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Endovascular thrombectomy in the treatment of large core ischemic stroke: an updated meta-analysis of randomized control trials

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202490114

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 September 2024 and was last updated on 26 September 2024.

INTRODUCTION

Review question / Objective

Aims: 1. To determine if thrombectomy leads to improved outcomes as measured by the modified Rankin Scale (mRS) in adult patient with large core ischemic strokes compared to medical therapy.
2. To assess the safety of thrombectomy in adult patients with large core ischemic strokes by comparing rates of symptomatic intracranial hemorrhage (ICH), neurologic worsening as determined by an increase of ≥ 4 points in the NIHSS score within 24 hours of presentation, any other procedural complications, and death.

Patients: Adult patients (>18) with ischemic stroke within 24-hour onset with:

- Pre-stroke modified Rankin scale (mRs) of 0 or 1
- Large infarct defined as meeting either of the following criteria:
  - Alberta Stroke Program Early Computed Tomography Score (ASPECTS) value of 3 to 5
  - 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) is a highly effective intervention for the management of patients with acute large vessel occlusions (LVO), with numerous randomized controlled trials (RCTs) demonstrating a clear benefit in functional outcome after stroke when compared to medical management alone.[1-4] However, the benefits of endovascular therapy for large-volume ischemic infarcts as determined by computed tomography (CT) imaging or via the Alberta Stroke Program Early CT Score (ASPECTS) has not been well-defined.[2,5] Though current guidelines support the use of ET for large vessel strokes, there remains hesitation in the utilization of ET in large-volume infarcts specifically due to potential risk of ICH or lack of functional benefit.[6,7] In the past years, several RCTs have been published investigating the benefits of ET for large-volume infarcts specifically. The RESCUE-JAPAN LIMIT, ANGEL-ASPECT, SELECT2, TENSION, LASTE, and most recently, the TESLA trials, were conducted in Japan, China, several international centers including North American, Europe, Australia and New Zealand, Europe, an international group, and the United States, respectively.[8-13] Most notably, though several studies report improved outcomes, the magnitude of the effect is unclear, and rates of complications are not consistent. Furthermore, the most recent TESLA trial reported no benefit of ET compared to medical management. [8-13] Thus, we sought to perform a systematic review of the literature for RCTs that include large-volume ischemic strokes and to conduct a meta-analysis of the results. In doing so, we hope to better understand the true benefit of ET compared to medical management for large volume ischemic strokes and to better understand the risk profile for this intervention.

Condition being studied

The utility of endovascular therapy (ET) in large-volume infarcts confirmed on non-contrast CT imaging or perfusion imaging are not well established. These patients have poor functional and neurologic outcomes, and symptoms often proceed to death.

METHODS

Search strategy

Medline/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- Present

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- Present

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-Present

Participant or population
Adult patients (>18) with ischemic stroke, presenting within 24-hour of onset, pre-stroke mRS of 0 to 1, and large volume infarct defined as:

1) ASPECTS value of 3 to 5 or 2
2) An estimated ischemic core volume of 50mL or greater

Intervention
Endovascular therapy.

Comparator
Medical Management.

Study designs to be included
Randomized Control Trials published since 2010.

Eligibility criteria
Exclusion: Non randomized clinical and observational studies, case series, case reports, brief reports, pilot reports, opinion pieces, theses, conference proceedings, letters, editorials, meta-analysis, reviews, surgical technique papers, abstracts, presentations, and any non-English language articles without translations available

Information sources
Medline, Embase, Scopus, Cochrane Central, Google Scholar, Pubmed

Main outcome(s)
Primary Outcome:

1. Ordinal Shift across the range of modified mRS scores towards a better outcome at 90 days

Additional outcome(s)
Secondary Outcome:

1. Functional Independence, defined as a mRS score of 0 to 2 at 90 days
2. Independent ambulation, defined as a mRS score of 0 to 3 at 90 days

Safety Outcomes

1. Symptomatic ICH, any ICH, death at 90 days, need for decompressive hemicraniotomy

Rationale for outcome measures:
These stated primary and secondary outcomes are the stated outcomes for previously published RCTs that investigate ET for acute ischemic stroke with large infarcts.[9,10] The mRS is a well validated, clinician-reported measure of general neurologic disability and is applied in stroke literature to evaluate patient outcomes following stroke, and is commonly utilized as an endpoint in RCTs.[14] This scale comprises 7 grades (0-6) of stroke severity, ranging from 0 being “no symptoms at all” to 5 “severe disability” and 6 being “death”.[15] An ordinal shift across the range of mRS is the most well validated measure of outcome to measure the benefit derived from ET in these patients with LVO. Secondary outcomes, such as functional independence, independent ambulation, and other safety outcomes were all secondary outcomes of the recent RCTs. Functional independence is generally measured in the most recent RCTs and is defined as a mRS score of 0 to 2 at the endpoint of 90-day follow-up. [8-13] Independent ambulation is described as a score of 0 to 3 on the mRS.[16] Due to the increasing risk of ICH in the setting of these large-volume occlusions, safety outcomes of ICH, neurological worsening, procedural complications, and death are considered as well.[17]

Data management
Two databases will be created, with one database used for describing the selected studies, and the second database for data extraction of pre-selected variables for meta-analysis.
Selection Process:
Two independent reviewers will screen 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 of selection by consensus decision or by a third reviewer.

Data Collection Process:
Each selected study will be distributed to two individuals for data extraction in duplicate using a predetermined excel database with the selected variables. We do not anticipate any need to contact the authors of the selected studies to obtain patient level data.

Data items for extraction

- Study (first author followed by et al.)
- Year of publication
- Effect size of 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 in each treatment arm)
- Standard Error
- Demographic and Patient enrollment characteristics

Metadata

- Journal name where study was published
- Year of publication
- Analysis approach: intention-to-treat vs per-protocol
- Adherence to CONSORT
- Sources of Bias

Quality assessment / Risk of bias analysis

Risk of bias will be assessed at the study level:

1. The Risk of Bias in randomized trials (RoB 2) tool will be used for RCTs[18]
2. Competing interest in studies will be noted, particularly studies with an industry sponsor
3. Studies will be assessed on quality based on adherence to EQUATOR network guidelines (CONSORT)[19]

A funnel plot using Egger tests will be used to assess publication bias.[20]

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.[21]

Strategy of data synthesis

Due to the expected variability in patient selection among the RCTs, we plan on using a random effects model with restricted maximum-likelihood estimation for data synthesis and meta-analysis. We will assess heterogeneity using the inconsistency index (I^2).[22]

Subgroup analysis

All subgroups with equivocal ORs (95% CI crosses 1.0) in the individual studies will be combined to better determine the potential impact these factors may have on primary and secondary outcomes when larger numbers are present. These subgroups will include:

1. Age
2. Time from last known well,
3. Use of IV thrombolytics,
4. Size of ischemic core volume
5. Cervical ICA occlusion,
6. ASPECTS score

Sensitivity analysis

Sensitivity analysis will be performed by investigating 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 utilizing the Cochran χ2 tests and the I2 statistic, respectively. Publication bias will be assessed using the Egger test and visually assessed using funnel plots.[20] Statistical analyses will be performed using STATA/MP version 17 (StataCorp) and R studio (version 4.3.1).[23,24] Alpha shall be set at 0.05 and all tests for significance will be 2-sided. To reduce the risk of type I error due to multiple testing, we will use Bonferroni corrections to adjust p-values.[25] Data and syntax used for analysis will be made publicly available on GitHub.

Language restriction English Language publications without translations.

Country(ies) involved United States.

Other relevant information: N/A

Keywords: Ischemic stroke; Endovascular thrombectomy.

Dissemination plans: Publish in peer reviewed journal.

Contributions of each author (Describe each author's contribution after their names).

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