OBJN
ONLINE BRAZILIAN JOURNAL OF NURSING
ISSN: 1676-4285

REVIEW PROTOCOL

Polyhexamethylene biguanide versus saline on microbial load in wounds: a systematic review protocol*

Polihexametilenobiguanida *versus* solução salina na carga microbiana em feridas: protocolo de revisão sistemática

Priscila Gleice Mariano Garcia[1]
ORCID: 0000-0002-3297-7575

Fernanda Soares Pessanha[2]
ORCID: 0000-0002-8082-5242

Bruna Maiara Ferreira Barreto Pires[1]
ORCID: 0000-0002-5584-8194

Beatriz Guitton Renaud Baptista de Oliveira[1]
ORCID: 0000-0001-7494-7457

[1]Fluminense Federal University, Aurora de Afonso Costa School of Nursing, Academic Program in Health Care Sciences, Niterói, RJ, Brazil
[2]Rio de Janeiro State University, Nursing School, Departament of Fundamental Nursing, Rio de Janeiro, RJ, Brazil

Editors:
Ana Carla Dantas Cavalcanti
ORCID: 0000-0003-3531-4694

Paula Vanessa Peclat Flores
ORCID: 0000-0002-9726-5229

Omar Pereira de Almeida Neto
ORCID: 0000-0002-7933-9925

Corresponding author:
Priscila Gleice Mariano Garcia
E-mail: enfapriscilagleice@gmail.com

Submission: 02/11/2022
Approved: 06/07/2022

ABSTRACT

Objective: To analyze the effectiveness of polyhexamethylene biguanide (PHMB) compared to saline on the microbial load of wounds. **Method**: Systematic review protocol, built according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the Joanna Briggs Institute's (JBI) methodology. Studies will be evaluated by two independent researchers in the following databases: Latin America and the Caribbean Literature on Health Sciences (LILACS), Nursing Database (BDENF), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Excerpta Medica Database (Embase). Studies published in Portuguese, English, or Spanish will be included, and the search will not be restricted by publication date. Animal or in vitro studies, reviews, letters to the editor, and case studies will be excluded. After selecting studies, data extraction will take place systematically, and the corresponding records will be presented in a narrative and tabular way.
Descriptors: Wounds and Injuries; Wound Infection; Nursing.

RESUMO

Objetivo: Analisar a efetividade de Polihexametileno Biguanida (PHMB), comparado à solução salina na carga microbiana de pacientes com feridas. **Método:** Protocolo de revisão sistemática, construído segundo o *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA), de acordo com metodologia do Joanna Briggs Institute (JBI). Os estudos serão avaliados por dois pesquisadores independentes, nas bases de dados: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Base de Dados de Enfermagem (BDENF), Sistema Online de Busca e Análise de Literatura Médica (MEDLINE)e *Excerpta Medica Database* (Embase). As pesquisas a serem incluídas serão aquelas publicadas em português, inglês ou espanhol e a busca não definirá recorte temporal. Serão desconsiderados estudos em animais ou *in vitro*, revisões, cartas ao editor ou estudos de casos. Após a seleção dos estudos, a extração de dados ocorrerá de maneira sistemática e os registros correspondentes serão feitos de forma narrativa e tabular.
Descritores: Ferimentos e Lesões; Infecção dos Ferimentos; Enfermagem.

INTRODUCTION

A wound can be defined as a loss of constant integumentary tissue, represented not only by the rupture of the skin and subcutaneous tissue but also by some structures, such as muscles, tendons, and bones[1]. Wounds can be classified as acute or chronic. Acute wounds are those that occur suddenly but heal promptly[1]. A wound that does not heal on time, despite adequate treatment and a holistic approach, is considered chronic[2].

Unintentional traumatic injuries (derived from falls or accidents, such as burns) or intentional (operative wounds) can be described as examples of acute wounds. Chronic wounds include pressure ulcers, oncological wounds, and leg ulcers (arterial, venous, and diabetic foot ulcers).

From an epidemiological point of view, different populations can be affected by wounds, from pediatric patients to the elderly, with thousands of patients with wounds worldwide[3]. Chronic lesions affect 5% of the adult population in the western world and are commonly infected by microorganisms[3,4]. In acute wounds, the infection rate is approximately 3.5%[5].

The interaction between microorganisms and wounds can occur at different levels. When there is contamination, microorganisms are present and adhered to the tissue without proliferation. Colonization is characterized by microbial proliferation without a clinically significant immunological host reaction[6]. Despite not initially triggering a harmful immune response, bacterial colonization can cause the expression of virulence factors by the microorganisms present, such as the development of biofilms, with tolerance to the host's defense mechanisms, being a risk factor for the development of infections[7].

This problem is highlighted by the capacity of biofilm formation by microorganisms in the wounds. Biofilms are aggregates of microorganisms incorporated into a matrix of extracellular polymeric substances, which exhibit altered growth and behaviors that make them highly tolerant to antibiotics and the host's defenses[8]. Biofilms are present in most chronic wounds[3] and have been identified as a cause of delayed healing and drivers of chronic and persistent infections[8].

The development of infections is the most common complication in wounds, causing delays in healing, increased risk of amputations, compromised quality of life, and consequent increase in the cost of treatment[2,8]. Therefore, antiseptic agents are important for the healing process of injured tissue. In this sense, polyhexamethylene biguanide (PHMB) based products are available in the form of solutions and gels[9].

Despite the reported effectiveness of PHMB in vitro tests with bacteria frequently found in wounds, preliminary research in the International Prospective Register of Systematic Reviews (PROSPERO), Medical Literature Analysis and Retrieval System Online(MEDLINE), Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis did not retrieve current or ongoing systematic reviews on the effect of PHMB in vivo[9].

Thus, it is necessary to carry out investigations on this topic to measure results that can be shared with the scientific community and patients who live with wounds.

The objective of this research is to analyze the effectiveness of polyhexamethylene biguanide (PHMB) compared to saline on the microbial load of wounds.

The research question guiding the review is: How effective is polyhexamethylene biguanide (PHMB) versus saline solution in reducing the microbial load of chronic wounds in adult and elderly patients?

METHOD

This systematic review protocol will be carried out following the JBI (Joanna Briggs Institute) methodology. The registration number in PROSPERO is 226093. The formulation of the research question was based on the components of the PICO framework, in which the patients will be individuals with wounds, the intervention will be the use of PHMB, the comparison will be saline, and the outcome will be microbial load.

Eligibility criteria

Participants

This review will consider studies that included adult and elderly patients with acute or chronic wounds.

Intervention

This review will cover studies that evaluated PHMB in the following presentations and recommendations for topical application: PHMB irrigation solution, PHMB-impregnated gauze, PHMB-impregnated dressings, PHMB-incorporated collagen scaffold, PHMB foam dressings, and PHMB-impregnated drain sponge dressing combined with negative pressure. PHMB concentrations between 0.1% and 0.4% will be considered.

Comparison

This review will consider studies that compared the intervention with 0.9% saline solution applied to irrigate the wounds.

Outcome

This review will include studies assessing microbial load as the primary outcome, considering the indicators: swab cultures of lesions: colony forming units (CFU) count; the prevalence of microorganisms; spectrophotometric bacterial counts; and wound biopsy: electron microscopy evaluation of tissue fragments.

Study designs

This review will encompass observational studies (cohorts and case series) and experimental and quasi-experimental studies (randomized controlled trials, non-randomized controlled trials, and before and after studies). No animal or in vitro studies, reviews, letters to the editor, or case studies will be considered.

Search strategies

The search strategies aim to find published and unpublished studies. An initial limited search

was carried out in the databases Latin America and the Caribbean Literature on Health Sciences (LILACS), Nursing Database (BDENF), MEDLINE via PubMed, and Excerpta Medica Database (Embase), on September 21, 2020, to define the search strategy. In this pilot test, 209 articles were retrieved with titles and abstracts evaluated by two independent reviewers to verify their adequacy to the review's inclusion criteria.

This screening resulted in the identification of 72 potentially relevant articles that were read in full format. Of these, 17 articles fully met the criteria. The initially constructed search strategies and the identified keywords and descriptors were adapted for each source of information included. Reference lists of selected studies were evaluated in order to identify additional studies. Studies published in Portuguese, English, and Spanish were included, with no time restriction. This pilot study allowed the construction of the search strategies presented in Figure 1, which will be used to retrieve the studies of interest in this systematic review.

Controlled thesauri will be used according to the terminology of the Health Sciences Descriptors (DeCS) from the Virtual Health Library (BVS) and the Medical Subject Headings (MeSH) from the US National Library of Medicine (US NLM), as highlighted below: wounds; injuries; wound healing. The following keywords will be used: polyhexamethylene biguanide and PHMB.

Selection of studies

Potentially relevant studies will be retrieved in full format, and the respective citation details will be imported into the ZOTERO reference manager, version 5.0, 2018. Two researchers will analyze the titles and abstracts individually, according to the study's incorporation criteria. Then, two independent researchers will also evaluate the full texts in detail. The reasons for the exclusion of studies will be recorded and reported. Any disagreements of opinion that arise between researchers at each stage of the study selection process will be resolved by a third researcher.

Methodological quality assessment

Eligible studies will be critically evaluated by two independent reviewers concerning the level of methodological quality, using JBI's standardized critical assessment tools for experimental, quasi-experimental, and observational studies.

The authors of the articles will be contacted to request missing or additional data for clarification if necessary. The evaluation results will be reported in a detailed table.

Data extraction

Elements will be taken from the studies incorporated in the review by two independent researchers using the established JBI data removal tool. The collected data will include populations, study methods, interventions, and relevant results considering the review's question. A third researcher will resolve discrepancies that may occur between the other two researchers. When necessary, authors of identified studies will be contacted for non-existent or necessary data for complementation.

Data synthesis

A graph will be used to assess publication bias and generate a meta-analysis if 10 or more studies are included in this review. Statistical tests for asymmetry (Egger's test, Begg's test, and Harbord's test) will be used as appropriate.

The Grading of Recommendations, Assessment, Development, and Evaluation system (GRADE) will be used to assess the certainty of the evidence, and the findings will be reported using GRADE pro. The summary of findings will present the following information as appropriate: absolute risks to treatment and control, relative risk estimates, ranking of the quality of evidence based on the risk of bias, heterogeneity, and accuracy of the review results.

*Paper extracted from the master thesis "Effectiveness of polyhexamethylene-biguanide versus crystalloid solutions on microbial load in patients with wounds: a quantitative systematic review", presented to Fluminense Federal University, Niterói, RJ, Brazil.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

Database	Search strategies
MEDLINE via PUBMED	("Wounds and Injuries"[mh] OR "Wounds and Injuries"[tiab] OR injur*[tiab] OR reinjury[tiab] OR "sprains and strains"[tiab] OR "trauma"[tiab] OR traumat*[tiab] OR "skin tissue lesions"[tiab] OR "skin tissue lesion"[tiab] OR ulcer[mh] OR ulcer*[tiab] OR burn*[tiab] OR burn[mh] OR lesion*[tiab]) AND ("polymeric biguanidepolihexanide"[tiab] OR "polymeric biguanidepolihexanide"[sh] OR "poly(hexamethylenebiguanide)"[tiab] OR "polyhexamethylenebiguanide"[tiab] OR "polyhexamethylenebiguanide"[tiab] OR vantocil[tiab] OR "PHMB"[tiab] OR "Polyhexamethylbiguanid"[tiab]) AND ("Wound Healing"[mh] OR "Wound Healing"[tiab] OR "Healing, Wound"[tiab] OR "Healings, Wound"[tiab] OR "Wound Healings"[tiab] OR "microbial load"[tiab] OR "pathogen load"[tiab] OR "infection load"[tiab] OR "infectious burden"[tiab] OR "infectious load"[tiab] OR "microbe burden"[tiab] OR "microbe load"[tiab] OR "microbial burden"[tiab] OR "microbial load"[tiab] OR "pathogen burden"[tiab] OR "pathogen load"[tiab] OR "pathogenic burden"[tiab] OR "pathogenic load"[tiab] OR microb*[tiab] OR infect*[tiab] OR Antimicrobial*[tiab] OR "Bacterial Load"[mh] OR "Bacterial Load"[tiab])
Embase	('injury'/exp OR injur*:ti,ab OR 'reinjury':ti,ab OR 'sprains and strains':ti,ab OR 'trauma':ti,ab OR 'traumatic lesion':ti,ab OR 'wounds and injuries':ti,ab OR 'traumatic injury':ti,ab OR 'burn'/exp OR burn*:ti,ab) AND ('poly hexamethylenebiguanide'/exp OR 'poly(hexamethylenebiguanide)':ti,ab OR 'polyhexamethylenebiguanide':ti,ab OR 'polyhexamethylenebiguanide':ti,ab OR 'vantocil':ti,ab OR 'phmb':ti,ab OR 'polyhexamethylbiguanid':ti,ab) AND ('wound healing'/exp OR 'healing, wound':ti,ab OR 'wound healing':ti,ab OR 'pathogen load'/exp OR 'microbial load':ti,ab OR 'pathogen load':ti,ab OR 'infection load':ti,ab OR 'infectious burden':ti,ab OR 'infectious load':ti,ab OR 'microbe burden':ti,ab OR 'microbe load':ti,ab OR 'microbial burden':ti,ab OR 'pathogenic burden':ti,ab OR 'pathogenic load':ti,ab OR 'bacterial load':ti,ab OR 'bacterial load'/exp)
LILACS	(mh:("Wounds and Injuries" OR ulcer) OR tw:("Wounds and Injuries" OR injur* OR reinjury OR "sprains and strains" OR trauma* OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer* OR burn* OR lesion* OR ferida* OR ferimento* OR lesao OR lesoes OR lesion* OR herida* OR "Heridas y Traumatismos" OR "Ferimentos e Lesões")) AND tw:("polymeric biguanidepolihexanide" OR "poly(hexamethylenebiguanide)" OR "polyhexamethylenebiguanide" OR "polyhexamethylenebiguanide" OR vantocil OR "Polihexametileno-biguanida" OR "PHMB" OR "Polyhexamethylbiguanid" OR "polihexametilbiguanida") AND (mh:("Wound Healing" OR "Bacterial Load") OR tw:("Wound Healing" OR "Healing, Wound" OR "Healings, Wound" OR "Wound Healings" OR "microbial load" OR "pathogen load" OR "infection load" OR "infectious burden" OR "infectious load" OR "microbe burden" OR "microbe load" OR "microbial burden" OR "microbial load" OR "pathogen burden" OR "pathogen load" OR "pathogenic burden" OR "pathogenic load" OR microb* OR infect* OR Antimicrobial* OR Cicatrização OR Cicatrización OR "cargamicrobiana" OR infecc* OR "Bacterial Load" OR "CargaBacteriana" OR microbian* OR antibacterian*))
BDENF	(mh:("Wounds and Injuries" OR ulcer) OR tw:("Wounds and Injuries" OR injur* OR reinjury OR "sprains and strains" OR trauma* OR "skin tissue lesions" OR "skin tissue lesion" OR ulcer* OR burn* OR lesion* OR ferida* OR ferimento* OR lesao OR lesoes OR lesion* OR herida* OR "Heridas y Traumatismos" OR "Ferimentos e Lesões")) AND tw:("polymeric biguanidepolihexanide" OR "poly(hexamethylenebiguanide)" OR "polyhexamethylenebiguanide" OR "polyhexamethylenebiguanide" OR vantocil OR "Polihexametileno-biguanida" OR "PHMB" OR "Polyhexamethylbiguanid" OR "polihexametilbiguanida") AND (mh:("Wound Healing" OR "Bacterial Load") OR tw:("Wound Healing" OR "Healing, Wound" OR "Healings, Wound" OR "Wound Healings" OR "microbial load" OR "pathogen load" OR "infection load" OR "infectious burden" OR "infectious load" OR "microbe burden" OR "microbe load" OR "microbial burden" OR "microbial load" OR "pathogen burden" OR "pathogen load" OR "pathogenic burden" OR "pathogenic load" OR microb* OR infect* OR Antimicrobial* OR Cicatrização OR Cicatrización OR "cargamicrobiana"

Figure 1 -Search strategies used in the databases. Niterói, RJ, Brazil, 2022
Source: Prepared by the authors, 2020.

REFERENCES

1. Dai C, Shih S, Khachemoune A. Skin substitutes for acute and chronic wound healing: an updated review. J Dermatolog Treat. 2020;31(6):639-648. https://doi.org/0.1080/09546634.2018.1530443

2. Bowers S, Franco E. Chronic Wounds: Evaluation and Management. Am Fam Physician [Internet]. 2020 [cited 2021 Out 13];101(3):159-166. Available from: https://pubmed.ncbi.nlm.nih.gov/32003952/

3. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol Rev. 2019;99(1):665–706. https://doi.org/10.1152/physrev.00067.2017

4. Oliveira AC, Rocha DM, Bezerra SMG. Quality of life of people with chronic wounds de vida de pessoas com feridascrônicas. Acta Paul Enferm. 2019;32(2):194-201 https://doi.org/10.1590/1982-0194201900027

5. Payne B, Simmen HP, Csuka E, Hintzpeter M, Pahl S, Brill FHH. Randomized controlled clinical trial on the antiseptic efficacy of polihexanide 0.04% on acute traumatic wounds. J Hosp Infect. 2018;98(4):429-432. https://doi.org/10.1016/j.jhin.2017.12.020

6. Kramer A, Dissemond J, Kim S, Willy C, Mayer D, Papke R, et al. Consensus on wound antisepsis: Update 2018. Skin Pharmacol and Physiol. 2018;31(1):28–58. https://doi.org/10.1159/000481545

7. Percival SL. Importance of biofilm formation in surgical infection. Br J Surg. 2017;104(2):85-94. https://doi.org/10.1002/bjs.10433

8. Schwazer S, James GA, Goeres D, Bjarnsholt T, Vickery K, Percival SL, et al. The efficacy of topical agents used in wounds for managing chronic biofilm infections: A systematic review. J Infect. 2020;80(3):261-270. https://doi.org/10.1016/j.jinf.2019.12.017

9. Borges EL, Frison SS, Honorato-Sampaio K, Guedes ACM, Lima VLAN, Oliveira OMM, et al. Effect of polyhexamethylenebiguanide solution on bacterial load and biofilm in venous leg ulcers: a randomized controlled trial. J Wound Ostomy Continence Nurs. 2018;45(5):425-431. https://doi.org/10.1097/WON.0000000000000455

AUTHORSHIP CONTRIBUTIONS
Project design: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB
Data collection: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB
Data analysis and interpretation: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB
Writing and/or critical review of the intellectual content: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB
Final approval of the version to be published: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB
Responsibility for the text in ensuring the accuracy and completeness of any part of the paper: Garcia PGM, Pessanha FS, Pires BMFB, Oliveira BGRB