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REVIEW PROTOCOL

Low molecular weight heparin on tissue injuries healing: systematic review protocol

Heparina de baixo beso molecular na cicatrização de lesões tissulares: protocolo de revisão sistemática

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ABSTRACT

Objective: to investigate the effectiveness of low molecular weight heparin in tissue Injury healing. **Method:** a systematic review will be carried out of the literature conducted by recommendations of Joanna Briggs Institute (JBI) and PRISMA checklist extension for Systematic Reviews (Reporting Items for Systematic Reviews and Meta-Analyses). Data basis MEDLINE (via PubMed), Embase, LILACS, CINAHL, Scopus e Web of Science. Research question: Do patients with lesions in cutaneous tissue using low molecular weight heparin present Improvement in healing compared to conventional therapies? Inclusion Criteria: Randomized and almost experimental clinical trials that evaluate the use of Low Molecular Weight Heparin in the healing of injuries in 18-year-old or over humans with tissue injuries.
Descriptors: Heparin, Low-Molecular-Weight; Wounds and Injuries; Nursing.

RESUMO

Objetivo: investigar a efetividade do uso da heparina de baixo peso molecular na cicatrização de lesões tissulares. **Método:** será realizado uma revisão sistemática da literatura conduzida pelas recomendações do *Joanna Briggs Institute* (JBI) e *checklist* PRISMA *Extension for Systematic Reviews* (*Reporting Items for Systematic Reviews and Meta-Analyses*). Bases de dados: MEDLINE (via PubMed), Embase, LILACS, CINAHL, Scopus e *Web of Science*. Pergunta de pesquisa: Pacientes com lesões em tecido cutâneo em uso de heparina de baixo peso molecular apresentam melhora na cicatrização quando comparada às terapias convencionais? Critério de inclusão: Ensaios clínicos randomizados e quase experimentais, que avaliam o uso da Heparina de Baixo Peso Molecular na cicatrização de lesões em seres humanos de 18 anos ou mais com lesões tissulares.
Descritores: Heparina de Baixo Peso Molecular; Ferimentos e Lesões; Enfermagem.

INTRODUCTION

Tissue injuries are considered a public health problem worldwide due to their high morbidity and treatment costs, which burden health systems. They are defined by interruptions in the continuity of the skin that can extend from one more superficial layer until affecting deeper structures, such as muscles, tendons, and bones[1-2].

The process of injury tissue repair is complex and involves a cascade of cell and Biochemical vents. To better understand these events, they are divided didactically into stages, such as hemostasis, the inflammatory phase, proliferative and remodeling of the tissue, or maturation[3].

Heparin, a glycosaminoglycan, is a complex, linear polysaccharide that is highly sulfated[4-6]. It is noteworthy that when linked to growth factors, it has antithrombotic action, stimulates angiogenesis, improves wound healing, protects cells, and accelerates epithelial growth, in addition to having anti-inflammatory properties[7].

Experimental studies with laboratory animals have demonstrated the effect of heparin on the cutaneous healing process[8-10]. A study carried out in rats showed that injuries caused by burns and those who recei-

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ved low-weight molecular heparin as treatment by subcutaneous route resulted in shortening in the healing time[11]. Another study used a topical heparin/chitosan complex to treat wounds in rats, demonstrating that the treated group obtained better healing than the control group[12].
In humans, several clinical studies show that heparin can be used to treat burns, accelerating the healing process of these injuries[7, 13-17].
Topical treatment with heparin was introduced as a safe, inexpensive, and effective treatment for burns. The study found that heparin therapy was associated not only with faster healing of second-degree burns, as evidenced by the wound size and number of healed wounds or days required for healing, but also with decreased pain and need for analgesic drugs[13].
The publication of the review protocol in a scientific journal allows other authors to transparently and reproducibly use the review methods. Some international journals accept the publication of review protocols, and in Brazil, the journal OBJN, among the journals indexed in bases, has been the pioneer in publishing revision protocols since 2021, with a significant number of publications on various topics[18].
In view of the above, this article aims to investigate the effectiveness of using low-molecular--weight heparin to heal tissue injuries.
The research question was: Does using low molecular weight heparin in patients with lesions in cutaneous tissue improve healing compared to conventional therapies?

METHOD

Study design
This systematic literature review protocol discusses the use of Low-Molecular-Weight Heparin in tissue injury healing[19].
The proposed systematic review will be conducted according to the Joanna Briggs methodology Institute (JBI) for systematic reviews of evidence of effectiveness[20]. The review was registered in PROSPERO (International Prospective Register of Systematic Reviews) with CRD registration number 42020217970.

Inclusion criterion

Participant
Randomized and almost experimental clinical trials evaluate the use of low molecular weight heparin in healing injuries in humans 18 years or older with tissue injuries. After that, a search will be performed in the selected databases for the study. This review will delete ongoing studies, research protocols, and publications such as editorials, letters to the editor, and reviews of economic analysis.

Intervention
This review will consider studies that examine the effect of low-weight molecular heparin on the healing of cutaneous injuries. No restriction will be placed on the dosage, duration of application, or frequency of treatment of Low-Molecular-Weight Heparin.

Comparator
It was defined in this research as a comparator of conventional therapies since the authors delimited the product of comparison according to the studies evaluated to identify the effectiveness of low molecular weight heparin in the healing process of tissue lesions. The dressings considered conventional consist of gauze, cotton (absorptive and adherent or non-adherent fabrics depending on the product), alginates (compounds capable of forming a gelatinous colloid in the presence of moisture conferring occlusive character to the dressing)[21], and other existing coverings in the market, not there being a restriction of therapies/interventions by the researchers.

Outcomes
This review will consider studies that include the following results: complete injury healing and reduction of the lesion area in the follow-up period, clinical signs (improvement of tissue quality, exudate, angiogenesis), and adverse events (pain, bleeding, and others).

Search strategy
The bibliographic search will be carried out by a professional specialized in the area, and the search strategy will aim to locate published and unpublished studies. An initial search will be performed to identify articles on the topic, and the specific words on the subject used in the titles and abstracts will be considered for developing the search strategy (Figure 1).
This search strategy will include keywords and index mesh terms identified and will be adapted for each source of information included. The following descriptors in health science will be used: "Wounds and Injuries,"; "Diabetic Foot"; "Ulcer"; "Burns"; "Wound Healing"; and "Heparin, Low-Molecular-Weight".

Figure 1 - Search strategy used in the databases. Niterói, RJ, Brazil, 2022

Database	Search strategy
MEDLINE (via PubMed)	("Heparin, Low-Molecular-Weight"[mh] OR "Heparin, Low-Molecular-Weight"[tiab] OR "Heparin, Low Molecular Weight"[tiab] OR "LMWH"[tiab] OR "Low-Molecular-Weight Heparin"[tiab] OR "low molecular weight heparin"[tiab]) AND (ulculs[tiab] OR burns[mh] OR burn*[tiab] OR "Wounds and Injuries"[tiab] OR ulcer[mh] OR "diabetic foot"[tiab] OR "Wounds and Injuries"[mh] OR "back injuries"[tiab] OR "back injury"[tiab] OR "back trauma"[tiab] OR "injuries"[tiab] OR "injury"[tiab] OR "injury force"[tiab] OR "injury pattern"[tiab] OR "injury rate"[tiab] OR "major trauma"[tiab] OR reinjury[tiab] OR "trauma"[tiab] OR "trauma mechanism"[tiab] OR "traumatic injury"[tiab] OR "traumatic lesion"[tiab] OR "skin tissue lesions"[tiab] OR "skin tissue lesion"[tiab] OR ulcer*[tiab]) AND ("Wound Healing"[mh] OR "tissue repair"[tiab] OR (Wound[tiab] AND (Healing*[tiab] OR granulation[tiab] OR repair[tiab] OR regeneration[tiab]))) NOT Thromb*[tiab]
LILACS	(mh:"Heparin, Low-Molecular-Weight" OR tw:("Heparin, Low-Molecular-Weight" OR "Heparin, Low Molecular Weight" OR "LMWH" OR "Low-Molecular-Weight Heparin" OR "low molecular weight heparin" OR "Heparina de Baixo Peso Molecular" OR "HBPM")) AND (mh:("Wounds and Injuries" OR burns OR ulcer) OR tw:(ferida* OR ferimento* OR lesao OR lesoes OR Trauma* OR herida* OR lesion* OR queimadura* OR Quemaduras OR "Wounds and Injuries" OR Wound* OR injur* OR reinjur* OR trauma* OR lesion* OR ulcer* OR burn* OR ulculs OR "diabetic foot" OR "skin tissue lesions" OR "skin tissue lesion")) AND (mh:"Wound Healing" OR tw:"tissue repair" OR tw:cicatrizac* OR tw:"reparo tecidual" OR tw:"reparos teciduais" OR tw:((Wound AND (Healing* OR granulation OR repair OR regeneration))))
Embase	('low molecular weight heparin'/exp OR 'Heparin, Low-Molecular-Weight':ti,ab OR 'Heparin, Low Molecular Weight':ti,ab OR 'LMWH':ti,ab OR 'Low-Molecular-Weight Heparin':ti,ab OR 'low molecular weight heparin':ti,ab) AND (ulculs:ti,ab OR burn/exp OR burn*:ti,ab OR 'diabetic foot':ti,ab OR 'back trauma':ti,ab OR 'injuries':ti,ab OR 'injury'/exp OR 'injury':ti,ab OR reinjury:ti,ab OR 'trauma':ti,ab OR 'traumatic lesion':ti,ab OR 'skin tissue lesions':ti,ab OR 'skin tissue lesion':ti,ab OR ulcer*:ti,ab OR ulcer/exp) AND ('Wound Healing'/exp OR 'tissue repair':ti,('Heparin, Low-Molecular-Weight':ti,ab OR 'Heparin, Low Molecular Weight':ti,ab OR 'LMWH':ti,ab OR 'Low-Molecular-Weight Heparin':ti,ab OR 'low molecular weight heparin':ti,ab) AND (ulculs:ti,ab OR burn/exp OR burn*:ti,ab OR 'diabetic foot':ti,ab OR 'back trauma':ti,ab OR 'injuries':ti,ab OR 'injury'/exp OR 'injury':ti,ab OR reinjury:ti,ab OR 'trauma':ti,ab OR 'traumatic lesion':ti,ab OR 'skin tissue lesions':ti,ab OR 'skin tissue lesion':ti,ab OR ulcer*:ti,ab OR ulcer/exp) AND ('Wound Healing'/exp OR 'tissue repair':ti,ab OR (Wound:ti,ab AND (Healing*:ti,ab OR granulation:ti,ab OR repair:ti,ab OR regeneration:ti,ab))) NOT Thromb*:ti,ab OR (Wound:ti,ab AND (Healing*:ti,ab OR granulation:ti,ab OR repair:ti,ab OR regeneration:ti,ab))) NOT Thromb*:ti,ab
CINAHL	(MM "heparin, low-molecular-weight" OR TI ("Heparin, Low-Molecular-Weight" OR "Heparin, Low Molecular Weight" OR "LMWH" OR "Low-Molecular-Weight Heparin" OR "low molecular weight heparin") OR AB ("Heparin, Low-Molecular-Weight" OR "Heparin, Low Molecular Weight" OR "LMWH" OR "Low-Molecular-Weight Heparin" OR "low molecular weight heparin")) AND (MM burns OR MM ulcer OR MM (wounds and injuries) OR TI (ulculs OR burn* OR "Wounds and Injuries" OR "diabetic foot" OR "Wounds and Injuries" OR "back injuries" OR "back injury" OR "back trauma" OR "injuries" OR "injury" OR "injury force" OR "injury pattern" OR "injury rate" OR "major trauma" OR reinjury OR "trauma" OR "trauma mechanism" OR "traumatic injury" OR "traumatic lesion" OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer*) OR AB (ulculs OR burn* OR "Wounds and Injuries" OR "diabetic foot" OR "Wounds and Injuries" OR "back injuries" OR "back injury" OR "back trauma" OR "injuries" OR "injury" OR "injury force" OR "injury pattern" OR "injury rate" OR "major trauma" OR reinjury OR "trauma" OR "trauma mechanism" OR "traumatic injury" OR "traumatic lesion" OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer*)) AND (MM wound healing OR TI tissue repair OR AB tissue repair OR TI ((Wound AND (Healing* OR granulation OR repair OR regeneration))) OR AB ((Wound AND (Healing* OR granulation OR repair OR regeneration))))
Scopus	TITLE-ABS(("Heparin, Low-Molecular-Weight" OR "Heparin, Low Molecular Weight" OR "LMWH" OR "Low-Molecular-Weight Heparin" OR "low molecular weight heparin") AND (ulculs OR burn* OR "Wounds and Injuries" OR "diabetic foot" OR "Wounds and Injuries" OR "back injuries" OR "back injury" OR "back trauma" OR "injuries" OR "injury" OR "injury force" OR "injury pattern" OR "injury rate" OR "major trauma" OR reinjury OR "trauma" OR "trauma mechanism" OR "traumatic injury" OR "traumatic lesion" OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer*) AND (("tissue repair" OR (Wound AND (Healing* OR granulation OR repair OR regeneration)))))
Web of Science	TS=("Heparin, Low-Molecular-Weight" OR "Heparin, Low MolecularWeight" OR "LMWH" OR "Low-Molecular-Weight Heparin" OR "lowmolecular weight heparin") AND TS=(ulculs OR burn* OR "Wounds and Injuries" OR "diabetic foot" OR "Wounds and Injuries" OR "back injuries" OR "back injury" OR "back trauma" OR "injuries" OR "injury" OR "injury force" OR "injury pattern" OR "injury rate" OR "major trauma" OR reinjury OR "trauma" OR "trauma mechanism" OR "traumatic injury" OR"traumatic lesion" OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer*) AND TS=(("tissue repair" OR (Wound AND (Healing* OR granulation OR repair OR regeneration))))

Sources of information
The databases to be searched include: MEDLINE (via PubMed), Embase, LILACS, CINAHL, Scopus, and Web of Science.
The search for unpublished studies will include: the international registration platform of clinical trials of the World Health Organization (International Clinical Trials Registry Platform - ICTRP) and the US government clinical research registration platform, ClinicalTrials.gov.

Selection of studies
After the search, all the identified articles will be grouped and loaded in Endnote, and duplicates will be removed. Two independent reviewers will then select the titles and abstracts and supervise the senior researcher for evaluation according to the inclusion criteria for the review and the differences found.
Selected studies will be read in full, and their data will be directed to JBI - Unified Management, Evaluation and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). The selected articles will be thoroughly evaluated according to the inclusion criteria by independent reviewers and supervised by the senior researcher. Those who do not meet the selection criteria will have their reasons recorded in the research report. The research results will be fully reported in the final systematic review and presented in a flowchart of Report Items Preferred for Systematic Reviews and Meta-Analysis (PRISMA)[22].

Evaluation of methodological quality
The articles selected for recovery will be regarding the methodological validity before inclusion in the review, using standardized critical evaluation instruments from JBI – Critical Appraisal Tool for RCTs. The authors of the articles will be contacted to request missing or additional data when necessary. All studies, regardless of the results of their methodological quality, will be submitted for data extraction and synthesis.

Risk of bias
The included studies will be evaluated individually for the risk of bias following the JBI Instrument—Critical Appraisal Tool for Randomized Clinical Trial, taking into account the design and methodological rigor of the studies and evaluating the methodological aspects, such as the number of participants, interventions, outcomes, comparator, statistical analysis, and results[23].

Data extraction
The data will be extracted from the studies included in the review by two reviewers in an independent form using the standardized JBI data extraction tool. The dual input data will be used for all results. After analyzing the titles and abstracts, all those selected for inclusion will have the complete texts read and apply the exclusion criteria.
The studies eligibility instrument will be completed for every study selected, and a list of excluded articles and reasons for exclusions (Figure 2) will be drawn up. For the synthesis of the documents included in the final analysis, a database will be built containing identification data, objective, methodological information, and results of research treated with low molecular weight heparin, in addition to pharmaceutical presentations and the appropriate concentrations, adverse events and outcomes in the healing process.

Figure 2 – Data extraction instrument. Niterói, RJ, Brazil, 2022

Review Title:										
General information										
Researcher's Name who extracted the data:										
Data of data extraction:										
Extraction of the characteristics and details of the study										
N°	**AUTHOR**	**COUNTRY YEAR**	**OBJECTIVE**	**TYPE OF STUDY**	**POPULATION SAMPLE**	**INTERVENTION**	**CONTROL**	**MAIN RESULTS**	**CONFLICT OF INTEREST**	**ADVERSE EVENTS**

Data synthesis
As for statistical analysis, the data will be discussed in a simple, descriptive way, including tables and charts.
As the data is extracted, the possibility of performing the meta-analysis through statistical software will be analyzed. For this purpose, the relative risk, confidence interval of 95%, and the evaluation of heterogeneity through the Chi-square test will be considered.

Assessing certainty in discoveries
The approach and analysis of the articles will be carried out by taking into account the level of evidence and the quality of the studies to classify the certainty of the evidence.
The Grading System of Recommendations Assessment, Development, and Evaluation (GRADE) will be used. The evidence will be classified as high, moderate, low, or very low.

*Paper extracted from the master's thesis "Low molecular weight heparin in the healing of tissue injuries: a systematic review with meta-analysis", presented to the Universidade Federal Fluminense, Niterói, RJ, Brazil.

CONFLICT OF INTERESTS
The authors have declared that there is no conflict of interests.

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Data collection: Baptista CT de CH, Oliveira BC, Oliveira BGRB de
Data analysis and interpretation: Baptista CT de CH, Oliveira BC, Oliveira BGRB de
Writing and/or critical review of the intellectual content: Baptista CT de CH, Oliveira BC, Oliveira BGRB de
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