrombectomy procedure [12], but this hypothesis was not confirmed when studied in a larger cohort [13]. Following the assumption that IVT patients are recanalized faster than those receiving MT only, we hypothesized that other factors, including location of the thrombus and stroke etiology, could influence revascularization time.

## Materials and Methods

Among patients prospectively included in the Besançon stroke registry (RUN-FC, previously described) [14, 15] from January 1, 2015, to December 31, 2016, we conducted a retrospective study including all patients with acute ischemic stroke (AIS) who were referred for an MT procedure. The local legal agreements were obtained (CNIL agreement 1042748). The study population included 123 stroke patients. Seventeen of those patients were excluded from this study because the MT was not performed due to angiographic technical difficulties (puncture failure or failure to catheterize the common or internal carotid artery [ICA]). Nine patients, all of whom underwent IVT, appeared recanalized at the diagnostic angiography step before MT and were also excluded. One hundred six patients were included in our study. The data concerning the duration of the IVT and MT procedures was collected prospectively by the on-duty neurology team. The clinical data was analyzed by the neurology team. The imaging data was collected by a neurologist qualified in neurovascular pathology and reviewed by an interventional neuroradiologist and a neurologist qualified in neurovascular pathology. Medical records were used to determine stroke etiology, which was categorized according to the TOAST [16] classification by 2 neurologists. The classification procedure was standardized in staff meetings for the neurovascular department or multidisciplinary meetings.

### *Parameters Related to the Revascularization Procedure*

The variables studied were: (1) the duration of the procedure, defined as the time from groin puncture to the first image from the first cerebral angiographic test acquired after

revascularization, which is used to calculate the revascularization time; (2) the time from angiographic clot visualization to revascularization, reflecting the duration of catheterization and avoiding problems concerning femoral puncture or catheterization of the vessels from the aortic arch; (3) the modified Thrombolysis in Cerebral Ischemia (mTICI) scale score [17] (0, no flow beyond the occlusion; 1, minimal reperfusion; 2a, less than 50% of the affected vascular territory reperfused; 2b, greater than 50% reperfusion; and 3, complete reperfusion), which was considered successful at 2b or 3; and (4) prognosis at 3 months as defined by the modified Rankin scale [18] (functional independence corresponding to a score of 0–2), which was collected by a physician from the RUN-FC stroke network.

#### *Successful Revascularization Subgroup*

To determine the effect of IVT on the MT procedure, we analyzed a subgroup of patients who were considered to have successful revascularization (mTICI 2b or 3). The other cases (TICI <2b) were not considered, because the interventional neuroradiologist stopped the procedure as a result either of technical difficulties or a long time between symptom onset and the procedure. Within this subgroup, we compared revascularization times for the combined procedure group versus the MT-only group.

#### *Statistical Analysis*

A Mann-Whitney-Wilcoxon test was completed for mean comparisons. Qualitative variables were compared using a Fischer test.  $p < 0.05$  was considered statistically significant. Analyses were performed using R software.

## Results

Out of 106 patients, 83 patients underwent the combined procedure and 23 patients underwent the MT procedure only. The time of artery puncture was not indicated in 9 cases. The NIHSS score was not reported in 2 patients. The mRS score at 3 months was not recorded for 1 patient who moved to another country. The patients' characteristics are summarized in Table 1.

The patients treated with combined IVT and MT procedures were younger than the patients who underwent MT only (mean age: 67 vs. 74 years) and the time from the onset of symptoms to clot visualization was longer (mean time: 308 vs. 300 min). Patients treated solely by MT were more often under anticoagulant therapy (52 vs. 8%;  $p < 0.001$ ) or under both anticoagulant and antiplatelet therapy (22 vs. 2%;  $p = 0.0051$ ) on admission, and the stroke etiology was more often of cardioembolic origin (91 vs. 51%;  $p < 0.001$ ). There was no significant difference regarding sex, NIHSS score, or antiplatelet therapy. In the MT-only group, the causes of contraindication to IVT were a period of time exceeding 4.5 h in 52% of the cases, patients under anticoagulant treatment in 39% of the cases, and other hemorrhagic risk in 17% of the cases. Regarding the etiology for the whole cohort, 63 strokes were cardioembolic in origin (mean age: 73 years) and 43 strokes were noncardioembolic (mean age: 62 years).

#### *Analysis of the Full Cohort*

In the full cohort, there was no significant difference in revascularization time for patients who received MT-only treatment and patients who underwent a combined procedure (Table 1; 73 vs. 69 min, respectively;  $p = 0.36$ ). Among the full cohort of patients who received MT-only treatment, those who were receiving treatment with anticoagulants at admission had a revascularization time comparable to that of those who were not receiving this treatment

**Table 1.** Patient characteristics and comparison between the IVT+MT and MT groups

Characteristic	Total (n = 106)	IVT+MT (n = 83)	MT (n = 23)	p
Females	54 (51)	39 (47)	15 (65)	0.16
Age, years	69	67	74	0.029
Median NIHSS score at admission	18	18	19	0.62
mTICI 2b-3	72 (68)	57 (69)	15 (65)	0.8
Anticoagulant therapy at admission	19 (18)	7 (8)	12 (52)	<0.001
Antiplatelet therapy at admission	29 (27)	21 (25)	8 (35)	0.43
Anticoagulant and antiplatelet therapy at admission	7 (7)	2 (2)	5 (22)	0.0051
Location				
Right	40 (38)	32 (39)	8 (35)	0.85
Tandem	19 (18)	17 (20)	2 (9)	0.25
Dissection	2 (2)	2 (2)	0 (0)	1
Distal ICA occlusion	25 (24)	21 (25)	4 (17)	0.58
M1	66 (62)	53 (64)	13 (57)	0.63
M2	7 (7)	4 (5)	3 (13)	0.17
Posterior circulation	8 (8)	5 (6)	3 (13)	0.37
Revascularization attempts				
Attempts, n	2.5	2.4	2.7	0.31
Stent retriever	48 (45)	36 (43)	12 (52)	0.49
Duration				
From onset of symptoms to puncture	292	290	298	0.23
From onset of symptoms to clot visualization	307	308	300	0.045
From puncture to revascularization	70	69	73	0.36
From clot visualization to revascularization	53	52	56	0.24
General anesthesia				
Before the procedure	42 (40)	31 (37)	11 (48)	0.47
During the procedure	8 (8)	5 (6)	3 (13)	0.37
Rankin score mRS 0–2	27 (26)	23 (28)	4 (17)	0.42

Values are presented as means or numbers (%) unless otherwise stated.

(80.5 vs. 63.5 min,  $p = 0.197$ ). In the full cohort, patients with tandem occlusion had a revascularization time similar to that of those who did not present with tandem occlusion, and patients with or without cardioembolic infarct presented with similar revascularization times (Table 2).

#### *Analysis of the Successful Revascularization Subgroup*

In the successful revascularization (mTICI 2b-3) subgroup, we found no significant difference regarding the revascularization time in patients who received MT-only treatment and patients who underwent a combined procedure (Table 3). Patients in the MT-only group were more likely to be scored mTICI 3 although the difference was not statistically significant (47 vs. 21% in the combined procedure group;  $p = 0.056$ ).

Patients with tandem occlusion in this subgroup were revascularized less quickly, with an average revascularization time of 76 versus 61 min among those without carotid occlusion, but the difference was not significant ( $p = 0.075$ ; Table 4). In this cohort only 1 patient required balloon angioplasty on the extracranial ICA, and no ICA stenting was performed.

There was no significant difference within the successful revascularization subgroup in terms of the puncture-revascularization time between patients with a cardioembolic

**Table 2.** Association of tandem occlusion and cardioembolic etiology with revascularization in the whole cohort

Full cohort	Tandem	Non-tandem	<i>p</i>	Cardio-embolic	Non-cardio-embolic	<i>p</i>
Patients, <i>N</i>	19	87		63	43	
Mean time from puncture to revascularization, min	74	68	0.20	63	78	0.076
Mean time from clot visualization to revascularization, min	58	52	0.20	47	61	0.12
mTICI 2b-3, <i>n</i> (%)	11 (58)	61 (70)	0.59	45 (71)	27 (63)	0.4
mRS 0–2, <i>n</i> (%)	5 (26)	22 (25)	0.79	15 (24)	12 (28)	0.66
Attempts, <i>n</i>	2.9	2.4	0.20	2.4	2.7	0.27

**Table 3.** Comparison between patients who received IVT therapy and patients who did not in the TICI 2b-3 subgroup

mTICI 2b-3 subgroup	IVT+MT	MT	<i>p</i>
Patients, <i>N</i>	57	15	
Mean time from puncture to revascularization, min	64	64	0.84
Mean time from clot visualization to revascularization, min	46	47	0.081
mTICI 3, <i>n</i> (%)	12 (21)	7 (47)	0.056
mRS 0–2, <i>n</i> (%)	20 (36)	4 (27)	0.76
Attempts, <i>n</i>	2.3	2.3	0.62

**Table 4.** Association of tandem occlusion and cardioembolic etiology with revascularization in the TICI 2b-3 subgroup

mTICI2b-3	Tandem	Non-tandem	<i>p</i>	Cardio-embolic	Non-cardio-embolic	<i>p</i>
Patients, <i>N</i>	11	61		45	27	
Mean time from puncture to revascularization, min	76	61	0.075	57	73	0.09
Mean time from clot visualization to revascularization, min	62	44	0.053	41	56	0.024
mTICI 3, <i>n</i> (%)	0 (0)	17 (28)	0.27	15 (33)	4 (15)	0.1
mRS 0–2, <i>n</i> (%)	5 (45)	19 (32)	0.29	13 (29)	11 (41)	0.32
Attempts, <i>n</i>	3.1	2.1	0.084	2.1	2.5	0.36

etiology compared to the others (Table 4). However, the time between clot visualization and revascularization was significantly shorter in the cardioembolic group (41 vs. 56 min;  $p = 0.024$ ).

Among patients with successful revascularization after MT-only treatment, those who were under anticoagulant therapy had a revascularization time comparable to that of those who were not receiving anticoagulant therapy (59.7 vs. 68.9 min;  $p = 0.93$ ).

## Discussion

In our experience, the time taken for the MT procedure for AIS was not shorter in patients treated with combined IVT and MT procedures versus patients treated with MT only. These results do not support the first data published on the subject [12], but they are similar to those of a more recent study [13]. However, in our series the 2 groups were not homogeneous; patients in the MT-only group were older. It is possible that these patients had more advanced atheromatous lesions, which would have presented a less favorable prognosis and made the procedure more difficult. Ongoing randomized controlled trials (MR CLEAN NO IV and SWIFT DIRECT) are necessary to confirm the influence of IVT on MT. A higher number of MT-only patients presented with cardioembolic infarction and so the procedure could have been affected by histology-specific thrombi. In addition, this group also contained more patients under anticoagulation therapy, which is likely to be secondary to more prevalent cardioembolic pathologies. Anticoagulation could have an impact on thrombus dissolution during the procedure.

Demographic data from our cohort was similar to that of HERMES patients [19] regarding the mean age (68 years), the percentage of women (48% in the intervention group and 46% in the control group), and the baseline NIHSS score (median: 17). On the other hand, in our series 59% of the patients were diagnosed with a cardioembolic stroke at discharge, with 51% in the IVT+MT group and 91% in the MT-only group. In a recent meta-analysis [11], a cardioembolic etiology was reported in 46.7% of the cases in the IVT+MT group and in 56.6% of the cases in the MT-only group. These results seem to be similar regarding the combined therapy; however, in our MT-only group the percentage of patients with a cardioembolic etiology was higher (91 vs. 56.6%). This may not be significant and could be related to the fact that our MT-only group is small (23 patients) and has a higher average age than the meta-analysis (74 vs. 67 years).

We analyzed the subgroup of patients with successful revascularization in order to avoid including potential reduced revascularization times linked to the decision to stop or continue a procedure. This situation was quite frequent in 2015–2016, because most neurointerventionists respected the 6-h window advised by the first positive randomized controlled trials [1, 3, 5]. In the subgroup of patients with favorable revascularization scores (mTICI 2b-3), a nonsignificantly higher number of patients undergoing MT-only treatment achieved mTICI 3. This suggests that IVT therapy may have a negative influence on revascularization. We could hypothesize that partial fragmentation of the thrombus due to IVT leads to distal emboli that affect the final mTICI score. In our subgroup of mTICI 2b-3 patients, the shorter time from clot visualization to revascularization in patients presenting with cardioembolic infarction seems to contradict the data in the literature from another cohort [20]. This could be explained by the fact that in the published series the patients were younger (mean age: 58 and 59 years in the cardioembolic and noncardioembolic groups, respectively) compared to our cohort. This could be due to the fact that those patients were recruited from 2011 to 2014, before the first positive thrombectomy randomized controlled trials were published. In our cohort with older patients, the frequent atherosclerotic lesions potentially associated with a noncardioembolic etiology could play a predominant role. We can therefore hypothesize that age could have more of an impact on recanalization time than stroke etiology.

The revascularization time of patients presenting with tandem occlusion suggests that these patients remain good candidates for endovascular therapy. Our cohort displayed an additional mean delay of an average of 6 min for puncture-revascularization time among these patients, with no significant difference between these patients and patients not presenting with carotid occlusion. There was no difference in the mRS scores. This data is consistent with previous studies [21, 22]. However, in the mTICI 2b-3 subgroup, the revascu-



larization time showed a tendency to be longer for patients presenting with tandem occlusion by an additional 15 min. The fact that this is not highlighted in the full cohort leads us to believe that there is a large bias toward the MT procedure being stopped prematurely for patients with an mTICI score lower than 2b. Moreover, patients presenting with tandem occlusion have prolonged times between clot visualization and revascularization. This could be explained by specific problems concerning revascularization other than carotid recanalization. One explanation could be the higher prevalence of distal ICA occlusion in the tandem group (79 vs. 11%,  $p < 0.001$ ).

Our study has some limitations. We present a relatively small series, and so we cannot rule out a detectable statistical link for an increased number of patients. However, the statistical difference in terms of procedure time that was found previously was with a smaller series [12]. The retrospective analysis cannot rule out causal links between the factors studied and patient outcomes.

### Conclusion

Among our retrospective cohort of patients revascularized by MT, there was no difference in reperfusion time between those who received IVT+MT treatment and those who underwent MT-only treatment. Patients presenting with tandem occlusion tended to have their procedure extended by a mean time of 15 min, but with no difference in terms of clinical prognosis. More studies about the procedure time of MT for stroke analyzing patients with successful revascularization are needed.

### Statement of Ethics

This study was approved according to local legislation.

### Author Contributions

G.C. and L.B. conceived this study. G.C., L.B., A.B., and T.M. wrote this paper. G.C., L.B., B.B., F.V., G.V., and E.M.B. contributed to data collection.

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