Original Paper

Mechanical Thrombectomy for Middle Cerebral Artery Division Occlusions: A Systematic Review and Meta-Analysis

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Keywords

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Abstract

Background: Middle cerebral artery division (M2) occlusion was significantly underrepresented in recent mechanical thrombectomy (MT) randomized controlled trials, and the approach to this disease remains heterogeneous. **Objective:** To conduct a systematic review and meta-analysis of outcomes at 90 days among patients undergoing MT for M2 middle cerebral artery (MCA) occlusions. **Methods:** Five clinical databases were searched from inception through September 2016. Observational studies reporting 90-day modified Rankin Scale scores for patients undergoing MT for M2 MCA occlusions with an M1 MCA control group were selected. The primary outcome of interest was good clinical outcome 90 days after MT of an M1 or M2 MCA occlusion. Secondary outcomes of interest included mortality and excellent clinical outcome, recanalization rates, significant intracerebral hemorrhage, and procedural complications. **Results:** A total of 323 publications were identified, and 237 potentially relevant articles were screened. Six studies were included in the analysis (M1 = 1,203, M2 = 258; total $n = 1,461$). We found no significant differences in good clinical outcomes (1.10 [95% CI, 0.83–1.44]), excellent clinical outcomes (1.07 [0.65–1.79]), mortality at 3 months (0.85 [0.58–1.24]), recanalization rates (1.06 [0.32–3.48]), and significant intracranial hemorrhage (1.19 [0.61–2.30]). **Conclusions:** MT of M2 MCA occlusions is as safe as that of main trunk MCA occlusions, and comparable in terms of clinical outcomes and hemorrhagic complications. Randomized clinical trials are needed to assess the impact of MT in patients with M2 occlusions, given that M1 MCA occlusions have different natural histories than M2 occlusions.

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Introduction

There is class IA evidence for treatment of acute stroke due to anterior circulation large vessel occlusion with mechanical thrombectomy (MT), which is translated into the current treatment guidelines [1]. Most of the studies conducted on MT in large vessel anterior circulation strokes involved the internal carotid artery or main middle cerebral artery (MCA) trunk (M1). The first division of the MCA (M2) segment is a common arterial occlusion site, comprising about 20–41% [2] of anterior circulation strokes. Recanalization with intravenous tissue plasminogen activator (IV tPA) only occurs in about one-third of patients with M2 occlusions [3], of which one-third may suffer from early reocclusion [4]. Occlusions in M2 vessels are more likely to be due to clots lodged in distal vessels [5] than due to large atherosclerotic plaques [6]. The smaller caliber of the vessels, thinner vessel walls, acute angles, and increased tortuosity of distal vessels make MT of M2 vessels more challenging [7].

M2 occlusions have been significantly underrepresented in randomized studies conducted until now [8–12]. This makes the role of MT in the management of M2 occlusions unclear. In view of this uncertainty and the clinical and public health importance of M2 occlusions, we conducted a systematic review and meta-analysis to evaluate the safety and efficacy of MT in M2 occlusions.

Materials and Methods

Data Sources and Searches

The systematic review was carried out in accordance with the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13, 14] (see online supplement for the review protocol and suppl. Table IV for the PRISMA checklist; for all online suppl. material, see www.karger.com/doi/10.1159/000477589).

On September 6, 2016, the search strategies and subsequent literature searches were performed by an experienced health sciences reference librarian (Wade Lee). Search strategies which leveraged both controlled vocabularies and keyword synonyms were developed for PubMed. This strategy was translated to be used in Embase, the Cochrane Central Register of Controlled Trials, the Web of Science Core Collection databases on the Thomson Reuters Web of Science platform, and ClinicalTrials.gov. The searches combined the following concepts: thrombectomy/embolectomy and occlusion and the M2/secondary division of the cerebral artery. Within the results for those combined concepts, additional filters, publication types, and keyword strategies were used to identify and exclude the most common article types which did not report trial results (see online supplement for an exemplary PubMed search). To identify further articles, references were hand searched. All results were downloaded into EndNote (Thomson ISI ResearchSoft, Philadelphia, PA, USA), a bibliographic database manager, and duplicate citations were identified and removed.

Study Selection

The abstracts of all studies were reviewed by two authors (H.S. and A.E.). Case reports, case series, reviews, editorials, and unpublished data [15, 16] were excluded, limiting the results to clinical trials and observational studies with an M1 MCA control group.

The primary outcome of interest was good clinical outcome at 90 days defined as a modified Rankin Scale (mRS) score ≤ 2 after MT of an M1 or M2 MCA occlusion. Secondary outcomes of interest included mortality and excellent clinical outcome at 90 days (defined as an mRS score ≤ 1), recanalization rates, symptomatic intracerebral hemorrhage, and procedural complications.

Full texts of selected abstracts were obtained for review for inclusion into the study. Articles published in languages other than English were excluded if no translation was available. Definition of the M2 segment was taken as provided. Studies were excluded if they did not compare M2 occlusions to an M1 control group, if they did not include separate measures of outcome for the respective groups, or if mRS scores at 90 days for each group were not available.

Data Extraction and Quality Assessment

Each study was evaluated for the following information: geographical location, inclusion and exclusion criteria, study design, control groups, primary outcomes, MT device, MT cutoff times, imaging criteria used for patient selection, patient baseline characteristics, baseline NIHSS score, Alberta Stroke Program Early CT Scan (ASPECTS) score, treatment times, procedural complications, and clinical outcomes at 90 days. All papers were independently reviewed and data extracted by two separate reviewers (H.S. and A.E.). In cases of disagreement between the two reviewers, where a consensus could not be obtained, a third reviewer (M.J.) was used.

Two reviewers (H.S. and A.E.) independently assessed the methodological quality of the selected studies using the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies. This scale subjectively assesses the selection of patients in each study, comparability of the patients within the two groups, and the quality of assessment of primary outcomes and follow-up [17].

Data Synthesis and Statistical Analysis

For dichotomous variables, we computed an OR with 95% CI. Cochran's Q test and the I^2 statistic were used to assess heterogeneity between studies [18]. We performed a fixed-effects analysis for studies with minimal-to-no heterogeneity and a random-effects analysis for studies with moderate-to-substantial heterogeneity. A sensitivity analysis based on patient eligibility for IV tPA and the type of MT device used was performed. Publication bias was assessed using a contour funnel plot and Egger's test. The statistical analyses were conducted using Review Manager version 5.3.5 and Comprehensive Meta-Analysis version 3.

Results

Study Selection and Characteristics

The librarian-performed search revealed 236 abstracts available for review from 5 online databases after removal of duplicates. After reviewing the abstracts, 25 full-text papers were reviewed for determination of the quality of fit. A total of 6 papers [19–24] were left from the full-text review process after excluding abstracts, studies without the relevant outcome of interest, analyses without control groups, or papers with overlapping data (Fig. 1).

Of the 6 included studies, 3 were post hoc analyses of pooled data from prospective studies. Goyal et al. [21] evaluated patients from 5 recent randomized controlled trials [8, 10, 12, 25, 26], and Lemmens et al. [22] evaluated patients from the SWIFT [27], STAR [28], DEFUSE 2 [29], and IMS III [30] studies. Shi et al. [24] evaluated clinical outcomes of secondary division occlusions treated with MERCI stents from the MERCI [31] and Multi-MERCI trials [32]. Studies containing overlapping data [33, 34] were selected based on the primary endpoint evaluated and in order to include the largest data set.

Three other case-control studies [35–37] were excluded due to differences in duration to assessment of clinical outcomes. The study by Protto et al. [38] was excluded as it examined different endpoints based on the same data as from a study [23] by the same author used in our analysis.

Three included case-control studies were performed after June 2010. Two of these studies – those by Dorn et al. [19, 20] – included patients from Germany, one [20] of which was a multicenter study from a stroke registry, and Protto et al. [23] looked at patients in Finland. The 3 post hoc analyses [21, 22, 24] included data from multiple countries.

Online supplementary Table I summarizes the study characteristics of the 6 included studies. The baseline characteristics are summarized in online supplementary Table II and the treatment outcomes in online supplementary Table III.

Assessment of the Quality of the Included Studies

Assessment of bias was performed at the individual study level, and it revealed that the included studies were of good methodological quality (online suppl. Table IV). There was

Fig. 1. PRISMA flow diagram.

excellent agreement between the reviewers for inclusion of studies, data extraction, and quality assessment ($\kappa = 1.0, 1.0$, and 0.93 , respectively).

Primary Analysis

This meta-analysis reviewed 6 studies on 1,203 patients with M1 occlusion and 258 patients with M2 occlusion. We found no significant differences in recanalization rates, significant intracranial hemorrhage, and clinical outcomes and mortality at 3 months between the patients treated with endovascular therapy for M1 occlusion and those treated for M2 occlusion.

We constructed a fixed-effects model (minimal heterogeneity; $I^2 = 0\%$) for assessment of good clinical outcomes (mRS score ≤ 2) at 3 months, mortality, and significant intracranial hemorrhage. Good clinical outcomes at 90 days occurred in 534/1,191 (44.8%) of the patients with M1 occlusions and in 121/257 (47.1%) of the patients with M2 occlusions, with a pooled effect estimate of 1.10 (95% CI, 0.83–1.44). Excellent clinical outcomes occurred in a similar proportion of patients in the M2 group (32.4%; 71/219) as in the M1 group (31.0%; 303/977),

(Figure continued on next page.)

Fig. 2. Forest plots of good (mRS score ≤ 2) clinical outcomes (a), excellent (mRS score ≤ 1) clinical outcomes (c), and mortality (d) at 90 days, and funnel plot showing the risk of publication bias in the included studies (b). mRS, modified Rankin Scale.

and the results of the meta-analysis did not show a statistically significant difference (pooled OR = 1.07; 95% CI, 0.65–1.79). Mortality did not differ either between the M1 group (18.3%; 206/1,123) and the M2 group (15.9%; 39/246), with a pooled effect estimate of 0.85 (95% CI, 0.58–1.24) (Fig. 2).

The studies investigating successful recanalization had higher between-group heterogeneity ($I^2 = 78\%$) and similar rates of recanalization in both the M2 group (61.7%; 121/196) and the M1 group (67.2%; 463/689), with a pooled effect estimate of 1.06 (95% CI, 0.32–3.48). There were a total of 13 (6.6%) cases of significant intracranial hemorrhage among 196 cases of M2 thrombectomies and 39 (5.7%, $n = 689$) cases in the M1 group. There were no significant differences between the groups in significant intracranial hemorrhage (1.19; 95% CI, 0.61–2.30) and procedural complications (0.51, 95% CI, 0.09–2.79), although details regarding procedural complications were lacking in most of the studies (Fig. 3b; online suppl. Fig. I).

There was visual symmetry in the contour funnel plot (Fig. 2b). Egger's test did not reveal any evidence of publication bias.

Sensitivity Analysis

We performed a sensitivity analysis while evaluating clinical outcomes, mortality, recanalization rates, and symptomatic intracranial hemorrhage. A subgroup analysis evaluating patients treated with second-generation MT devices only (excluding MERCI) and studies evaluating patients eligible for IV tPA failed to reveal any significant differences in results (online suppl. Table V; online suppl. Fig. II).

Fig. 3. Forest plots of recanalization rates (**a**) and rates of significant intracranial hemorrhage (ICH) (**b**).

Discussion

Our meta-analysis comparing patients with secondary MCA branch occlusions ($n = 258$) to those with main MCA occlusions ($n = 1,203$) revealed similar rates of recanalization, significant intracranial hemorrhage, and clinical outcomes. The present work is the largest and most current meta-analysis of MT in patients with M2 MCA occlusions.

The duration to endovascular treatment varied between the studied populations. Three [21, 22, 24] of the 6 analyzed studies mentioned varying cutoff times to MT. These studies included patients from the MR CLEAN [9] (cutoff time 6 h), STAR [28] (8 h), ESCAPE [10], and DEFUSE 2 [29] (each 12 h) trials. The 3 other studies [19, 20, 23] did not specify a cutoff time used for MT. There were inconsistencies in reporting of door-to-recanalization times between the studies, with 3 studies reporting mean times [19, 20, 23], 1 study reporting median times [21], and 2 studies not providing any time to recanalization [22, 24]. The patients from the MERCI and Multi MERCI studies had significantly longer procedure times, possibly due to different endovascular techniques, less experience, and use of first-generation stent retrievers in these earlier studies.

The median ASPECT score was comparable across all studies in both groups. The selection of patients was based on similar modalities (CT or MR angiogram) across the recently performed studies [20, 21, 23]. In patients who did not undergo noninvasive vessel imaging, confirmation of the occlusion was made by digital subtraction angiography. Dorn et al. [19] did not specify the imaging modality used, and the study by Lemmens et al. [22] included IMS III [30] trial patients only if there was digital subtraction angiography evidence of intracranial occlusions. The imaging selection criteria likely did not have a significant effect on our results, given that classifications of stroke occlusion were confirmed retrospectively.

The rates of tPA administration also varied between the studies, ranging from 14 to 74%. Dorn et al. [20] evaluated large vessel occlusion in patients who were ineligible for tPA, and they found similar clinical outcomes and overall rates of intracranial hemorrhage.

The Solitaire FR thrombectomy device was the most commonly used device, followed by MERCI and Trevo, but other stents including ERIC [23], CAPTURE [23], REVIVE [23], and PRESET [20] were also used. Dippel et al. [39] found no evidence for a differential effect based on the type of stent used when assessing 233 patients with Trevo or Solitaire stents from the MR CLEAN trial [9]. The SWIFT trial [27] clearly demonstrated a superiority of the Solitaire device over first-generation MERCI devices, and thus inclusion of these stents, albeit few could affect rates of recanalization and clinical outcome. Thrombectomy with MERCI devices was performed in the MERCI [31] and Multi MERCI [32] trials included in the analysis by Shi et al. [24] as well as in the IMS III [30], SWIFT [27], and DEFUSE 2 trials included in the analysis by Lemmens et al. [22]. The sensitivity analysis excluding studies [22, 24] using these devices did not affect our results. Technical considerations such as vessel diameter and tortuosity, risk of embolization downstream or to unaffected territory, and clot resistance may favor one device over the other and should be studied in a prospective manner.

Rates of recanalization were measured by TIC1 (thrombolysis in cerebral infarction) 2b–3 recanalization, with the exception of patients from the MERCI [31], Multi MERCI [32], and SWIFT [27] trials, in which recanalization was classified by TIMI (thrombolysis in myocardial infarction) score. The increased heterogeneity in recanalization rates may be related to differing cutoff times for MT, use of different devices and center protocols, and varying user experiences.

We analyzed the rates of symptomatic intracranial hemorrhage across the included studies. We found no significant differences in intracranial hemorrhage between the two groups after adjusting for type of stent used and type of study performed. There was significant heterogeneity in the definition of symptomatic intracranial hemorrhage, with some studies not clearly defining symptomatic intracranial hemorrhage, while others used the ECASS or SITS MOST criteria; therefore, we used the term “significant intracranial hemorrhage” in our study.

Procedural complications were not uniformly evaluated across the studies. Only 2 studies reported procedural complications for each group, both of which revealed lower complication rates in the M2 MCA group (OR = 0.74; 95% CI, 0.13–4.18).

Current data on the natural history of M2 MCA occlusions are relatively sparse. An analysis of untreated patients with proximal intracranial arterial occlusions by Lima et al. [40] found a 46% rate of poor clinical outcomes amongst patients with M2 MCA occlusions ($n = 48$) and found no association between intracranial arterial occlusion level (i.e., internal carotid artery vs. M1 vs. M2) and clinical outcome. The largest cohort used for evaluating M2 occlusions was in a multicenter retrospective study [41] with pooled data from 10 US centers. This study also revealed that MT is reasonable, safe, and effective for treatment of M2 MCA occlusions.

Limitations

Our study has multiple limitations. The results of our analysis are weakened by limitations inherent in the meta-analysis and the limitations of the included studies. The small number of studies included in our analysis increases the risk of confounding. The studies included patients with similar baseline characteristics, although some studies were not powered or designed to detect differences in clinical outcomes between M1 and M2 MCA occlusions. The most severe limitation of this study is the lack of an adequate control group, given that studies comparing clinical outcomes in patients undergoing MT for M2 occlusions and the natural history of the disease were largely lacking. By using patients undergoing MT for M1 occlusion, we compared the outcomes to those of patients undergoing MT for currently approved indications, albeit for a different disease. Another potential limitation is the possibility of misclassification bias, since most of the studies did not clearly define the M2 MCA region. Furthermore, our study evaluated a heterogeneous group of studies performed over a long period of time; the inclusion of patients from the older MERCI [31] and Multi MERCI [32] trials may have resulted in the loss of a treatment effect with new-generation stents. Additionally, varying definitions of symptomatic intracranial hemorrhage were used across the evaluated studies. Additionally, it is conceivable that this comparison may not be beneficial, given the differences in natural history [42] and response to IV tPA [3] between the two groups. Lastly, our analysis included studies in which patients were not randomized to treatment, likely resulting in the selection of only the most severely affected M2 occlusion patients for MT.

Our findings are consistent with those of previous studies, including recent retrospective cohorts [41] and a pooled analysis of 5 randomized controlled trials [21]. Inconsistencies in defining the M2 MCA branch, evaluating treatment times, defining symptomatic intracranial hemorrhage, and describing procedural complications are the main limitations of our analysis. A selection bias while evaluating patients with M2 MCA occlusions remains the largest obstacle to an adoption of aggressive approaches for this disease; data from the Trevo, Solitaire, and HERMES registries may help provide further evidence on M2 occlusions.

Conclusion

MT for M2 MCA occlusions appears to be as safe and effective as MT for main trunk MCA occlusions, with comparable clinical outcomes and hemorrhagic complications. Future randomized controlled trials are warranted.

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Disclosure Statement

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