

Primary Thrombectomy Versus Combined Mechanical Thrombectomy and Intravenous Thrombolysis in Large Vessel Occlusion Acute Ischemic Stroke

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Mechanical thrombectomy (MT) in combination with intravenous thrombolysis (IVT) is the standard of care for patients with acute ischemic stroke with anterior circulation large vessel occlusion. The particular benefit of IVT in these patients is unknown. We performed a retrospective analysis of patients submitted to MT at our center between January 2015 and June 2017. Functional outcome was prospectively assessed using modified Rankin scale (mRS) at 3 months. A total of 234 patients were enrolled, 152 (65%) in the combined treatment group and 82 (35%) in the direct MT group. Patients receiving combined treatment had a higher frequency of intracranial internal carotid artery occlusion (48 [31.6%] versus 16 [19.5%], $P = .048$) and significantly less strokes of cardioembolic etiology (72 [47.4%] versus 57 [69.5%], $P = .01$). Other baseline characteristics did not differ between the 2 groups. Good functional outcome at 3 months (mRS 0-2) was trending toward being higher in patients in the combined treatment group (98 [64.9%] versus 42 [52.5%], $P = .066$). Rates of symptomatic intracranial hemorrhage (5 [3.3%] versus 4 [4.9%], $P = .723$) and mortality (15 [9.9%] versus 14 [17.5%], $P = .099$) did not differ between groups. In multivariate logistic regression analysis, we did not find a statistically significant association between the use of IVT and any of the outcomes studied. Our results suggest that combined treatment carries similar effectiveness and safety than direct MT. Randomized controlled trials regarding this subject are warranted.

Key Words: Primary mechanical thrombectomy—stroke—thrombectomy—thrombolysis

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Introduction

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) was the only reperfusion therapy with a proven clinical benefit in acute ischemic stroke

for over 20 years.¹ In 2015, 5 randomized controlled trials established that mechanical thrombectomy (MT) in combination with IVT (combined MT+IVT) was superior to IVT alone in patients with large vessel occlusion (LVO) in the anterior circulation.²⁻⁶ Although current guidelines

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Received June 27, 2018; revision received October 3, 2018; accepted November 3, 2018.

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1052-3057/\$ - see front matter

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<https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.002>

recommend that patients eligible for IVT should receive it without delay even if MT is being considered,⁷ the particular benefit of IVT in patients with LVO is a matter of debate.

On the one hand, IVT could positively influence the outcome since it can be started earlier than MT and enhance the fibrinolytic process, possibly obviating the need of MT, especially in more distal and harder to reach thrombi.⁸ Additionally, it may soften the thrombus, reducing the duration of the procedure and the number of passes needed to achieve successful recanalization.^{9,10} On the other hand, IVT is not effective in most patients with LVO, particularly in those with high clot burden,¹¹ and can induce thrombus migration leading to an untreatable occlusion.^{12,13} It may also increase the risk of hemorrhagic complications and limit the administration of antiplatelets or anticoagulants.¹

Therefore, the question whether pretreatment with IVT in patients submitted to MT is beneficial remains unanswered. The aim of this single-center retrospective analysis was to compare the efficacy and safety of direct MT versus combined MT+IVT in patients with anterior circulation strokes caused by LVO.

Methods

We analyzed individual patient data from all consecutive acute ischemic stroke patients with anterior circulation LVO (intracranial internal carotid artery [intracranial ICA], M1 or proximal M2 segments of the middle cerebral artery, including tandem occlusions) who were submitted to endovascular treatment at our center, between January 2015 and June 2017.

Baseline characteristics such as demographic data, pre-morbid modified Rankin scale (mRS), vascular risk factors, clinical findings, stroke etiology, and times from symptom onset (or last seen well – LSW) to needle, groin puncture, and recanalization were recorded for all patients. Details about patient selection have been published elsewhere.¹⁴ The study was approved by the local ethics committee.

The primary efficacy outcome was functional outcome at 3 months, which was prospectively assessed in an outpatient visit using mRS; excellent outcome was defined as mRS 0-1 and good outcome as mRS 0-2. Other effectiveness outcome variables included times from symptom onset to groin puncture and recanalization, number of passes with stent retriever and rate of successful recanalization (defined as modified Thrombolysis in Cerebral Ischemia 2b or higher at the end of the procedure).

Safety outcomes included the incidence of intracranial hemorrhage (ICH) and mortality within 90 days from hospital stay. ICH was classified as asymptomatic or symptomatic ICH (sICH), according to the European Cooperative Acute Stroke Study-III protocol.¹⁵

Statistical analysis was conducted using the SPSS version 22 software package (IBM Corp, Armonk, NY). All reported *P* values are 2-tailed, with a *P* value of less

than .05 indicating statistical significance. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Normal distribution was checked using Shapiro-Wilk test or skewness and kurtosis. Baseline characteristics, peri-procedural data and outcome measures were compared between patients receiving direct MT and combined MT+IVT, using the Mann-Whitney *U* test or Student's *t* test for continuous variables and Fisher's exact test or the Chi-square test for categorical variables, as appropriate. Using a multivariate logistic regression analysis, we adjusted our outcome results for variables which are known predictors of our outcomes or with a *P* < .05 in univariate analysis. These variables were age, National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, intracranial ICA occlusion, cardioembolic stroke, and time from symptom onset to recanalization.

Results

Within the study period, a total of 234 patients with anterior circulation LVO were treated with MT. Of the 234 patients, 152 (65%) underwent combined MT+IVT and 82 (35%) underwent direct MT. Information on functional outcome was missing for 3 patients. The contraindications for IVT in patients who were treated with direct MT are reported in Table 1. The most common were time since symptom onset or LSW greater than 4.5 hours and previous anticoagulation or international normalized ratio over 1.7.

Comparisons of baseline characteristics are shown in Table 2. Patients receiving combined MT+IVT had a higher frequency of intracranial ICA occlusion (48 [31.6%] versus 16 [19.5%], *P* = .048) and significantly less strokes of cardioembolic etiology (72 [47.4%] versus 57 [69.5%], *P* = .01). Other baseline characteristics did not differ between the 2 groups.

Table 1. Contraindications for IVT

Contraindication	Number of patients (%)
Time since symptom onset or LSW >4.5 h	37 (45.1)
Oral anticoagulation or INR >1.7	24 (29.4)
Active bleeding/potential bleeding diathesis	7 (8.5)
Platelets <100.000/mm ³	2 (2.4)
aPTT >40 s or PT >15 s	2 (2.4)
Other	6 (7.3)
Multifactorial	4 (4.9)

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; IVT, intravenous thrombolysis; LSW, last seen well; PT, prothromboplastin time.

Table 2. Baseline characteristics of the study patients*

	Direct MT (n = 82)	Combined MT+IVT (n = 152)	P value
Age, mean (SD), y	71.93 (13.67)	70.90 (12.60)	.565
Female	43 (52.4)	82 (53.9)	.825
Premorbid mRS			.094
0-1	72 (87.8)	143 (94.1)	
2-3	10 (12.2)	9 (5.9)	
Hypertension	54 (65.9)	104 (68.4)	.689
Diabetes	24 (29.3)	30 (19.7)	.099
Hyperlipidaemia	49 (59.8)	79 (52)	.254
Current smoker	13 (15.9)	17 (11.2)	.308
NIHSS, mean (SD)	15.67 (4.48)	16.28 (4.98)	.354
ASPECTS, mean (SD)	8.11 (1.50)	8.08 (1.32)	.864
<u>Location of occlusion</u>			
Tandem ICA	8 (9.8)	18 (11.8)	.627
Intracranial ICA	16 (19.5)	48 (31.6)	.048
MCA – M1 segment	50 (61)	77 (50.6)	.131
MCA – Proximal M2 segment	16 (19.5)	27 (17.8)	.742
<u>Stroke etiology</u>			
Cardioembolic	57 (69.5)	72 (47.4)	.01
Large-artery atherosclerosis	11 (13.4)	25 (16.4)	.540
Undetermined or other	14 (17.1)	55 (36.2)	.02
Left side occlusion	51 (62.2)	82 (53.9)	.269

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, Middle cerebral artery; MT, Mechanical thrombectomy; NIHSS, National Institute of Health Stroke Scale.

*Data are presented as number (percentage) of patients unless otherwise indicated.

Details of the MT procedure and clinical outcomes are presented in Table 3. Median times since symptom onset to groin puncture were slight, but not significantly, higher in the direct MT group (268 versus 245 minutes, $P = .665$), and there were no differences between the median number of passes in the 2 groups. We found that successful recanalization occurred more frequently in the combined MT+IVT group (143 [94.1%] versus 71 [87.7%], $P = .088$), but the difference was not statistically significant. A good outcome at 90 days was trending toward being higher in patients treated with combined MT+IVT compared with

direct MT (98 [64.9%] versus 42 [52.5%], $P = .066$). Rates of ICH and sICH were not significantly different between groups. Mortality was also similar in both groups.

Results of the multivariate analysis are reported in Table 4. We did not find a statistically significant association between the use of IVT and any of the outcomes studied.

Discussion

Our single-center retrospective *real-world* study showed no statistically significant differences between combined

Table 3. Details of procedural, functional, and safety outcomes*

	Direct MT (n = 82)	Combined MT+IVT (n = 152)	P value
Symptom onset to needle, median (IQR), min	–	135 (87)	-
Symptom onset to groin puncture, median (IQR), min	267.5 (203)	245 (140)	.665
Symptom onset to recanalization, median (IQR), min	336.5 (217)	308 (146)	.960
Number of passes with stent retriever, median (IQR)	2 (2)	1 (2)	.164
mTICI 2b or 3 recanalization	71 (87.7)	143 (94.1)	.088
mTICI 3 recanalization	42 (51.9)	86 (56.6)	.490
Any ICH	11 (13.4)	21 (13.8)	.932
Symptomatic ICH	4 (4.9)	5 (3.3)	.723
<u>Outcome at 90 days</u>			
mRS score of 0-2	42 (52.5)	98 (64.9)	.066
mRS score of 0-1	27 (33.8)	61 (40.4)	.322
Mortality	14 (17.5)	15 (9.9)	.099

Abbreviations: ICH, intracranial haemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction.

*Data are presented as number (percentage) of patients unless otherwise indicated.

Table 4. Multivariate analysis*

	Direct MT (n = 82)	Combined MT+IVT (n = 152)	OR (95% CI)	
			Unadjusted	Adjusted
mRS score of 0-2	42 (52.5)	98 (64.9)	1.67 (0.96-2.90)	2.19 (0.93-5.19)
mRS score of 0-1	27 (33.8)	61 (40.4)	1.33 (0.76-2.34)	1.42 (0.59-3.39)
Any ICH	11 (13.4)	21 (13.8)	1.04 (0.47-2.27)	0.82 (0.31-2.13)
Symptomatic ICH	4 (4.9)	5 (3.3)	0.66 (0.17-2.54)	0.93 (0.17-4.99)
Mortality	14 (17.5)	15 (9.9)	0.52 (0.24-1.14)	0.64 (0.22-1.91)

Abbreviations: CI, confidence interval; ICH, intracranial haemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin scale; MT, mechanical thrombectomy; OR, odds ratio.

*Adjusted for age, National Institutes of Health Stroke Scale (NIHSS), Alberta Stroke Program Early CT Score (ASPECTS), intracranial internal carotid artery occlusion, cardioembolic stroke, and time from symptom onset to recanalization.

MT+IVT and direct MT regarding functional and safety outcomes. Identical findings were reported in a posthoc analysis of Solitaire With the Intention for Thrombectomy (SWIFT) and Solitaire Flow Restoration Thrombectomy for Acute Revascularization trials,¹⁶ who also enrolled more than 200 patients (160 [55%] in the combined MT+IVT group versus 131 [45%] in the direct MT group).

In contrast with these findings, a recent meta-analysis comprising a total of 13 studies¹⁷ reported that patients submitted to combined MT+IVT had better functional outcomes, lower mortality and similar incidence of sICH compared to direct MT.

To date, only 3 observational studies addressed the use of direct MT in patients eligible to IVT.¹⁸⁻²⁰ In the Swiss study,¹⁹ patients in the combined MT+IVT group had higher asymptomatic ICH rates and lower mortality but similar rates of functional independence at 3 months, sICH, and successful recanalization. Likewise, Wang et al²⁰ found a lower rate of asymptomatic ICH in the direct MT group and a higher successful recanalization rate in this group. Authors argue that these findings may be explained by more distal thrombi migration in the combined MT+IVT group, which might render these clots inaccessible to thrombectomy. On the contrary, Bellwald et al,¹⁸ did not find statistically significant differences between these groups, except for higher mortality in ICA occlusion in patients in the combined MT+IVT group. Nonetheless, these studies share common pitfalls and these results should be interpreted with caution. Foremost, the absence of randomization of patients eligible to IVT to either direct MT or combined treatment. The choice of treatment was based on individual preferences and the reasons not to provide IVT were not recorded, yielding these patients susceptible to selection biases. Additionally, the 3 studies reported higher symptom to groin puncture times in the combined MT+IVT group, suggesting that administration of rtPA might delay MT. Like IVT, earlier endovascular treatment is associated with improved outcomes.²¹

One of the main advantages of IVT is early recanalization, which is related with occlusion site and length.²²⁻²⁴ Whereas ICA and tandem occlusions are less likely to benefit from IVT, distal middle cerebral

artery occlusions seem to achieve more favorable outcomes with rtPA.²² Therefore, direct MT could be an option, especially in patients with tandem and/or proximal LVO. These findings may explain the heterogeneous results from studies comparing combined MT+IVT and direct MT and could lead to a more tailored approach to patients using IVT. Notwithstanding, recent evidence¹⁷ and current guidelines state that all patients eligible for IVT should receive it without delay, even if they are being considered for MT.

Our study has limitations that also warrant comment. First and foremost, this is a single-center retrospective analysis and there was no randomization between groups. Since the assignment to a group was based on contraindications to IVT, the 2 groups may be inherently different. Although main baseline characteristics did not differ between groups and our results were adjusted for known predictors of clinical outcome, other variables that were not addressed may exist. The most common reason for not administering rtPA was time since symptom onset greater than 4.5 hours, making patients in the direct MT group more prone to longer symptom to groin puncture times. Furthermore, these patients have more comorbid conditions and higher proportions of cardiogenic thrombi that have higher fibrin content, which is associated with lower recanalization rates.²⁵⁻²⁷ Second, we may have not observed statistically significant differences between the groups due to relatively small sample size.

In conclusion, we observed that combined treatment with MT and IVT carried the same benefit and harm than direct MT. This controversy underlines the need for randomized controlled trials addressing this subject. The SWIFT DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke) will evaluate if patients in comprehensive stroke centers who are candidates for IVT benefit from direct MT versus combined MT+IVT. The result could be a shift in the paradigm of treatment of acute ischemic stroke as direct MT could be the therapy of choice in selected patients in comprehensive stroke centers.

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