

Early Mobilization Decision after an Acute Ischemic Stroke: Protocol for an Umbrella Review

Decisão de Mobilização Precoce após AVC Isquémico Agudo: Protocolo para uma Revisão Umbrella

Catarina FERNANDES¹, João André SOUSA¹, Sara BERNARDO-CASTRO¹, Fernando SILVA¹, Helena DONATO², João SARGENTO-FREITAS^{1,3}
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ABSTRACT

Introduction: Stroke is considered one of the greatest public health challenges worldwide, with the ischemic subtype being the most prevalent. Various acute stroke clinical guidelines recommend early rehabilitation interventions, including very early mobilization. However, despite the studies conducted in recent years regarding when to initiate mobilization after an acute stroke, there are few systematic and personalized protocols based on the factors for which patient mobilization should ideally be performed. We aim to conduct an umbrella review of systematic reviews and meta-analyses to study the early mobilization decision after an acute ischemic stroke in comparison with conventional care and correlate the different approaches with patient clinical outcomes.

Methods and analysis: We will perform a systematic search on PubMed/MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Epistemonikos and Web of Science Core Collection databases. Retrieved studies will be independently reviewed by two authors and any discrepancies will be resolved by consensus or with a third reviewer. Reviewers will extract the data and assess the risk of bias in the selected studies. We will use the 16-item Assessment of Multiple Systematic Reviews 2 (AMSTAR2) checklist as the critical appraisal tool to assess cumulative evidence and risk of bias of the different studies. This will be the first umbrella review that compares early mobilization approaches in post-acute ischemic stroke. This study may help to define the optimal early mobilization strategy in stroke patients. PROSPERO registration number: CRD42023430494

Keywords: Cerebrovascular Disorders; Early Ambulation; Meta-analysis; Stroke; Systematic Review

RESUMO

Introdução: O acidente vascular cerebral (AVC) é considerado um dos principais problemas de saúde pública em todo o mundo, sendo o AVC isquémico o mais prevalente. Existem diferentes orientações clínicas relativas à abordagem do AVC na fase aguda que recomendam a mobilização precoce. No entanto, apesar dos estudos realizados nos últimos anos sobre quando iniciar a mobilização após um AVC, existem poucos protocolos sistemáticos e personalizados que abordam quais os fatores decisivos para a mobilização dos doentes. O objetivo deste trabalho será analisar revisões sistemáticas e meta-análises sobre a decisão de mobilização precoce após um acidente vascular cerebral isquémico agudo em comparação com o tratamento convencional e verificar o impacto no resultado clínico das diferentes abordagens.

Métodos e análise: Iremos realizar pesquisa nas seguintes bases: PubMed/MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Epistemonikos e Web of Science Core Collection. Os estudos encontrados serão revistos de forma independente por dois autores e perante discrepâncias tentar-se-á obter um consenso entre os autores, ou será requerida a avaliação por um terceiro revisor. Os revisores extrairão os dados e avaliarão o risco de viés dos estudos selecionados. A lista de verificação de Avaliação de Revisões Sistemáticas Múltiplas 2 (AMSTAR2) com 16 itens será utilizada como ferramenta de avaliação crítica das evidências cumulativas dos diferentes estudos. Do nosso conhecimento, esta será a primeira revisão abrangente e sistemática que irá comparar as abordagens de mobilização precoce no AVC isquémico pós-agudo. Este estudo poderá contribuir para apoiar e estabelecer indicações sobre a estratégia ideal de mobilização precoce em doentes com AVC. PROSPERO número de registo: CRD42023430494

Palavras-chave: Acidente Vascular Cerebral; Doença Cerebrovascular; Meta-análises; Mobilização Precoce; Revisão Sistemática

INTRODUCTION

Stroke is considered one of the greatest public health challenges worldwide that remained the second-leading cause of death, with the ischemic subtype being the most prevalent corresponding to around 62% of the overall number of cases of stroke in 2019.¹ According to Wafa H *et al*, a study published in 2020, an increase of 27% in the number of Europeans living with stroke is expected in the next 30 years.²

The management in the acute phase of a stroke is well established in the guidelines and bed rest is recommended during the first hours after the event.^{3,4} A component of acute stroke unit care is mobilization and due to stroke

patient heterogeneity, clinical decision-making becomes a complex issue.⁵ Mobilization protocols are not well defined, despite the knowledge that early mobilization can prevent acute complications such as thromboembolic events and infections.^{5,6} Recent recommendations, including the European Stroke Organization consensus, state that early mobilization is safe but should not be too aggressive (not within the first 24 hours after stroke), according to the results of the AVERT clinical trial, and should be adapted to the patient's clinical and neurological situation.^{7,8}

The timing for initiating mobilization after the acute event has been debated in different systematic reviews and

1. Serviço de Neurologia. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.

2. Documentation and Scientific Information Service. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.

3. Faculdade de Medicina. Universidade de Coimbra. Coimbra. Portugal.

✉ **Autor correspondente:** Catarina Fernandes. catarinafernandes@hotmail.com

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meta-analyses.^{9,10} Very early interventions, defined as within the first 24 hours, showed a worse outcome when compared to early interventions, defined as between 24 - 72 hours post-acute event.^{8,10} Still, this is a large span of time that could not be adapted to every patient. For that reason, it is important to study the patient profile that benefits from an earlier mobilization protocol and which factors could inform this strategy.

Not only is the timing debatable, but also the type of mobilization is under discussion. Mobilization is an overarching term that includes passive mobilization at the bedside, sitting in bed, standing up, out-of-bed activity, and physical exercise.^{6,11} Defining the type of mobilization and a personalized program is also an important factor in patient management in an acute stroke unit care. Moreover, the evolution of cerebral hemodynamics after a stroke is heterogeneous between patients, with established clinical impact.¹² Therefore, effective mobilization strategies must take this heterogeneity into account.

Despite recent studies on the timing of mobilization after an acute stroke, there are few systematic and personalized protocols that specify the factors guiding patient mobilization and assess the clinical impact of such protocols. Ideally, studying these factors could support clinicians in patient mobilization decisions after a stroke and facilitate the development of guidelines for a standardized and personalized approach for different subgroups of patients. Therefore, the aim of this umbrella review is to study the different mobilization approaches during the post-acute phase of a stroke and the respective clinical outcomes.

The objective of this study is to investigate the early mobilization strategy compared with conventional care in patients after an acute ischemic stroke and explore the association between different approaches and the clinical outcomes of the patients.

METHODS AND ANALYSIS

This overview of systematic reviews will follow the methodological guidelines published in a measurement tool to assess systematic reviews (AMSTAR 2). The AMSTAR-2 is a 16-item checklist for systematic reviews of healthcare

interventions.¹³ It does not provide a numerical outcome to quantitatively assess the quality of the study, but it provides an assessment of confidence based on different weaknesses.

We will identify systematic reviews and meta-analyses that evaluate the timing of mobilization in patients after an acute ischemic stroke.

This project was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42023430494).

Eligibility criteria

This study will include systematic reviews and meta-analyses that assess the early mobilization approach after an acute ischemic stroke. The definition of mobilization will include sitting in bed, standing up, out-of-bed activity and physical exercise. Studies fulfilling the eligibility criteria shown in Table 1 will be selected for further review. If more than one article reports the same study, the article with the largest sample size or reporting more relevant data for our specific aim will be selected. No restriction regarding publication year will be set, and we will be including studies from inception to the June 30, 2023. No language restriction will be applied, and we will include studies in all languages. We will resort to a professional translator if needed.

Information sources

We will implement a computerized search strategy in the scientific literature to identify studies for inclusion in this umbrella review. We will search for both published and unpublished papers in the following databases: PubMed/MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Epistemonikos and Web of Science Core Collection.

Furthermore, in order to comprehensively include peer-reviewed systematic reviews that may not be indexed in academic databases, we will conduct searches in the repositories of the Campbell Collaboration and the EPPI-Centre.

In addition to this electronic search, a supplementary search of the grey literature will be conducted with the aim of including all possible existing systematic reviews on the

Table 1 – Inclusion and exclusion criteria used in study selection

Inclusion criteria	Exclusion criteria
- Only reporting studies performed in living humans	- Not a systematic review and/or meta-analysis
- Acute ischemic stroke patients	- Non-human studies
- Studies evaluating the protocol or decision of early mobilization	- Primary research
- Studies with a follow up for clinical outcome	- Studies reporting bed mobilization but not out-of-bed mobilization
- Only meta-analysis and systematic reviews	- Studies reporting physical exercise post stroke but not post-acute phase of stroke
- Any publication year	- No follow-up and no clinical evaluation of the patients
- No language restriction	

subject. No pre-prints will be included in this work.

Search strategy

Detailed search strategies will be conducted in the previously outlined databases, in consultation with a medical librarian with expertise in systematic review searching. The search strategy will incorporate controlled vocabulary (e.g., Medical Subject Headings-MeSH) and text word searches tailored to the unique requirements of each database. To merge the search terms effectively, Boolean operators “AND” and “OR” will be used. An example of the search strategy used in PubMed/MEDLINE is depicted in Table 2.

Data management

Following the literature search, all identified studies will be imported into Mendeley citation software. Within Mendeley, duplicates will be systematically managed and removed, and a thorough examination of titles and abstracts for all records will be conducted. The research question will include a population of ischemic stroke patients and will study the intervention of early mobilization in comparison to conventional care protocols.

Selection process

Two independent reviewers will conduct the selection process in January 2024. Any disagreements between the reviewers will be resolved through consensus or, if necessary, by involving a third reviewer. All records identified in the search stage will undergo title/abstract screening, and meta-analyses and systematic reviews that clearly do not match the criteria will be discarded. The reasons for exclusion will be recorded. The remaining studies will undergo full-text review, and inclusion or exclusion decisions will be made based on the criteria.

Details on the selection process of the studies will be documented in a flow chart following the AMSTAR 2 as presented in Fig. 1.

Data collection process and items

The reviewers will extract information from the articles to ensure that all necessary details are obtained from the selected studies and minimize the risk of bias. After the se-

lection, the data extracted will be reviewed and validated by a third reviewer. Then, they will extract selected features from all included studies such as index test, sample size, patients’ characteristics, type of intervention and clinical outcome. Among these categories, several items will be collected as presented in Table 3.

- Participants/population: will include studies involving adult patients diagnosed with acute ischemic stroke, for whom mobilization could be initiated within seven days of symptom onset. Studies involving patients with any other diseases besides acute ischemic stroke, including hemorrhagic stroke, will be excluded. There are no age or onset-of-symptoms restrictions.

The following study variables will be collected:

- Intervention(s), exposure(s)
 - Early mobilization decision (first out-of-bed episode in the first 48 hours) or conventional mobilization decision (defined as the usual mobilization practice).
 - All forms of mobilization will be considered (such as simple out-of-bed, assuming orthostatic positioning, starting to walk or beginning of out-of-bed rehabilitation). We will collect and compare the intensity and duration of the intervention.
 - The phase of the stroke (since onset) in which the imaging technique was performed: First 24h; First 48h; 3-4 days; 7 days.
 - Hemodynamic criteria used to guide early mobilization, namely persistent intracranial occlusion (any occlusion or only large vessel occlusion) and/or extracranial disease (only occlusion, > 70% stenosis or > 50% stenosis in the symptomatic artery).
 - The test used to characterize arterial disease in the symptomatic artery (angiography, CT-angiogram, MR-angiogram or ultrasound).
 - Blood pressure levels and the use of anti-hypertensive medication in the acute phase and pre-stroke.

Table 2 – Search strategy

PubMed/MEDLINE	
#1	((“Early Ambulation”[Mesh]) AND (“Cerebrovascular Disorders”[Mesh]) OR “Stroke”[Mesh])) AND ((systematic review OR meta-analysis))
#2	((mobilization[Title/Abstract] OR out of bed[Title/Abstract] OR mobility[Title/Abstract]) AND (stroke[Title/Abstract] OR poststroke[Title/Abstract] OR post-stroke[Title/Abstract] OR cerebrovascular[Title/Abstract])) AND ((systematic review[Title/Abstract] OR meta-analysis[Title/Abstract]))
#3	((mobilization[Title/Abstract] OR out of bed[Title/Abstract] OR mobility[Title/Abstract]) AND (stroke[Title/Abstract] OR poststroke[Title/Abstract] OR post-stroke[Title/Abstract] OR cerebrovascular[Title/Abstract])) filters applied: Meta-Analysis, Systematic Review.

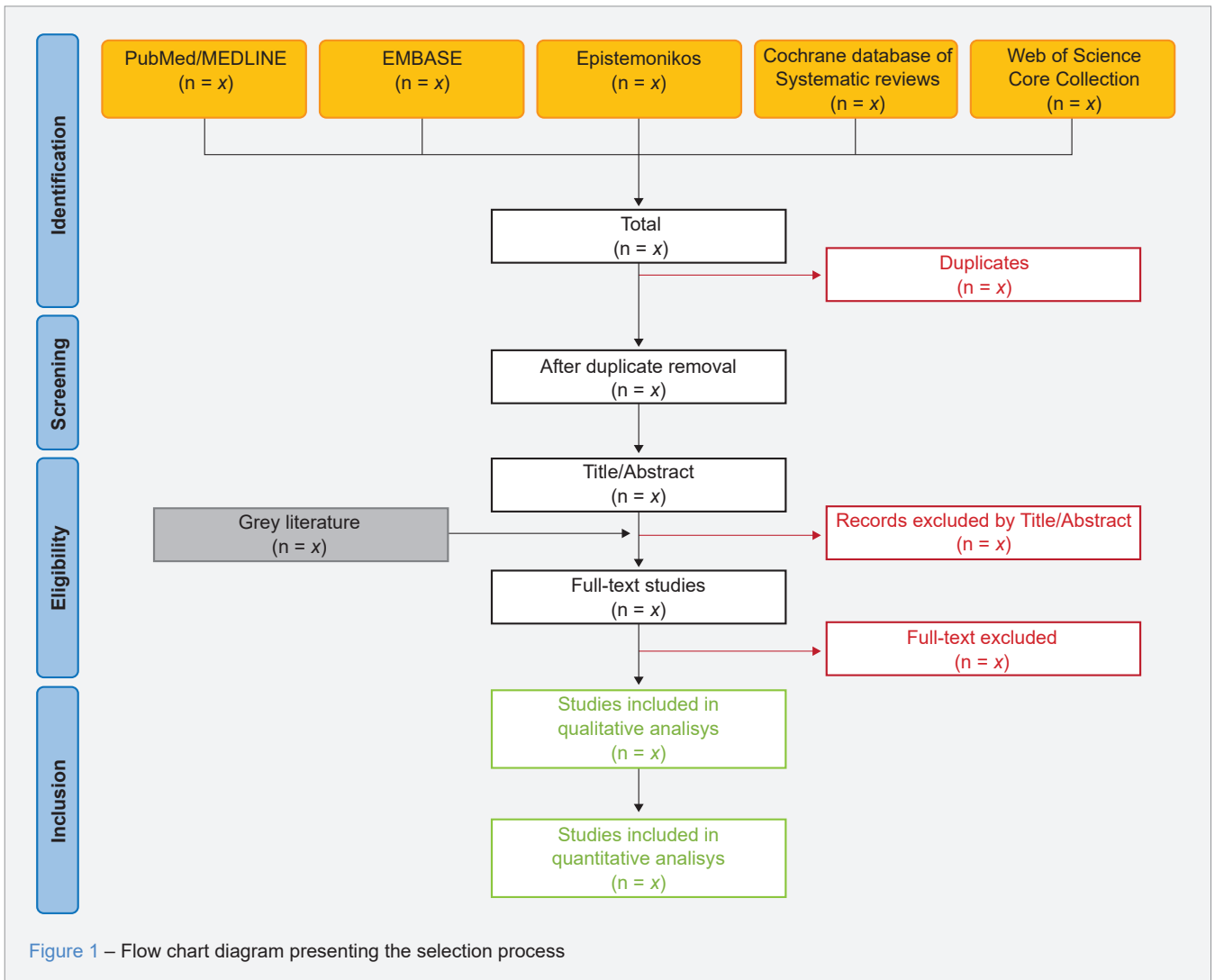


Figure 1 – Flow chart diagram presenting the selection process

Table 3 – Subgroup analysis

Subgroups according to:	
1. The mobilization protocol that has been performed	
2. The treatment given to the patients. This will be:	(A) Patients treated with IV-rTPA; (B) Patients treated with mechanical thrombectomy; (C) Patients treated with both techniques; (D) no acute phase treatment at all.
3. The etiological TOAST classification of the stroke:	(A) Cardioembolism; (B) Large-artery atherosclerosis; (C) Small-vessel occlusion; (D) Stroke of other specific etiology; (E) Stroke of undetermined etiology.
4. Different definition of mobilization	
5. Different definition of hemodynamic exclusion criteria	
6. Different imaging modality used to characterize arterial disease	
7. The blood pressure of patients	
8. Anti-hypertensive medication	

Outcomes and prioritization

This work has two primary outcomes:

- To compare the functional outcome according to the mobilization protocol of patients in the post-acute phase of an ischemic stroke, at the end of scheduled follow-up, ideally at discharge and at three months or longer after the stroke. Conventional metrics such as National Institutes of Health Stroke Scale (NIHSS) and/or Modifying Ranking Scale (mRS) will be used.
- To evaluate when (First 24h, First 48h, 3-4 days or subsequent days since stroke onset) and how mobilization protocols were defined.

If available, the following secondary outcomes will be collected:

1. Death: number of deaths from any cause at the end of the follow-up.
2. Adverse events: number or severity (or both) of adverse effects during the hospital stay, including deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), the incidence of urinary retention, chest and/or urinary infections, falls or injuries, and physiological variables (blood pressure, oxygen, temperature).
3. Dependence: the number of patients requiring institutional care at the end of scheduled follow-up where follow-up was performed at three months or longer after the stroke.
4. Performance in activities of daily living at the end of scheduled follow-up where follow-up was performed at three months or longer after the stroke.
5. Patient subjective health status or quality of life at the end of scheduled follow-up where follow-up was performed at three months or longer after the stroke.
6. Time to walking unassisted (without help from another person) reported alone or as part of a functional mobility scale, at the end of scheduled follow-up where follow-up was performed at three months or longer after the stroke.

Risk of bias

The validity of our review findings will depend on the quality and bias of the eligible systematic reviews and meta-analyses. The risk of bias in individual studies will be assessed using AMSTAR 2 by independent reviewers. In the case of any disagreement between the two reviewers, consensus will be sought, or a third reviewer will be involved if necessary.

Data synthesis

This umbrella review will include systematic reviews with quantitative meta-analysis, if possible. A narrative synthesis

of results will be performed, presenting only data available from reviews. Results from reviews will be synthesized narratively, accompanied by tabular presentation of findings. Summary tables describing review characteristics and findings will also be provided.

Subgroup analysis

To investigate the different outcomes of early mobilization compared to conventional care after an acute ischemic stroke, we will create two main groups based on the time of mobilization. Within each of these groups, the following subgroups represented in Table 3 will be formed, if possible.

Meta-bias(es)

To assess publication bias, we will conduct extracted aggregated study results and treatment effect estimates.

Confidence in cumulative evidence

The strength of the evidence base will be assessed using AMSTAR.¹³ The AMSTAR-2 assesses confidence based on identified weaknesses, which are categorized as 'critical' or 'non-critical.' The overall level of confidence, determined by the checklist, is classified into four degrees: high, moderate, low, or critically low. A high confidence score is assigned if there are ≤ 1 non-critical weakness. Moderate confidence is given if there are ≥ 2 non-critical weaknesses and no critical weaknesses. Low confidence is awarded when one critical weakness is present, irrespective of the presence of non-critical weaknesses. Critically low confidence is assigned when ≥ 2 critical weaknesses are identified following the checklist.

If necessary, any disagreement between the two reviewers will be solved by consensus or by a third reviewer.

Patient and public involvement

This umbrella review protocol relies on previously published data, eliminating the need for participant recruitment. Consequently, public involvement is not applicable to the recruitment and dissemination of results.

To our knowledge, this will be the first umbrella review that compares early mobilization approaches in post-acute ischemic stroke. This study may help to inform the optimal early mobilization strategy in stroke patients.

AUTHOR CONTRIBUTIONS

CF, SBC: Conceptualization, methodology, drafting of the manuscript preparation.

JAS, FS, HD, JSF: Conceptualization, methodology, critical review.

All authors approved the version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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