INPLASY PROTOCOL

To cite: Laskay et al. Endovascular thrombectomy for the treatment of large ischemic stroke: a systematic review and meta-analysis of randomized control trials. Inplasy protocol 202320107. doi: 10.37766/inplasy2023.2.0107

Received: 23 February 2023

Published: 23 February 2023

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Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None declared.

Endovascular thrombectomy for the treatment of large ischemic stroke: a systematic review and meta-analysis of randomized control trials

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Objective: **Aims: 1. Efficacy: Determine if thrombectomy leads to improved outcomes measured through the modified Rankin scale (mRs) in adult patients with large ischemic strokes when compared to medical management. 2. Safety: Determine the safety of thrombectomy in patients with large ischemic strokes by comparing rates of symptomatic intracranial hemorrhage, death, neurologic worsening (increase of ≥4 points in the NIHSS score within 24 hours after presentation), and procedural complications.**
Condition being studied: **Endovascular therapy (EVT) or thrombectomy in large territory acute ischemic stroke on noncontrast computed tomography (CT) or perfusion imaging have been underrepresented in thrombectomy trials. Consequently, the efficacy and safety of EVT in patients with a larger ischemic burden have not been well established. These patients generally have worse neurologic outcomes, including progression of symptoms related to their stroke, brain edema, and ultimately death.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 February 2023 and was last updated on 23 February 2023 (registration number INPLASY202320107).

INTRODUCTION

Review question / Objective: **Aims: 1. Efficacy: Determine if thrombectomy leads to improved outcomes measured through the modified Rankin scale (mRs) in adult patients with large ischemic strokes when compared to medical management. 2. Safety: Determine the safety of thrombectomy in patients with large ischemic strokes by comparing rates of symptomatic intracranial hemorrhage, death, neurologic worsening (increase of ≥4 points in the NIHSS score within 24 hours after presentation), and procedural complications.**

Research Question
Patients:
• Adult patients (>18) with ischemic stroke within 24-hour onset
• Pre-stroke modified Rankin scale (mRs) of 0 or 1
• Large infarct defined as meeting either of the following criteria:
o Alberta Stroke Program Early Computed Tomography Score (ASPECTS) value of 3 to 5
o An estimated ischemic-core volume of 50 mL or greater
Intervention: Endovascular therapy (thrombectomy)
Comparator: Medical management.
Outcomes:
1. Ordinal shift across the range of modified Rankin scale scores toward a better outcome at 90 days
2. Functional independence defined as a score on the modified Rankin scale of 0 to 2 at 90 days
3. Independent ambulation (a score on the modified Rankin scale of 0 to 3) at 90 days
Other outcomes: Symptomatic ICH, death, neurologic worsening (increase of ≥4 points in the NIHSS score within 24 hours after presentation), and procedural complications.

Rationale: Endovascular therapy (ET) has revolutionized the management for patients with acute large vessel occlusions (LVO). Numerous randomized control trials (RCTs) have demonstrated significant benefit in functional outcome (modified Rankin scale (mRS)) compared to medical management alone. (1-4) Moreover, the benefits of endovascular therapy have been supported even with increasing time from stroke onset to intervention. (1,5,6) The vast majority of patients included in these RCTs did not have large-volume ischemic infarcts based upon either computed tomography (CT) perfusion (CTP) studies or via the Alberta Stroke Program Early CT Score (ASPECTS). (2,7) Current guidelines support ET for large vessel ischemic strokes with ASPECTS (6), but the role of ET in patients with large-volume infarcts defined as ASPECTS 3-5 has been less well-defined due to perceived risk of intracranial hemorrhage (ICH) or absence of functional benefit. (8)
In the past year, three multicenter RCTs have been published specifically investigating the benefits of ET in patients with LVO and ASPECTS 3-5. The RESCUE-Japan LIMIT, ANGEL-ASPECT, and SELECT2 trials were conducted in Japan, China, and an international conglomerate (North America, Europe, Australia, and New Zealand), respectively. (9-11) These multicenter RCTs have all have demonstrated differing margins of benefit in functional outcome following ET in large-volume ischemic strokes, and they have also reported differing rates of ICH. (9-11) We sought to perform a systematic review of the literature for any recent RCT that includes large-volume ischemic strokes and to subsequently perform a meta-analysis of these results. In analyzing these major trials, we can better understand the true benefit in mRS and risk profile for patients with large-volume strokes receiving ET.

Condition being studied: Endovascular therapy (EVT) or thrombectomy in large territory acute ischemic stroke on noncontrast computed tomography (CT) or perfusion imaging have been underrepresented in thrombectomy trials. Consequently, the efficacy and safety of EVT in patients with a larger ischemic burden have not been well established. These patients generally have worse neurologic outcomes, including progression of symptoms related to their stroke, brain edema, and ultimately death.

METHODS

Search strategy: Pubmed ((ischemic stroke[Title/Abstract]) OR (large vessel occlusion[Title/Abstract])) AND ((endovascular treatment[Title/Abstract]) OR (endovascular therapy[Title/Abstract]) OR (thrombectomy[Title/Abstract])) AND (((randomized[Title/Abstract]) OR (randomised[Title/Abstract])) AND ((trial[Title/Abstract]) OR (study[Title/Abstract])))

Filters:
• Years 2010-present ((ischemic strokes[Title/Abstract]) OR (large vessel occlusion[Title/Abstract])) AND ((endovascular treatment[Title/Abstract]) OR (endovascular therapy[Title/Abstract]) OR (thrombectomy[Title/Abstract])) AND (((randomized[Title/Abstract]) OR (randomised[Title/Abstract])) AND ((trial[Title/Abstract]) OR (study[Title/Abstract])))
Filters:
• Years 2010-2023
Embase
('ischemic stroke':ti,ab OR 'large vessel occlusion':ti,ab) AND ('endovascular treatment':ti,ab OR 'endovascular therapy':ti,ab) AND (randomised:ti,ab OR randomized:ti,ab OR 'randomized controlled trial'/exp)
Cochrane Central
((ischemic stroke) OR (large vessel occlusion)) AND ((endovascular treatment) OR (endovascular therapy) OR (thrombectomy)) AND (((randomized) OR (randomised)) AND ((trial) OR (study))) in Title Abstract Keyword
Filters:
• Years 2010-2023
• English Language
Scopus
TITLE-ABS-KEY (((ischemic AND stroke) OR (large AND vessel AND occlusion)) AND ((endovascular AND treatment) OR (endovascular AND therapy) OR (thrombectomy)) AND (((randomized) OR (randomised)) AND ((trial) OR (study)))) AND (LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar"))
Google scholar
("randomized clinical trial" OR "randomised clinical trial") AND ("endovascular therapy" OR "endovascular treatment" OR "thrombectomy") AND ("ischemic stroke" OR "large vessel occlusion") AND ("large core" OR "large volume")
Filters:
• Years 2010-2023.

Participant or population: Adult patients (>18) with ischemic stroke within 24-hour onset, pre-stroke modified Rankin scale (mRS) of 0 to 1, and large infarct defined as: 1) Alberta Stroke Program Early Computed Tomography Score (ASPECTS) value of 3 to 5 or 2) an estimated ischemic-core volume of 50mL or greater.

Intervention: Endovascular therapy (thrombectomy).

Comparator: Medical Management.

Study designs to be included: Randomized Clinical Trials published since 2010.

Eligibility criteria: Study exclusion criteria: Clinical and observational studies, case series with available abstracts and published as full-scale original articles, brief reports in peer-reviewed academic journals, pilot reports, opinion pieces, theses, conference proceedings, letters, editorials, meta-analysis, reviews, surgical technique papers, case reports, abstracts, presentations, and any non-English language publications without translations.

Information sources: Medline, Embase, Scopus, Cochrane Central, Google Scholar, and PubMed.

Main outcome(s): Primary outcome:
○ Ordinal shift across the range of modified Rankin scale scores toward a better outcome at 90 days.

Additional outcome(s): Secondary outcomes:
○ Functional independence defined as a score on the modified Rankin scale of 0 to 2 at 90 days.

○ Independent ambulation (a score on the modified Rankin scale of 0 to 3) at 90 days
○ Safety outcomes: Symptomatic intracerebral hemorrhage, any intracerebral hemorrhage, death at 90 days, and need for decompressive hemicraniectomy.

Outcome Rationale:

The aforementioned outcomes were the primary and secondary outcomes for recently published RCTs examining endovascular therapy (EVT) for acute ischemic stroke with large infarcts. (9, 10) The mRS is a validated, clinician-reported measure of global neurologic disability and is widely applied in the stroke literature to evaluate stroke patient outcomes and as an endpoint in RCTs. (14) The tool comprises 7 grades (0-6) of stroke severity ranging from 0 or "no symptoms at all" to 5 "severe disability" and 6 "death." (15) Thus, an ordinal shift across the range of mRS, our primary outcome measure, is the most well validated measure of the degree to which EVT in patients with large core infarcts affects neurological disability versus no EVT. Secondary outcomes, such as functional independence, independent ambulation, and safety outcomes were all secondary outcomes of the aforementioned recent RCTs. (9–11) Functional independence has been measured in the most recent RCTs and is defined as a score of 0 to 2 on the mRS at an endpoint of 90 days at follow up. (9–11) Independent ambulation has been determined to be a score of 0 to 3 on the mRS. (16) Late EVT, especially in patients with a large ischemic stroke, is has been debated and determination of the appropriate candidate for EVT must be weighed against the increasing risk of ICH into this area of dead brain. (17) Safety outcomes such as ICH, death, neurological worsening, and procedural complications must be considered.

Data management: Two databases will be created for this study. One database will be for selected studies (study design, sample size, year of publications, PMID, database, etc.) and the second database will be for data extraction with preselected variables for meta-analysis.

Selection Process:

Two independent reviewers will assess remaining articles for relevance first based on titles and abstracts, and then will assess full-text articles for eligibility. Disagreements between reviewers will be resolved in both phases by either consensus or by a third reviewer.

Data Collection Process:

Each selected study will be distributed to two individuals for data extraction in duplicate using an excel database with preselected variables (see data items below). We anticipate no effort needed to contact authors of selected studies to obtain patient level data.

Data Items for extraction:

- Study: (First author name followed by et al.)
- Year of publication
- Effect size for each pre-defined outcome variable
- Upper limit CI for each pre-defined outcome variable
- Lower limit CI for each pre-defined outcome variable
- Study size (number of patients enrolled in the trial and on each arm)
- Standard Error
- Demographic and patient enrollment characteristics

Metadata:

- Journal name where study was published.
- Year of publication
- Enrollment criteria
- Analysis approach: intention-to-treat vs per-protocol.
- Adherence to CONSORT
- Potential sources of bias.

Quality assessment / Risk of bias analysis: Risk of bias will be determined at the study level:

- Should there be randomized control trials, we plan on employing the Risk of Bias in randomized trials (RoB 2) tool. (18)
- In any study competing interests in each study will be noted if any author had ties to industry, particularly those funded by an industry sponsor, have the potential for bias in favor of the sponsor's product or if such information was not disclosed.

• Studies will be assessed on quality based on compliance to EQUATOR network guidelines. (19)
We plan on using a funnel plot using Egger tests to assess the for publication bias. (20)
Confidence in cumulative evidence:
Studies will be assessed on quality based on compliance to EQUATOR network guidelines (CONSORT). (19) We will also use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the evidence that thrombectomy compared standard care improves outcomes as measured through mRS. (24)

Strategy of data synthesis: We expect variability in patient selection among the RCTs. Therefore, we plan on using a random-effect model with restricted maximum-likelihood estimation to perform. (21) We plan on using an inconsistency index (I2) to assess for heterogeneity. (22)

Subgroup analysis: • All subgroups with equivocal ORs (95% CI crosses 1.0) in the individual studies will be combined in attempt to better determine the potential impact these factors may have on primary and secondary outcomes when larger numbers are present.
• These subgroups will include:
o Age, time from last known well, use of IV thrombolytics, size of ischemic core volume, cervical ICA occlusion, and ASPECTS.

Sensitivity analysis: We will perform a sensitivity analyses by exploring how global effect sizes and p-values were affected by adjusting to the between-study variance parameter τ2. Statistical heterogeneity and the magnitude of heterogeneity will be assessed using Cochran χ2 tests and the I2 statistic, respectively. Publication bias will be assessed using the Egger test and visually using funnel plots. (23) Statistical analyses will be performed using STATA/MP version 17 (StataCorp). Alpha will be set at 0.05 and all test of significance will be 2-sided. To reduce the potential for type I error due to multiple testing, we will use Bonferroni corrections to adjust p-values. Data and syntax used for the analysis will be made publicly available through GitHub.

Language restriction: English language publications without translations.

Country(ies) involved: United States.

Keywords: Ischemic stroke; Endovascular thrombectomy.

Contributions of each author:
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Support: This project is supported in part by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number R25NS079188 (DEO). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. DEO is also a Cornwall Clinical Scholar supported by the University of Alabama at Birmingham.

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