



Endovascular treatment versus intravenous thrombolysis alone in isolated M2 occlusion: a meta-analysis

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Abstract

Background Optimal reperfusion strategies for M2 occlusion are still uncertain, with previous studies questioning benefit of mechanical thrombectomy (MT) over intravenous thrombolysis alone (IVT). Here we systematically reviewed and meta-analyzed data from studies comparing IVT alone vs MT with/without previous IVT, to define risk/benefit profile of each paradigm.

Methods The study followed PRISMA guidelines. PubMed, EMBASE, and Cochrane Central were searched only for RCTs comparing MT with or without IVT vs IVT alone in adults with acute ischemic stroke and M2 occlusion. Primary endpoint was functional independence at 90 days (modified Rankin Scale <3); secondary endpoints were represented by symptomatic intracranial hemorrhage (sICH) and good recanalization (TICI >2a). Odds ratios for endpoints were pooled with meta-analysis and compared between reperfusion strategies.

Results Seven studies ($n=779$) were included, all of high quality. Rate of good functional outcome was similar for MT and IVT (62.4% vs 66.3%; OR=0.73; 95%CI: 0.38–1.41; $p_{\text{heterogeneity}}=0.008$) (Fig. 1). sICH was significantly more frequent in the MT group (8.5%) vs IVT group (3%) (OR 2.76, 95%CI 1.19–6.36, $p_{\text{heterogeneity}}=0.14$). Good recanalization (TICI >2a) rate was higher in MT group vs IVT alone group (81.2% vs 51.4%; OR 3.99; 95%CI: 1.98–8.94; $p_{\text{heterogeneity}}=0.80$).

Conclusions IVT alone provides similar clinical benefit compared to MT with/without IVT in cases of M2 occlusion. MT quadruplicates rates of good recanalization, but triplicates risk of sICH. Further trials are needed to define if MT confers any advantage over IVT for M2 occlusion.

Keywords Ischemic stroke · Thrombolysis · Mechanical thrombectomy · Isolated M2 occlusion meta-analysis

Introduction

Mechanical thrombectomy (MT) with intravenous thrombolysis (IVT) is superior to IVT alone in patients with large vessel occlusion (LVO) [1–4]. However, while the benefits of MT have been well documented for the occlusion of internal carotid and proximal middle cerebral artery (MCA-M1), it is still debated if the endovascular treatment has advantageous benefit/risk ratio when occlusion happens in the first division

of the MCA segment (M2). Previous meta-analyses compared the clinical benefit and the risk of symptomatic intracerebral hemorrhage (sICH) between patients with M1 and M2 occlusions treated with IVT and MT [5, 6]. Another individual-data meta-analysis included patients treated with MT with or without IVT and patients treated with best medical treatment (including IVT) [7]. However, none of these compared the two treatments only in M2 occlusions, which has different anatomical features, including caliber and tortuosity, compared to the proximal MCA. Here we compared clinical outcome of patients with isolated M2 occlusion treated with IVT alone or MT with or without IVT.

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Methods

Search strategy

The methods and guidelines of this study-level meta-analysis followed PRISMA guidelines, and study description was

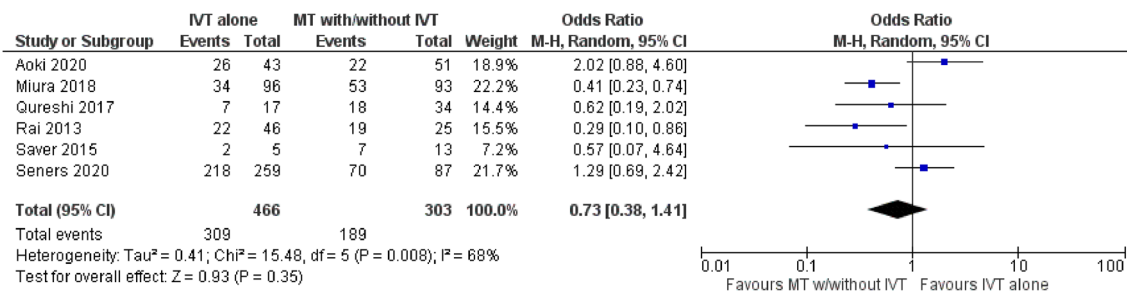


Fig. 1 Forest plot for primary endpoint

registered on osf.io register (DOI 10.17605/OSF.IO/ZTDJF). Two reviewers systematically searched Pubmed, EMBASE, and Cochrane Central register of Controlled Trials for studies comparing MT to IVT alone published between January 1990 and May20, 2020. Search strategy included the combination of the following terms as either keywords or MeSH terms: “cerebrovascular disorder”, “stroke”; “thrombolysis”, “thrombectomy”; “M2 occlusion”. Reference lists and citing articles were also reviewed to increase the identification of relevant studies.

Selection criteria

In this pooled analysis, we included randomized controlled trials and prospective or retrospective observational studies comparing the clinical efficacy and safety of MT or combined treatment among adult (≥18) patients with acute ischemic stroke due to isolated M2 occlusion. We limited the studies to English language and excluded case reports, small case series (<20), conference proceedings, and reviews. The interventional group comprised patients treated with MT with or without IVT, while the control group was represented by IVT alone treatment.

Endpoints

The primary endpoint was functional independence at 90 days from stroke onset, defined as modified Rankin Scale<3. Secondary endpoints were represented by the occurrence of symptomatic intracranial hemorrhage (sICH) as by study definition, and good recanalization (TICI grades: 2b and 3). Two reviewers independently extracted data on baseline and outcome characteristics of each included study. We reported the

lack of data on outcome, when appropriate. Overall quality of included clinical trials was assessed using the Jadad score (positive if > 2) [8].

Statistical analysis

We performed a statistical analysis pooling data in the intervention group and the control group. Outcome heterogeneity was evaluated with Cochrane’s Q test and I². An overall p value of < 0.05 was considered statistically significant. Fixed- and random-effects models were applied, according to the statistical significance of the heterogeneity. Odds ratio (OR) and 95% confidence interval (CI) values were calculated using DerSimonian and Laird model for primary and secondary endpoints. We report the analysis results graphically using forest plots for outcomes of single included trials and the total treatment effects. Data analysis was performed using Review Manager (version 5.3, The Cochrane Collaboration 2012, Copenhagen, Denmark).

Results

We included in this analysis 7 studies with a total of 779 patients (PRISMA flowchart, [Supplementary Material](#)) [9–15]. Overall, 303 patients underwent MT and 466 patients underwent IVT alone. No statistically significant difference emerged for age, vascular risk factors (hypertension, atrial fibrillation, and diabetes mellitus), and clinical severity between groups. Randomized clinical trials included in the analysis were overall of high quality, presenting Jadad score of 3.

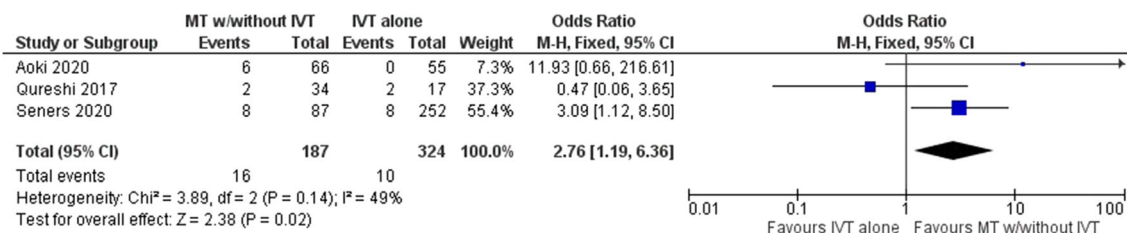


Fig. 2 Forest plot for sICH

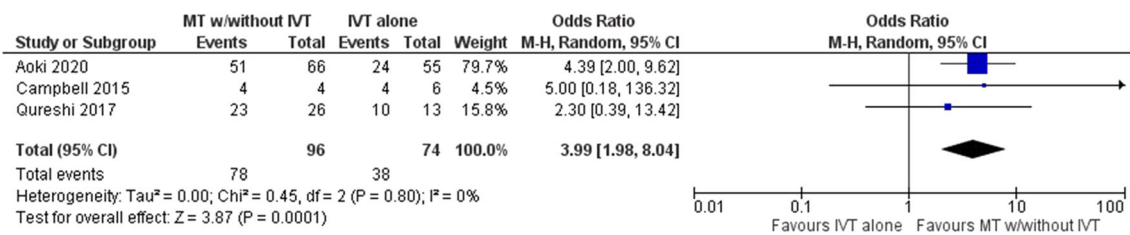


Fig. 3 Forest plot for good recanalization

Primary endpoint

Considering the primary endpoint, a good functional outcome occurred in 62.4% and 66.3% of patients treated with MT and IVT alone, respectively. This difference was not statistically significant (OR 0.73; 95%CI: 0.38–1.41; $p_{\text{heterogeneity}}=0.008$). Forest plot for this endpoint is represented in Fig. 1.

Secondary endpoints

For the secondary endpoints, we observed an increased rate of sICH in the MT group (8.5%) compared to the IVT group (3%), with a pooled OR significantly in favor of IVT alone (OR 2.76, 95%CI 1.19–6.36, $p_{\text{heterogeneity}}=0.14$) (Fig. 2). Regarding the rate of a good recanalization (TICI>2a) was higher in MT group compared to IVT alone group (81.2% vs 51.4%), with pooled estimate consistently in favor of MT (OR 3.99; 95%CI: 1.98–8.94; $p_{\text{heterogeneity}}=0.80$). Forest plot for this endpoint is represented in Fig. 3.

Discussion

In this meta-analysis, IVT alone was comparable to MT with or without IVT in providing a good clinical outcome in patients with MCA M2 occlusion. LVO has been shown to benefit most from MT plus IVT than IVT alone [1–4], but data are limited to distal M1 occlusion, with low consistent insight in what happens more distally [1]. M2, the major continuation of M1, has peculiar anatomical features, including bi/tri/quadrifurcation, caliber reduction, and varying anatomy, and has little influence on vascularization of the basal ganglia, which is crucial to motor function and recovery [16]. Trials have failed to investigate M2 occlusion, and HERMES meta-analysis questioned benefit of MT distally to M1 [1], a hypothesis that finds support in our findings.

The observed high heterogeneity in the primary endpoint is probably due to the different study designs (i.e., randomized controlled trials versus observational studies or data extraction from registries) and the small number size of some included subgroups of studies.

In this meta-analysis, MT was associated with a 4-fold increase in recanalization but a 3-fold increase in

risk of sICH compared to IVT, translating into similar rates of good functional outcome compared to IVT alone. These findings might suggest that aggressive endovascular approach to a distal occlusion might not be worth it and might potentially frustrate efforts directed towards a good clinical recovery. To this extent, results might be influenced by rates of futile recanalization as well as by rates of procedural complications, given the consistent increase in risk of sICH. Randomized controlled trials are needed to investigate MT in occlusion distal to M1, to avoid over-intervention and reserve endovascular intervention to those who benefit from it the most.

Study limits

Limitations to this meta-analysis can be found in the relatively small sample size and the inability to pursue a meta-regression analysis given the small number of studies included (<10). However, considering that the systematic review process followed predefined and registered protocol, and that statistical analysis and bias assessment were previously defined, our findings seem robust enough to support the hypothesis that M2 occlusion might equally benefit from IVT alone and MT, although with more sICH in MT group.

Conclusions

IVT alone provides similar benefits compared to MT with or without IVT in M2 occlusion, showing lower sICH rate. Our results might help to set up and provide appropriate power calculation for trials investigating M2 reperfusion strategies.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10072-021-05124-2>.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and Informed consent Not Applicable.

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