Review Article

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Early mobilization on clinical and functional outcomes, and adverse events in neurocritical patients: a systematic review protocol with meta-analysis

Mobilização precoce em desfechos clínicos, funcionais e eventos adversos em pacientes neurocríticos: um protocolo de revisão sistemática com metanálise

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Abstract

Background: Early mobilization (EM) seems to be viable and safe to prevent adverse outcomes. However, evidence in neurocritical patients remains limited. **Aim**: To analyze whether EM programs are more effective than conventional physiotherapy in the mobility and functionality outcomes of neurocritical patients. To analyze their effect on mechanical ventilation duration, length of ICU and total hospital stay, rate of clinical complications, and number of adverse events. Also to provide safety parameters for carrying out the EM in neurocritical patients. **Method**: Systematic review of randomized clinical trials that applied EM protocols compared to conventional physical therapy in adult neurocritical patients. Searches will be performed in databases EMBASE, Pubmed, PEDro, EBSCO, Lilacs, Scopus and Cochrane Central, with no language or date restrictions. Studies will be independently selected by two authors. The inclusion of the studies will be carried out initially by title and abstract, followed by reading the full text. The methodological quality of the studies will be assessed by the RoB 2.0 scale and the level of certainty of evidence by the GRADE system. The quality of the intervention descriptions will be assessed by the Consensus on Therapeutic Exercise Training (CONTENT) scale. **Results**: The registration of the systematic review protocol was approved in July 2024 (CRD42024560900). The studies recruitment and data collection are ongoing. The results of this review will likely be published in late 2025. **Conclusion**: EM can reduce the deleterious effects of immobilization in critical patients, and we believe that the same can be applied to neurocritical patients.

Keywords: Critical Care; Early Mobilization; Mobility Limitation; Physiotherapy, Specialty.

Resumo

Introdução: A mobilização precoce (MP) parece ser viável e segura para prevenir desfechos adversos, embora as evidências em pacientes neurocríticos permaneçam limitadas. **Objetivos**: Analisar se programas de MP são mais eficazes que a fisioterapia convencional na mobilidade e funcionalidade de pacientes neurocríticos. Analisar seu efeito nos tempos de ventilação mecânica, tempos de hospitalização na UTI e total, taxa de complicações clínicas, número de eventos adversos, e fornecer parâmetros de segurança para realização de MP em pacientes neurocríticos. **Métodos**: Revisão sistemática de ensaios clínicos aleatorizados que aplicaram protocolos de MP em comparação à fisioterapia convencional em pacientes neurocríticos adultos. As buscas serão realizadas nas bases de dados EMBASE, Pubmed, PEDro, EBSCO, Lilacs, Scopus e Cochrane Central, sem restrição de idioma ou data. Os estudos serão selecionados por dois autores de forma independente. A seleção dos estudos para inclusão será realizada inicialmente pelo título e resumo, seguido do texto completo para a tomada de decisão. A qualidade metodológica dos estudos será avaliada pela escala RoB 2.0 e o nível de certeza da evidência pelo sistema GRADE. A qualidade das descrições de intervenções será avaliada pela escala Consensus on Therapeutic Exercise Training (CONTENT). **Resultados**: Em julho de 2024 o registro do protocolo da revisão sistemática

foi aprovado (CRD42024560900). O recrutamento dos estudos e a coleta de dados estão em andamento. Os resultados desta revisão provavelmente serão publicados no final de 2025. **Conclusão**: A MP pode reduzir os efeitos deletérios da imobilização em pacientes críticos, acreditamos que o mesmo possa se aplicar nos neurocríticos.

Palavras-chave: Cuidados Críticos; Mobilização Precoce; Limitação de Mobilidade; Fisioterapia, Especialidade.

INTRODUCTION

Neurocritical patients have mobility limitations influenced by numerous factors, such as primary brain injury, altered level of consciousness, presence of delirium, or restrictions related to the Intensive Care Unit (ICU) stay, as well as cultural barriers within the health care team[1,2]. Furthermore, postural changes may compromise brain self-regulation and generate a risk of cerebral ischemia given the close relationship between head position, Mean Arterial Pressure (MAP), and Intracranial Pressure (ICP)[1]. The presence of invasive brain devices such as External Ventricular Drains (EVD), ICP catheters, and subdural drains is another factor able to restrict the mobility of neurocritical patients[1,3].

All these factors can culminate in functional impairments that may lead to a longer Mechanical Ventilation (MV) time, a higher risk of hospital infections, a longer ICU and general hospital stays, as well as a higher risk of morbidity along with mortality for neurocritical patients[4-8]. In this context, current evidence suggests that Early Mobilization (EM) is a viable and safe alternative to reduce the incidence of myopathy in critically ill patients, improve functional capacity, increase the number of days without MV, and the rate of hospital discharge in critically ill ICU patients[9].

Nevertheless, evidence in the literature indicates that EM programs are less implemented in neurocritical patients than in other patient profiles[10,11], on account of concerns related to possible neurological instability, risk of complications, lack of specific protocols, limited resources and the perception that these patients are more fragile or at greater risk than the others[10,11].

That being said, some findings present the benefits of EM programs in neurocritical patients, like: improving physical function, reducing pressure ulcers, infection rates, length of ICU stay, anxiety levels, MV duration, and even reducing health costs associated with this population[12-14]. However, this evidence is limited because it is only provided by observational studies. The sole systematic review found in this area compares EM programs executed for up to 72 hours and within the first 24 hours after an stroke, suggesting that very early mobilization did not increase the number of survivors, but reduced hospitalization time by about one day, even though these results were based on low methodological quality evidence[15].

Evidence of the effects contrasting a progressive, individualized EM program with conventional physiotherapy has not yet been established for hospitalized neurocritical patients through a systematic review with high scientific rigor. The AVERT multicenter clinical trial compared the effects of EM programs initiated within 72 hours *versus* very early (first 24 hours). The program consisted of passive, active, or assisted orthostatism, out-of-bed ambulation, and seating with stroke patients. AVERT identified worse outcomes in the very early group, but did not compare the EM with conventional physiotherapy, which includes bed positioning, passive and/or active-assisted mobilization exercises of hemiparetic or hemiplegic limbs, as well as active in-bed exercises of the unaffected limbs[16].

Therefore, the objective of the present systematic review will be to analyze whether EM programs are more effective than conventional physiotherapy for the mobility and functionality of hospitalized adult neurocritical patients. In addition, this work aims to evaluate the effect of EM on the MV time, on the duration of ICU and total hospital stays, on the clinical complication rate, and the number of adverse events. Finally, the purpose of this study is also to provide safety parameters for implementing EM program in the targeted population.

METHODS

The present review protocol will be conducted following the recommendations of the Cochrane Handbook of Systematic Reviews[17] guidelines and will be drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[17,18]. This study has been previously registered in the International Prospective Register of Systematic Reviews - PROSPERO (CRD42024560900).

Eligibility criteria

Studies included in this work must conform to the PICOT strategy: Patients (P), Interventions (I), Comparisons (C), Outcomes (O), and Type of study design (T).This refers to adult patients (P) hospitalized in Intensive Care Units (ICU) or stroke units with traumatic, vascular or neoplastic brain lesions; submitted to an intervention (I) with some type of progressive EM protocol, individualized according to the patient's consciousness levels; compared (C) with common treatments such as conventional physiotherapy, usual care or standard physiotherapy exercises with an unspecified pre-established progressive protocol; with at least one of the following outcomes (O) being evaluated: mobility, functionality, MV duration, length of ICU stay, total hospitalization time, ICU-Acquired Weakness (ICU-AW) rate, clinical complication rate, presence of adverse events; in randomized trial type (T) studies. Research published in any language and on any date will be included. Duplicated studies or works published only in protocol format (without the final results) or that use only passive exercises in the EM protocol will be excluded.

Primary outcomes

Mobility and functionality: measured using specific scales such as: ICU Mobility Scale[19,20], Functional Status Score[21], Perme Intensive Care Unit Mobility Score[20,22], Physical Function ICU Test[23,24], Chelsea Critical Care Physical Assessment Tool[25], Surgical Intensive Care Unit Optimal Mobilization Score[26], and Barthel scale[27]. Or by specific field walking tests, that is: six-minute walk test[28], one-minute sit-to-stand test[29], step test[30], timed up and go test[31,] or any other physical test described in the studies.

Secondary outcomes

MV duration: the number of days the patient remained on invasive ventilatory support will be recorded.

Length of stay: the number of days that the patient remained hospitalized in the ICU and the total hospital stay will be recorded, considering the sum of the hospitalization days in the ICU and in the nursing unit.

Adverse events: characterized by the presence of neurological alterations such as: lowering of the level of consciousness (characterized by reductions of two or more points on the Glasgow Coma Scale [GCS]), seizure crisis, significant changes in Intracranial Pressure (ICP) (characterized by sustained peaks with values greater than 20 mm Hg for more than five minutes, or MAP alterations generating changes in the Cerebral Perfusion Pressure [CPP] to values lower than 60 mm Hg or greater than 80 mm Hg), cerebral vasospasm, motor deficits (characterized by paresis or plegia and/or focal neurologic deficits, paresthesia, hypo or hyperesthesia[32]), hemodynamic changes such as arterial hypertension (characterized by Systolic Blood Pressure [SBP] greater than 150 mm Hg in patients with hemorrhagic stroke[33], SBP higher than 140 mm Hg in patients with Aneurysmal Subarachnoid Hemorrhage [SAH] without surgical treatment and SBP greater than 220 mm Hg in patients with aneurysmal SAH with surgical treatment[34], SBP greater than 220 mm Hg in patients with ischemic stroke without thrombolysis and SBP greater than 185 mm Hg in patients with ischemic stroke with thrombolysis[35]), hypotension (characterized by SBP lower than 90 mm Hg during dorsal decubitus and/or sitting position, or orthostatic hypotension, which is defined as a SBP reduction equal to or greater than 20 mm Hg), tachycardia or bradycardia (characterized by Heart Rate [HR] greater than 140 bpm or less than 60 bpm), drop in peripheral oxygen saturation (characterized by saturation lower than 94% in patients without prior lung disease or lower than 88% in patients with prior lung disease[36]), nausea, headache, diarrhea or vomiting, and accidental withdrawal and/or displacement of the subdural drains or EVDs[32].

Databases

The following databases will be consulted: EMBASE, Pubmed, PEDro, EBSCO, Lilacs, Scopus, and Cochrane Central. The research will also be carried out in two clinical trial registration databases: clinicaltrials.gov and ensaiosclinicos.gov.br. Finally, a secondary search will be performed using the references of the included studies.

Research strategy

Descriptors related to the research theme will be applied using Health Sciences Descriptors (DeCS), Medical Subject Headings (MeSH) and the keywords employed by related studies. The word clusters are described in Table 1. The strategy outlined in Table 1 will guide the research carried out in PubMed. For the other databases, the search will be adapted according to the appropriate specificities, as required.

Study selection

Following the exclusion of duplicates, the works will be independently selected by two authors using the Rayyan platform (https://www.rayyan.ai/). Based on the eligibility

Table 1. Research strategy of the systematic review.

Number	Clusters	Descriptors
1	Patient/Population	(Neurological Patients) OR (Neuro Critical Patients) OR (Brain Injuries) OR (Neurovegetative Disorders) OR (Cerebrovascular Disorders) OR (Basal Ganglia Cerebrovascular Disease) OR (Brain Ischemia) OR (Cerebral Small Vessel Diseases) OR (Intracranial Arterial Diseases) OR (Cerebral Hemisphere) OR (Hospitalization); OR (Hospitalized Patients) OR (Stroke) OR (Acute Stroke) OR (Ischemic Stroke) OR (Intracerebral Hemorrhage) OR (Intracranial Hemorrhages) OR (Brain Injuries, Traumatic) OR (Craniocerebral Trauma) OR (Subarachnoid Hemorrhage) OR (Vasospasm, Intracranial) OR (Intracranial Hemorrhage) OR (Intracranial Aneurysm) OR (Brain Hemorrhages) OR (Brain Vasospasm) OR (Brain Neoplasms); OR (Brain Tumor) OR (Brain Tumor); OR (Brain Carcinoma); OR (Brain Cancer); OR (Subdural Hematoma) OR (Brain Hematoma)
2	Intervention	(Mobilization) OR (Early Mobilization) OR (Very Early Mobilization) OR (Early Rehabilitation) OR (Rehabilitation) OR (Cycle Ergometer) OR (Ergometry) OR (Neuromuscular Electrical Stimulation) OR (Orthostatic Board) OR (Virtual Reality Training) OR (Resistance Exercise) OR (Resistance Training) OR (Exercise) OR (Exercise Program)
3	Study type	(clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]

criteria defined in the protocol herein, two authors will select the studies considered eligible under the reading of the titles and abstracts, followed by the full-text reading to determine if the study will be included or excluded from the present review. In the event of a disagreement over the decision made between the two authors, a third senior author will be in charge of the final decision.

Data extraction

Two independent authors will extract the data from the selected studies. A senior author will monitor and set possible inconsistencies of the extracted data. the authors will create an Excel spreadsheet to record the following data: authors, year of publication, country(ies) where the study was conducted, sample size, age, gender % of the participants, clinical characteristics of the included patients, study objectives, clinical inclusion and exclusion criteria as established by the authors, intervention onset time, EM protocol performed, intervention control performed, evaluation method of each outcome of interest, results of the outcomes of interest (in frequency, mean, standard deviation, median, minimum and maximum, confidence interval, p-value, standard error) and reported adverse events.

Methodological quality assessment

Two authors, supervised by a senior author, will assess the methodological quality using the Cochrane Risk of Bias Table (RoB 2.0) tool[37,38]. This instrument is structured into five domains that cover all types of bias that may potentially affect the results of randomized trials such as: bias arising from the randomization process; bias due to deviations in the intended intervention; bias caused by missing data; bias in the measurement of the outcome; and bias in the selection of the reported outcome. The response options for the scale items are: "yes", "probably yes", "probably not", "no", "there is no information", and "not applicable". The definitive "yes" and "no" answers often indicate that robust evidence is available. The "not applicable" option is only available for questions with a non-mandatory answer. Throughout the application of the instrument, the responses feed an algorithm that determines the risk of bias for each domain: high risk of bias, low risk of bias, or presence of some bias concern[38].

Evidence quality assessment

The quality of the evidence will be classified following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system available at the https://www.gradepro.org/ platform[39,40], and under the Cochrane Handbook of Systematic Reviews[39]. The quality of the evidence is based on five factors, where for each factor not found, the quality of the evidence may be reduced one level (from high to moderate, low, or very low). The five factors are:

- ✓ Methodological limitations (risk of bias): the quality of evidence will be lowered if there are methodological limitations that indicate a greater propensity for bias, thus reducing the confidence to estimate the effect of the study[41,42]. Evidence will be downgraded by one level if more than 25% of the studies included in a given comparison are classified as high risk of bias.
- ✓ Inconsistency: the quality of the evidence will be lowered if significant heterogeneity is observed in the results (overlapping of the standard deviations of the studies), even after performing a sensitivity analysis of the hypothesis[43]. Evidence will be downgraded by one level if the inconsistency is greater than 50%.
- ✓ Indirect evidence: the quality of evidence will be reduced if the participants, interventions, or results of the evaluated studies are found to be essentially different from those presented in the research subject matter or in the clinical guideline, or if there are no direct comparisons between interventions[44]. Evidence will be downgraded by one level if more than 50% of participants are not related to the study target audience.
- ✓ Inaccuracy: The main criterion used by the GRADE system to define the accuracy of estimates is the 95% confidence interval[44]. Evidence will be downgraded by a level if there are fewer than 400 participants in the comparison for continuous outcomes, and fewer than 300 participants for categorical outcomes.
- ✓ Publication bias: A funnel chart applied for meta-analysis with ten studies or more will be used to verify publication bias. Studies with low precision and small samples will be distributed symmetrically in the widest part of the funnel, while studies with greater precision and larger sample sizes will be closer to the actual result, being placed in the narrowest part of the funnel[44].

Interventions description quality assessment

The quality of the description of the interventions will be assessed by the Consensus on Therapeutic Exercise Training (CONTENT) scale, developed by Hoogeboom et al.[43] CONTENT evaluates the reporting of exercise-based interventions in clinical trials using 15 items, divided into three domains: description, rationale, and exercise progression. Each item is measured on a three-point scale (0 when there is no description, 1 when there is a partial description, and 2 when complete), with a maximum total score of 30 points. The CONTENT scale aims to improve the quality and transparency of studies based on the descriptions of the exercise interventions, facilitating the reproducibility of clinical trials and systematic assessments, or the Consensus on Exercise Reporting Template (CERT)[45].

Statistical analysis

When at least two studies are sufficiently homogeneous considering participants, interventions, and outcome measures across one of the endpoints, the outcomes will be

clustered into a meta-analysis. This will be performed using the inverse variance method along with the random and fixed effects models in the RevMan5 program. Continuous variables will be analyzed by the weighted mean difference with a 95% Confidence Interval (CI). Categorical variables will be analyzed through RR with a 95% CI.

In case of the selection of studies with insufficient data, the authors will be contacted to request access to the missing data. If at least 10 studies correspond to the same outcome, the publication bias will be evaluated by the funnel graph generated with the same RevMan5. The Egger test will be used for studies with a small sample or in situations where there is doubt in the definition of said bias.

The Higgins and Thompson inconsistency test[39] will be applied to estimate the amount of heterogeneity between studies in each meta-analysis. I^2 values range from 0 to 100%. Values close to 0% determine no heterogeneity between studies (homogeneity), low heterogeneity is established as close to 25%, moderate heterogeneity as close to 50% and high heterogeneity as close to or greater than 75%[39].

Depending on the literature volume, it may be considered analyzing the following subgroups to better guide the clinical practice: type of disease (stroke, TBI, SAH, neoplasms, etc.) and type of control intervention (passive exercises, neuromuscular electrostimulation, etc.). In addition, a sensitivity analysis will be performed to assert the methodological quality of the included studies, in accordance with the RoB 2.0 tool score ("good" [presence of some bias concern] or "excellent" [low risk of bias])[46], in order to determine whether this can be a contamination factor in the interpretation of the found results.

RESULTS

In July 2024, the registration of the present systematic review protocol was approved. Study recruitment and data collection for the review is still ongoing, and the results of this study are likely to be published by the end of 2025.

DISCUSSION

To the best of our knowledge, this will be the first systematic review of randomized trials with meta-analysis conducted to examine whether EM programs are more effective than conventional physiotherapy on functionality and mobility, along with other secondary clinical outcomes of hospitalized adult neurocritical patients.

The present ongoing systematic review aims to answer whether EM protocols impact outcomes such as mobility or functionality, as evaluated by specific scales that were developed and validated for ICU patients, or field tests already validated in the literature for this population. Concomitantly, this work seeks to describe the type and intensity of exercises prescribed to hospitalized adult neurocritical patients.

Moreover, this review further intends to identify whether EM reduces the length of stay in invasive ventilatory support, the length of stay in the ICU and in the hospital, as well as to verify both the frequency and type of adverse events that EM protocols may provoke in neurocritical patients.

Despite the potential beneficial effects of EM, aspects such as topography and brain injury extent can negatively impact the hemodynamic stability of neurocritical patients, restricting mobilization progressions in upper body postures, as well as other clinical criteria[2]. Thus, the present review intends to fill the existing gaps concerning the safety criteria that must be considered to initiate mobilization in this patient profile.

CONCLUSION

It is a known fact that EM can reduce the deleterious effects of immobilization in general critical patients. However, there is a gap in the current literature regarding these effects in neurocritical patients. Thus, the hypothesis proposed herein is that the same benefit may apply to neurocritical patients. To this end, the present systematic review will be conducted with meta-analysis following strict methodological criteria.

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CONFLICT OF INTEREST

Nothing to declare.

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