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Mechanical thrombectomy first versus direct angioplasty or stenting for the treatment of intracranial atherosclerotic stenosis-related large vessel occlusion: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Mechanical thrombectomy (MT) using stent retrievers or a direct aspiration first-pass technique has proven to yield better results over intravenous thrombolysis in treating acute ischaemic stroke caused by large vessel occlusion (LVO). However, the treatment of intracranial atherosclerotic stenosis-related LVO remains unclear and has been a critical problem in daily clinical practice, as it can cause a relatively high failure rate for MT. Whether direct angioplasty and/or stenting is clinically feasible and shows advantage in reducing delay to revascularisation with better functional outcome compared with MT with rescue angioplasty and/or stenting remains unclear. This study seeks to provide direct and practical clinical evidence for clinicians.

Methods and analysis The main databases of PubMed, the Cochrane library, Embase and Web of Science will be screened for related studies published after 1 January 2015. Primary outcomes include successful recanalisation and 90-day favourable outcome. Secondary outcomes include puncture to revascularisation time, vascular complication (perforation, dissection and vasospasm), intracerebral haemorrhage, hospital-related complications and 90-day mortality. The Newcastle-Ottawa Scale will be adopted to assess risk bias of observational studies. The I² statistic will be used to assess heterogeneity.

Ethics and dissemination No primary data of patients are needed. Therefore, ethics approval is unnecessary. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study focuses on the comparison between angioplasty and/or stenting as a rescue therapy in mechanical thrombectomy with direct angioplasty and/or stenting in the treatment of intracranial atherosclerotic stenosis-related large vessel occlusion.

⇒ The types of included studies in this meta-analysis includes non-randomised clinical trials, which increases heterogeneity at the advantage of generalisability.

⇒ Stringent rules will be kept when assessing the study risk of bias and data extraction to minimise the unfavourable impact on final results.

INTRODUCTION

Acute ischaemic stroke (AIS) caused by large vessel occlusion (LVO) is a global concern, with high mortality and morbidity. Several randomised clinical trials (RCTs) have proven the superiority of mechanical thrombectomy (MT), using stent retrievers or a direct aspiration first-pass technique, over intravenous thrombolysis.1 2 However, severe intracranial atherosclerotic stenosis (ICAS) can account for approximately 5%–6% of all strokes due to LVO in European countries and up to 12%–30% in Asian and Hispanic populations.3 However, treatment of ICAS-related LVO remains unclear and is a critical problem in daily clinical practice, as it has a relatively high rate of failed MT.3 4 Thus, rescue therapy using angioplasty and/or stenting is often required and can at times effectively resolve the stenosis and achieve successful reperfusion in these patients.3 5

Recently, several studies proposed direct angioplasty or direct stenting in ICAS-related AIS rather than rescue after failed MT.6–8 These propose that rescue therapy may prolong the total procedure time and contribute to poor outcomes. Additionally, less intravascular manipulation may hypothetically reduce complications such as vascular
injury, dissection or vasospasm. In addition, tortuous and resistant vascular systems may increase the difficulty performing MT in patients with ICAS. Compared with MT with rescue stenting, direct stenting shortens puncture-to-recanalisation time and is suggested to be related to a higher rate of favourable functional outcome. Thus, a comprehensive literature review and meta-analysis is warranted to update clinical evidence of the safety and effectiveness of this proposed new strategy using direct angioplasty or stenting for ICAS-related AIS.

METHODS AND ANALYSIS
This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021268061). The planned start date of the study is 1 October 2022, and the planned end date is 25 December 2022. Currently, the search strategy has been made (online supplemental file 1). Any amendment made to this study will be reflected on the PROSPERO database. This protocol was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (online supplemental file 2).

Inclusion criteria for study selection
Participants
Patients aged ≥18 with AIS due to ICAS will be included. Markers suggesting ICAS-related LVO have been described previously.

Intervention
Direct stenting and/or angioplasty approach. Direct stenting or angioplasty approach includes multiple manipulations, such as stenting with stent retrievers, balloon angioplasty with a percutaneous transluminal angioplasty (PTA) balloon catheter, and balloon angioplasty and stenting with a Wingspan stent system. In our meta-analysis, we will analyse these procedures together.

Comparator
MT with/without rescue therapy with stenting and/or angioplasty will be used.

Outcomes
Any information associated with postprocedural condition will be documented.

Primary outcomes include successful recanalisation and 90-day favourable outcome. The definition of successful recanalisation is a modified Thrombolysis in Cerebral Infarction score of 2b-3, and 90-day favourable outcome is accepted to be a modified Rankin Scale (mRS) score of 0–2 or equal to preprocedural mRS score.

Secondary outcomes include puncture to revascularisation time, vascular complication (perforation, dissection and vasospasm), intracerebral haemorrhage (ICH), hospital-related complications and 90-day mortality. ICH was assessed by European Cooperative Acute Stroke Study classification. The symptomatic ICH was confirmed if National Institutes of Health Stroke Scale score increased at least 4 points in 24 hours before intervention.

Studies
Studies included in this systematic review will be both RCTs and non-RCTs. The inclusion criteria for this review will be studies with outcomes comparing the aforementioned two treatment strategies. Search dates are identified according to a preliminary search in database. To assess the modern thrombectomy results and include enough qualified studies for analysis, we included studies published later than 2015 only, as little relevant information was mentioned in articles before 2015. Exclusion criteria are the following: (1) studies published before 1 January 2015 (ie, not modern thrombectomy devices); (2) studies that fail to report the aforementioned outcomes; (3) studies with outcome data that cannot extracted or are not available; and (4) observational studies with a sample size of less than 5, conference reports, abstracts, case reports, editorials, comments and reviews.

Search strategy
This meta-analysis will be performed in accordance with contemporary systematic search strategies to screen suitable literature in the main databases of PubMed, the Cochrane library, Embase and Web of Science. We will review all relevant articles comparing the functional outcomes of the two aforementioned approaches for ICAS-related AIS populations. All studies published after 1 January 2015 will be reviewed. An explicit search strategy will be designed for each database, and it will be based on terms such as “acute ischemic stroke”, “mechanical thrombectomy”, “stent retriever thrombectomy”, “stent retriever”, “ICAS”, “direct angioplasty” and “direct stenting”. When drafting and revising this search strategy, we will aim to meet the standards of the Peer Review of Electronic Search Strategies checklist.

Selection of studies
The first screening of research reports will depend mainly on titles and abstracts and will be conducted by two independent reviewers familiar with research in the field of thrombectomy. Second, full articles will be reviewed and screened. We will keep extremely rigorous rules when screening evidence of ICAS-related AIS to minimise the potential inclusion bias since patients with LVO and underlying occlusions could not be correctly identified at the moment of the procedure in some special cases. Selections will be cross-checked, and a third reviewer will be solicited in the event of any discrepancy or disagreement. Reasons for exclusion of articles will be recorded. The screening process is shown in figure 1.

Data selection
After the initial screening, the second stage of selection will also be performed by two independent reviewers using EndNote X8 (Clarivate Analytics, Philadelphia, Pennsylvania, USA) to manage literature. At this stage, the full texts will be reviewed. Data for each eligible study
will be extracted and evaluated independently by two reviewers. Included information is listed as follows:

- Basic information, such as authors, time of publication, type of study, countries where the study was conducted, number of included patients and a Newcastle-Ottawa Scale (NOS) score for each study.
- Patient characteristics. These include demographic characteristics (age and gender) and medical history (hypertension, diabetes mellitus, dyslipidaemia, stroke history and other related information). Medication taken before the stroke including anticoagulants and antiplatelet agents will be recorded. Data regarding alcohol consumption, smoking, interventions, location of the occlusion and onset time will be extracted and recorded.
- Primary outcomes and secondary outcomes are mentioned previously. Both the primary and secondary outcomes will be assessed and documented separately.

A formal spreadsheet will be designed for data documentation. In the event of any disagreement between the two reviewers about study screening or data extraction, a group discussion among all team members will be held for the final decision with possible arbitration by a third reviewer as needed.

**Data analysis**

Data analysis for the effect of each specific variable on thrombectomy outcomes will be practical only when at least two studies are accessible. The data analysis will be conducted by using Stata V.15.0. Presentation of the results will depend on the outcome variables and will include standardised mean difference for continuous outcomes and relative risk (RR) for dichotomous outcomes. The reporting of final results will be accompanied by 95% CIs. A random-effects model will generally be used for data analysis, but a fixed-effects model will be applied when there is little evidence of heterogeneity ($I^2 < 20\%$). Statistical significance is defined at $p < 0.05$.

If there are insufficient studies for some variables, we will consider formulating a narrative description of the particular factors. If studies have data that are unsuitable for extraction and analysis but appear to offer the possibility of meaningful results for a specific variable, we will attempt to contact the authors of the relevant reports through email in an effort to obtain the original data. Heterogeneity will be measured with the $I^2$ statistic before any outcome is pooled. The heterogeneity of mild ($<40\%$), moderate ($40\%–60\%$) or substantial ($>60\%$) will be graded, depending on the pooled results. On condition that the results have substantial heterogeneity and sufficient number of included trials, we will use subgroup analysis to examine the reasonable origins of heterogeneity. Subgroup analysis will be performed based on characteristics such as race and region, even based on different procedures regarding direct angioplasty or stenting, if practicable. Publication bias will also be evaluated using a funnel plot if there are sufficient studies for its construction.

**Assessment of risk bias**

Two independent reviewers will conduct assessment of bias risk in the studies selected during the second stage. The NOS will be adopted for observational studies with high quality (online supplemental file 3). Studies with scores of 5–9 points will be considered high-quality evidence. Any disagreement will be discussed and may be arbitrated by a third reviewer as necessary.

**Patient and public involvement**

No patients were involved in this study.

**DISCUSSION**

The optimal treatment strategy for ICAS-related AIS is an important area of research, especially in Asian countries where the prevalence can be particularly high. Whether direct angioplasty or stenting is clinically feasible and shows advantage in reducing delay to revascularisation while achieving better functional outcomes remains to be clarified. Thus, an updated and high-quality systematic review and meta-analysis of this distinct group of AIS patients are needed. We will apply stringent rules when assessing the risk of bias and data extraction to minimise the final trends when selecting observational studies. In addition, series with untreated patients should be also considered, since certain specialists believe that treatment of patients in this subgroup seems not to be useful, as LVOs with underlying atherosclerotic plaques represent...
an acute condition of a chronic pathology with the development of a solid and stable collateral circulation. This is another important question that will be further discussed as a new topic in our next review.

ETHICS AND DISSEMINATION
No primary patient data are needed. Therefore, ethics approval is unnecessary. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

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