Availability, Accessibility, Effectiveness, Safety, and Cost-utility of Mechanical Thrombectomy for Ischaemic Stroke in Latin American Countries, A Systematic Review Protocol

Protocol Registration

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Abstract— Introduction. Stroke is a significant cause of death and disability in Latin American countries. Intravenous recombinant tissue-plasminogen activator is the standard of treatment during the first 4.5 hours since stroke onset; however, a significant proportion of patients remain untreated due to late hospital arrival. Mechanical thrombectomy (MT) revolutionised stroke care by increasing the treatment window period up to 24 hours in eligible patients. Reports from Latin American countries describing the use of MT have been published, but no systematic review approach has evaluated MT in the region. Therefore, we present a systematic review protocol to assess the availability, accessibility, effectiveness, safety, and cost-utility of MT in Latin America. **Material and methods.** Randomised and non-randomised trials will be identified in CINAHL, MEDLINE, Web of Science, SciELO, EMBASE, and LILACS databases. Grey literature sources and clinical trial registries will be consulted. The approval of MT in the American Stroke Association was published in 2015; thus, the study search will be limited to papers published from 2015. The literature search will be conducted from February 1st, 2021, to March 31st, 2021. Additional search strategies will include citation tracking using Google Scholar and Web of Science and reference list check of the included articles. If necessary, authors from studies will be contacted for further data. **Results.** The results will be presented following the synthesis without meta-analysis (SWIM) guidelines.**Conclusions.** The results of this systematic review may be helpful for clinicians, policymakers, and stakeholders in the region. **PROSPERO Registration Number:** CRD42021231004. **Ictus 2021;2(2):e03052102014**

Keywords—protocol, systematic review, mechanical thrombectomy, stroke, Latin America.

Resumen— Disponibilidad, Accesibilidad, Efectividad, Seguridad y Costo-utilidad de la Trombectomía Mecánica para el Ictus Isquémico en Países de América Latina, Un Protocolo de Revisión Sistemática
Introducción. El ictus isquémico (II) es una causa principal de muerte y discapacidad en América Latina. La trombolisis intravenosa es el estándar de tratamiento durante las primeras 4.5 horas, sin embargo, una gran proporción de pacientes son excluidos por un arribo hospitalario tardío. La trombectomía mecánica (TM) permite tratar pacientes elegibles dentro de las primeras 24 horas. Estudios latino-americanos describen el uso de TM, sin embargo, no se ha evaluado sistemáticamente la TM en la región. Presentamos un protocolo de revisión sistemática para evaluar la TM en América Latina. **Material y Métodos.** Se identificarán ensayos aleatorios y no aleatorios en las bases de datos CINAHL, MEDLINE, Web of Science, SciELO, EMBASE y LILACS, así como fuentes de literatura gris y registros de ensayos clínicos. La aprobación de TM en la American Stroke Association se publicó en 2015, por lo que la búsqueda literaria se limitará publicaciones a partir de 2015. La búsqueda se realizará del 1 febrero 2021 al 31 de marzo de 2021. Estrategias de búsqueda adicionales incluirán el seguimiento de citas utilizando Google Scholar y Web of Science, y la verificación de la bibliografía de los artículos incluidos. Si es necesario, se establecerá contacto con los autores de los estudios para obtener más datos. **Resultados.** Los resultados se presentarán siguiendo las directrices de síntesis sin metaanálisis (SWIM). **Conclusiones.** Los resultados de esta revisión sistemática podrán ser útiles para personal del área clínica, responsables de la formulación de políticas y partes interesadas de la región. **Ictus 2021;2(2):e03052102014**

Palabras clave—protocolo, revisión sistemática, trombectomía mecánica, ictus, Latino América.

INTRODUCTION

Stroke is a significant cause of death in Latin America.[1] It occurs from the sudden stop of cerebral blood flow due to the rupture (haemorrhage) or blockage (ischaemia) of a cerebral artery, the latter representing more than 80 % of strokes.[2] In 2013, 75 % of deaths and 81 % of disability due to stroke occurred in low- and middle-income countries (LMICs), such as Latin American countries.[3] Recently, stroke deaths decreased in high-income countries (HICs) and LMICs due to the improvement in stroke care.[4] In Latin America, the proportion of stroke survivors has increased by 80 % from 1990 to 2019.[5]

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) is the gold standard treatment for acute ischemic stroke (AIS) and is associated with improved functional independence.6 This treatment is widely available in Latin American countries, and its accessibility has increased since it was introduced in the region. Further, a recent multinational stroke registry in Latin America revealed that the proportion of AIS patients receiving thrombolysis with rt-PA is similar to that of HICs.[7] Nonetheless, rt-PA's main limitation is that its administration is limited to the first 4.5 hours from stroke onset, thus limiting the number of patients benefiting from this treatment.

Stroke treatment improved after randomised trials (RTs) showed the effectiveness of mechanical thrombectomy (MT) to improve recanalisation and clinical outcomes.[8] Eligible stroke patients can receive treatment within a 24-hour time window.[4] However, MT is not widely available in Latin America, and less than 1 % of stroke patients from these countries benefit from MT.[7] According to Martins et al,[1] MT is scarcely accessible in the region and is mainly limited to private health care institutions. Studies from Latin America have described clinical effectiveness and efficacy similar to that of RTs from HIC and have also expressed some limitations to access MT.[9–14]

To date, no systematic approach has evaluated the status of MT in the region.

OBJECTIVES

To evaluate the availability, accessibility, effectiveness, safety, and cost-utility of mechanical thrombectomy in patients with acute ischemic stroke in Latin America.

METHODS

Eligility Criteria

Study types: Eligible studies include published randomised controlled trials, non-randomised controlled trials (RCTs), and observational studies. The articles should report original data on the availability, accessibility, effectiveness, safety, and cost-utility of mechanical thrombectomy.

Participants: Included studies must involve adult patients (>18 years) with AIS defined by neuroimaging (computed tomography or magnetic resonance imaging). Studies addressing other types of stroke (haemorrhagic or transient ischaemic attack) will be excluded.

Intervention: The intervention evaluated in this review is mechanical thrombectomy with or without concomitant IV thrombolysis administration.

Comparator: Patients without any form of endovascular treatment. These include patients with or without treatment with IV thrombolysis.

Context: Studies must have been developed in Latin American countries, including North and Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama), South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela), and the Caribbean (Cuba, Dominican Republic, Haiti, Guadeloupe, Martinique, Puerto Rico, Saint-Barthélemy, Saint-Martin)

Primary Outcomes: The studies will have to report data on availability, accessibility, effectiveness, safety, or cost-utility of mechanical thrombectomy

Information Sources

Reports will be identified by searching the CINAHL, MEDLINE, Web of Science, SciELO, EMBASE, and LILACS databases. Grey literature sources (OpenGrey, Database of abstracts of reviews and effects) will be consulted to identify studies not indexed in the searched databases. Clinical trial registries will also be consulted (ClinicalTrials.gov, ISRCTN registry, and World Health Organization International Clinical Trials Registry Platform). The approval of MT in the American Stroke Association, a reference in most Latin American countries, was published in 2015 (15). Thus, the literature search will include papers published from 2015. Reports in languages other than English, Spanish or Portuguese will be translated. The last search will be conducted on 28/February/2021. Additional search strategies will include citation tracking using Google Scholar and Web of Science and reference list check of the included articles. If necessary, we will contact the authors for further data.

Search Strategy

We will use a combination of the terms (cerebrovascular disease OR stroke) with (mechanical thrombolysis OR thrombectomy OR endovascular procedures). The search strategy will be restricted to humans as participants. All terms will be searched as free-text and controlled vocabulary (i.e., Medical Subjects Headings (MeSH)).

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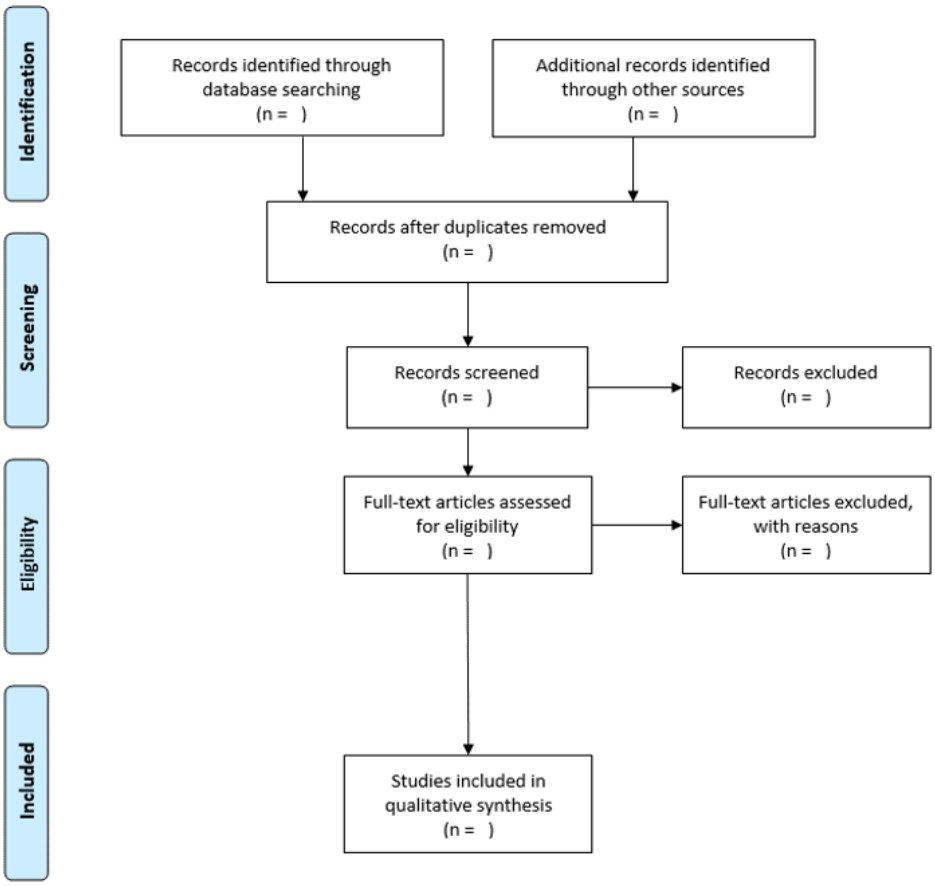

Figure 1: PRIMSA diagram of included studies. Taken from: Moher D et al.[16]

Study Records

Data management: Resulting records will be imported and organised in Mendeley, including title and abstract.

Selection process: Two review authors (AGA, ACCP) will be responsible for selecting studies. The reviewers will independently screen titles and abstracts. The full-text of the potentially included studies will be retrieved to assess inclusion and exclusion criteria. All disagreements will be solved by consensus or by a third author (FGR). Exclusion reasons will be recorded, and a PRISMA flow chart will be constructed (16) (figure 1).

Data collection process: Two authors (AGA, ACCP) will independently extract data using a predefined data extraction form (available from the request) template adapted from the EPOC Cochrane group. The template will be piloted with three studies and then adapted for this review. All disagreements will be solved by consensus or by a third author (FGR).

Data Items

We will search for the following data: *Study data:* first author's surname, year of publication, study design, study period, and location. *Patient data:* inclusion and exclusion criteria, patients' characteristics at baseline, diagnostic criteria used for acute ischaemic stroke (including whether MRI diffusion and perfusion mismatch, CT-angiography or CT perfusion were used to identify eligible patients, number of withdrawals, exclusions, and loss to follow-up. Intervention: a complete description of the intervention used; providers, co-interventions, and validated measurement tools. Outcomes: time-point measurements data of required outcomes and estimate adjustments; adverse events; time interval from stroke onset to procedure start; time interval from stroke onset to intracranial recanalisation; time interval from procedure start to recanalisation; specific of RTs: number of randomised participants in each arm; compliance and dropouts, reasons for dropouts, and ability to perform an intention-to-treat analysis; definition of outcomes.

Outcome and Prioritisation

Availability: The number of hospitals in which mechanical thrombectomy is available in the country divided by the stroke incidence rate in the year of publication.

Accessibility: The proportion of ischemic stroke patients that receive mechanical thrombectomy of the total of stroke cases in the hospital(s) during the study period.

Effectiveness:

1. The proportion of patients with favourable outcomes (0-2) at 90 days after hospital discharge measured using the modified Rankin scale (mRs).

2. Percentage of successful recanalisation after mechanical thrombectomy.

Economic Analysis:

1. Cost-utility: Measured in incremental cost-utility ratio (ICUR) or cost-utility ratio (CUR).

Safety Outcomes:

1. The proportion of symptomatic and asymptomatic intracranial haemorrhage

2. All-cause mortality at 90 days.

Risk of Bias in Individual Studies

The ROBINS-I tool[17] and the ROB 218 will be used for non-randomised and randomised trials, respectively. We will produce risk-of-bias graphics. Two authors (AGA, ACCP) will independently rate the quality of reporting. Authors will not be blinded. Disagreements will be resolved by consensus or by an independent third party (FGR).

Data Synthesis

A narrative synthesis will be realised following the SWIM guidelines.[19] The synthesis will be performed around (i) the quality of the included studies and (ii) outcomes of the included studies focusing on the primary objectives. Heterogeneity will be assessed based on the study designs and characteristics of the population.

Meta Bias(es)

To detect publication bias, we will consult "grey literature"databases. Moreover, authors of identified vital studies will be contacted and asked if they know unpublished work. For research with an available protocol, a comparison between planned and reported outcomes will be made. Statistical assessment of publication bias or selective outcome reporting will not be carried out.

Confidence in Cumulative Evidence

The strength of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE), which classifies evidence in high, moderate, low, or very low (20). Both RTs and observational studies will be evaluated.

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