PROTOCOL

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AUTOLOGOUS LEUKOCYTE-PLATELET FIBRIN MATRIX IN THE TREATMENT OF COMPLEX WOUNDS: A SYSTEMATIC REVIEW PROTOCOL

MATRIZ DE FIBRINA LEUCOPLAQUETÁRIA AUTÓLOGA NO TRATAMENTO DE FERIDAS COMPLEXAS: PROTOCOLO DE REVISÃO SISTEMÁTICA

MATRIZ DE FIBRINA DE LEUCOCITOS Y PLAQUETAS AUTÓLOGA EN EL TRATAMIENTO DE HERIDAS COMPLEJAS: PROTOCOLO DE REVISIÓN SISTEMÁTICA

[1]Milena Pereira
[2]Mariana Tyska Peroni
[3]Juliana Balbinot Reis Girondi

[1]Universidade Federal de Santa Catarina, Florianópolis, Brazil. Orcid: https://orcid.org/0000-0003-3326-6801
[2]Universidade Federal de Santa Catarina, Florianópolis, Brazil. Orcid: https://orcid.org/0009-0001-0687-373X
[3]Universidade Federal de Santa Catarina, Florianópolis, Brazil. Orcid: https://orcid.org/0000-0003-0271-259X

Corresponding Author
Milena Pereira
Rua Delfino Conti, 275, Trindade, Florianópolis, Santa Catarina, Brazil. CEP 88040-370, Phone +55(48) 999658411. mile.pe@gmail.com.

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ABSTRACT
OBJECTIVE: To perform a synthesis, with meta-analysis, to systematize the results regarding protocols for the production and use of Autologous Leukoplatelet Fibrin Matrix in complex or difficult-to-heal lesions. **METHODS**: This is a systematic review protocol, which will be structured according to the guidelines of the Joanna Briggs Institute, the Cochrane Handbook for Systematic Reviews of Interventions, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Published articles available in full, in Portuguese, English, and Spanish, will be included; randomized and non-randomized clinical trials that fully describe the protocol for preparation and/or use of Autologous Leukoplatelet Fibrin Matrix, and that include adults/elderly individuals with complex or difficult-to-heal lesions, without a time frame. Studies will be selected from the following databases: Cochrane Library, Embase, Medical Literature Analysis and Retrieval System Online, Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, Scientific Electronic Library Online, Latin American and Caribbean Literature in Health Sciences/Nursing Database, and Academic Search Premie. Study selection will be performed using the Rayyan® platform, and the extracted data will generate a database exported to a Google® Spreadsheet, where data extraction will be performed. Both selection and extraction processes will be performed by two independent researchers, and in cases of disagreement, a third reviewer may participate. The protocol was registered with the Prospective Register of Systematic Reviews platform under number CRD420251133263.
Keywords: Nursing; Clinical Protocols; Platelet-Rich Fibrin; Wound Healing.

RESUMO
OBJETIVO: Realizar uma síntese, com metanálise, para sistematizar os resultados em relação aos protocolos para a produção e utilização da Matriz de Fibrina Leucoplaquetária Autóloga em lesões complexas ou de difícil cicatrização. **MÉTODOS:** Trata-se de um protocolo de revisão sistemática, que será estruturado conforme as diretrizes do *Joanna Briggs Institute*, *Cochrane Handbook for Systematic Reviews of Interventions* e os *Preferred Reporting Items for Systematic reviews and Meta-Analyses*. Serão incluídos artigos publicados e disponíveis na íntegra, em português, inglês e espanhol; ensaios clínicos randomizados e não randomizados que descrevam de forma completa o protocolo de preparo e/ou utilização da Matriz de Fibrina Leucoplaquetária Autóloga, que incluam pessoas adultas/idosas com lesões complexas ou de difícil cicatrização, sem recorte temporal. Os estudos serão selecionados nas bases de dados: *Cochrane Library, Embase*, *Medical Literature Analysis and Retrieval System Online*, *Cumulative Index to Nursing and Allied Health Literature*, *Scopus, Web of Science, Scientific Electronic Library Online*, Literatura Latino-Americana e do Caribe em Ciências da Saúde/Base de Dados em Enfermagem e *Academic Search Premier*. A seleção dos estudos será realizada utilizando a plataforma Rayyan® e os dados extraídos gerarão um banco de dados exportado para uma Planilha Google® onde será realizada a extração dos dados. Ambos processos, de seleção e extração, serão realizados por dois pesquisadores independentes e, em casos de divergências, podem contar com a participação de um terceiro revisor. O protocolo foi registrado na plataforma Prospective Register of Systematic Reviews, sob o número CRD420251133263.
Palavras chave: Enfermagem; Protocolo Clínico; Fibrina Rica em Plaquetas; Cicatrização de Feridas.

RESUMEN
OBJETIVO: Realizar una síntesis, con metaanálisis, para sistematizar los resultados sobre protocolos para la producción y uso de Matriz de Fibrina Leucoplaquetaria Autóloga en lesiones complejas o de difícil cicatrización. **MÉTODOS**: Este es un protocolo de revisión sistemática, que se estructurará de acuerdo con las directrices del Instituto Joanna Briggs, el Manual Cochrane para Revisiones Sistemáticas de Intervenciones y los Elementos de Informe Preferidos para Revisiones Sistemáticas y Metaanálisis. Se incluirán artículos publicados disponibles en su totalidad, en portugués, inglés y español; ensayos clínicos aleatorizados y no aleatorizados que describan completamente el protocolo para la preparación y/o uso de Matriz de Fibrina Leucoplaquetaria Autóloga, y que incluyan adultos/personas mayores con lesiones complejas o de difícil cicatrización, sin un marco temporal. Los estudios se seleccionarán de las siguientes bases de datos: Biblioteca Cochrane, Embase, Medical Literature Analysis and Retrieval System Online, Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, Scientific Electronic Library Online, Latin American and Caribbean Literature in Health Sciences/Nursing Database y Academic Search Premier. La selección de los estudios se realizará mediante la plataforma Rayyan®, y los datos extraídos generarán una base de datos exportada a una hoja de cálculo de Google®, donde se realizará la extracción de datos. Tanto el proceso de selección como el de extracción serán realizados por dos investigadores independientes, y en caso de desacuerdo, podrá participar un tercer revisor. El protocolo se registró en la plataforma Prospective Register of Systematic Reviews con el número CRD420251133263.
Palabras clave: Enfermería; Protocolos Clínicos; Fibrina Rica en Plaquetas; Cicatrización de Heridas.

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INTRODUCTION

Failures in the healing process can lead to complex wounds, affecting approximately 40 million people worldwide, requiring prolonged and costly care from healthcare systems [1,2].

A wound is considered difficult to heal when it presents factors that prevent its progression to healing, which may arise from the beginning due to underlying conditions such as comorbidities or unfavorable anatomical location, or after the absence of response to evidence-based treatment. Associated with this definition, the term complex wound is used for those in which medical, clinical, psychological, socioeconomic complications or those inherent to the lesion increase the risk of non-healing within an orderly, consistent and timely pattern even with conventional therapy [3].

In this context, nursing plays a prominent role in the prevention of complications associated with this type of injury and in its treatment, since professional autonomy enables the construction of protocols, the selection of technologies and the making of clinical decisions based on evidence, always aiming at effectiveness and the rational use of available resources [4]. Therefore, it becomes essential to invest in evidence-based clinical strategies, integrating innovative technologies that assist in faster and more accurate decision-making, optimizing outcomes [5].

Despite advances in conventional topical therapies, many lesions do not show a satisfactory response, requiring complementary approaches. Among these, regenerative therapies stand out, especially the use of platelet concentrates, recognized as promising resources in the management of complex and difficult-to-heal wounds [6].

Among these resources, Autologous Leukocyte-Platelet Fibrin Matrix (ALFM), also known as Platelet-Rich Fibrin (PRF), promotes the release of growth factors and cytokines that act in different phases of healing. Such advanced therapies have proven effective in tissue regeneration of refractory lesions ([6,7].

ALFM consists of an autologous technique that uses the patient's own blood, processed by centrifugation. This represents an evolution of platelet concentrates by dispensing with anticoagulants, forming a membrane through natural polymerization, with a dense and organized fibrin network, ideal for promoting cell migration and tissue repair. Furthermore, it has a high concentration of leukocytes, especially mononuclear cells, which attach to the lesion site and contribute to regeneration, along with the release of platelet-derived growth factors [8].

Among emerging regenerative therapies, MFLA has shown itself capable of accelerating the healing of lesions of different etiologies and locations, resulting in functional improvement and quality of life, without reports of adverse events. Therefore, it is configured as an effective and safe option in the treatment of complex wounds, with good results regarding the quality of the tissue formed [6,7,9,10,11].

However, the variety of acronyms associated with MFLA can generate confusion

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among professionals, since these names relate to the preparation method, the type of centrifuge, and the parameters applied. Among them are L-PRF, A-PRF, A-PRF+, I-PRF, C-PRF, Alb-PRF, Bio-PRF®, among others. Some are used as synonyms and others correspond to registered trademarks [12].

Thus, current protocols differ in terms of centrifugation time and applied g-force, which impacts cell concentration and biological activity of the material, potentially influencing processes such as angiogenesis, histogenesis, tissue biostimulation, and modulation of the inflammatory response [1,7,9]. The success of MFLA preparation therefore depends on the interval between blood collection and centrifugation, as well as the parameters adopted in this process [13].

Therefore, it is necessary to develop clinical protocols for obtaining and preparing samples with standardized parameters, based on robust evidence, aiming to expand the safe and effective use of this technique.

With the aim of verifying studies already carried out on the subject, searches were conducted in the International Prospective Register of Systematic Reviews (PROSPERO), Cochrane Library, Cochrane Database of Systematic Reviews (CDSR), and Joanna Briggs Institute (JBI) databases, where no records of systematic reviews were found.

Therefore, the objective of this systematic review was to perform a synthesis, with meta-analysis, to systematize the results regarding protocols for the production and use of MFLA in complex or difficult-to-heal lesions.

METHODS

Study Type

This involves the structuring of a Systematic Review protocol, adopting the guidelines of the Joanna Briggs Institute (JBI) [14], Cochrane Handbook for Systematic Reviews of Interventions [15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16], which was registered in the Prospective Register of Systematic Reviews (PROSPERO), under number CRD420251133263.

Review Question

The research question was established using the mnemonic PICO, where P (population) refers to adults and elderly individuals with complex or difficult-to-heal wounds; I (intervention) refers to the techniques for obtaining and applying MFLA; C (comparison) refers to the techniques for producing and using MFLA; and O (outcomes) refers to better outcomes in wound healing, with control of exudate, edema, odor, and pain. The research question was: Which MFLA preparation and application techniques yield the best results in the healing process of complex or difficult-to-heal wounds in adults and the elderly?

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Inclusion Criteria

Inclusion criteria were: articles published and available in full text, in Portuguese, English, and Spanish; randomized and non-randomized clinical trials that fully describe the MFLA preparation and/or use protocol, including adults/elderly individuals with complex or difficult-to-heal wounds, without a time frame. Exclusion criteria included: studies related to dentistry, acute and surgical wounds, duplicate studies, qualitative studies, observational studies, clinical trial protocol records, article abstracts, conference abstracts, literature reviews (narrative, integrative, and systematic), opinion articles, letters to the editor, proceedings, abstracts, dissertations, and theses. Sources of Information to be Researched

Studies will be selected from the following databases: Cochrane Library, Embase, Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences/Nursing Database (LILACS/BDENF), and Academic Search Premier (ASP).

Access to these databases will be through the Federal University of Santa Catarina (UFSC) subscription via the Virtual Private Network (VPN) and the Federated Academic Community (CAFE) on the CAPES Portal.

Search Strategies

Search strategies and descriptors were selected in partnership with a librarian expert in bibliographic search, using Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS). The selected descriptors were “platelet-rich fibrin”; “wound healing”; “wounds and injuries”; “clinical trial” and “randomized clinical trial”, along with their female, male, singular, plural and similar variables. The strategies used are described in Chart 1.

Chart 1 - Search strategies in databases.

BASE DE DADOS	ESTRATÉGIA DE BUSCA
Cochrane Library	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds

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	and Injuries" OR Wound* OR "Injuries" OR "Injury")
Embase	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed)	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Academic Search Premier (ASP)	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration"

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	OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Scopus	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Web of Science	("Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma"

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	OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Scientific Electronic Library Online (SciELO)	("Fibrina Rica em Plaquetas" OR "Fibrina Rica em Leucócitos" OR "Plasma Rico em Fibrina" OR "Fibrina leucoplaquetária" OR "Fibrina de segunda geração" OR "Plaquetas em matriz de fibrina" OR "Fibrina autóloga" OR "Fibrina Rica en Plaquetas" OR "Fibrina Rica en Leucocitos" OR "Plasma Rico en Fibrina" OR "Fibrina de segunda generación" OR "Plaquetas en matriz de fibrina" OR "Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Cicatrização" OR "Regeneração tecidual" OR "Regeneração de tecidos" OR "Reparo de tecidos" OR "Regeneração de tecidos" OR "Ferimentos e Lesões" OR Ferimento* OR Ferida* OR "Lesão" "Lesões" OR "Cicatrización de Heridas" OR "Regeneración tisular" OR "Regeneración de tejidos" OR "Heridas y Lesiones" OR Herida* OR Lesion* OR "Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Ensaios Clínicos Controlados Aleatórios como Assunto" OR "Ensaio Clínico Controlado Aleatório" OR "Ensaio Controlado Aleatório" OR "Ensaios Clínicos como Assunto" OR "Ensaios

	Clínicos" OR "Ensaio Clínico" OR "Método Duplo-Cego" OR "Ensayos Clínicos Controlados Aleatorios como Asunto" OR "Ensayo Clínico Controlado Aleatorio" OR "Ensayos Clínicos como Asunto" OR "Ensayos Clínicos" OR "Ensayo Clínico" OR "Método Doble Ciego" OR "Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")
Literatura Latino-Americana e do Caribe em Ciências da Saúde/Base de Dados em Enfermagem (LILACS/BDENF)	("Fibrina Rica em Plaquetas" OR "Fibrina Rica em Leucócitos" OR "Plasma Rico em Fibrina" OR "Fibrina leucoplaquetária" OR "Fibrina de segunda geração" OR "Plaquetas em matriz de fibrina" OR "Fibrina autóloga" OR "Fibrina Rica en Plaquetas" OR "Fibrina Rica en Leucocitos" OR "Plasma Rico en Fibrina" OR "Fibrina de segunda generación" OR "Plaquetas en matriz de fibrina" OR "Platelet-Rich Fibrin" OR "L-PRF" OR "I-PRF" OR "Platelet Rich Fibrin" OR "Fibrin-Rich Plasma" OR "Fibrin Rich Plasma" OR "Leukocyte-rich fibrin" OR "Leukocyte rich fibrin" OR "Leukocyte- and platelet-rich fibrin" OR "Leukocyte and platelet rich fibrin" OR "Second-generation fibrin" OR "Platelets in fibrin matrix" OR "Autologous fibrin") AND ("Cicatrização" OR "Regeneração tecidual" OR "Regeneração de tecidos" OR "Reparo de tecidos" OR "Regeneração de tecidos" OR "Ferimentos e Lesões" OR Ferimento* OR Ferida* OR "Lesão" "Lesões" OR "Cicatrización de Heridas" OR "Regeneración tisular" OR "Regeneración de tejidos" OR "Heridas y Lesiones" OR Herida* OR Lesion* OR "Wound Healing" OR "Wound Healings" OR Cicatri* OR "Tissue regeneration" OR "Tissue Repair" OR "Regenerating tissues" OR "Wounds and Injuries" OR Wound* OR "Injuries" OR "Injury") AND ("Ensaios Clínicos Controlados Aleatórios como Assunto" OR "Ensaio Clínico Controlado Aleatório" OR "Ensaio Controlado Aleatório" OR "Ensaios Clínicos como Assunto" OR "Ensaios Clínicos" OR "Ensaio Clínico" OR "Método Duplo-Cego" OR "Ensayos Clínicos Controlados Aleatorios como Asunto" OR

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	"Ensayo Clínico Controlado Aleatorio" OR "Ensayos Clínicos como Asunto" OR "Ensayos Clínicos" OR "Ensayo Clínico" OR "Método Doble Ciego" OR "Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Clinical Trials as Topic" OR "Clinical Trials" OR "Trial" OR "Trials" OR "Double-Blind Method" OR "Double-Blind" OR "Double Blind")

Study Selection and Data Extraction

The initial phase of the systematic review will involve three stages: study identification, defining strategies with their descriptors and searching for studies in established databases; study selection, where two independent researchers, after reading titles and abstracts, will select studies following inclusion and exclusion criteria; and data extraction, where a complete reading of the studies will occur, at which point the inclusion and exclusion criteria will be reapplied, and a PRISMA flowchart will be developed to represent the study selection and inclusion process transparently.

Study selection will be performed using the Rayyan® platform, and the extracted data will generate a database exported to a Google® Spreadsheet where data extraction will be performed.

This spreadsheet will include information such as title, author, year, journal, database, objective, population, method, preparation technique, treatment technique, main outcomes, and conclusions.

For the meta-analysis, statistical data will be collected: sample size, mean values, standard deviation, medians, interquartile range, confidence interval, and interpretation of graphs, when necessary.

When there is disagreement, there will be a discussion to reach a consensus, and a third reviewer may be invited.

The intention is to disclose the justifications for the exclusion of articles, maintaining the method transparent. When there is insufficient data, the authors will be contacted in an attempt to obtain the necessary information.

Methodological Quality Assessment

Critical appraisal of methodological quality for Randomized Clinical Trials will use the JBI Critical Appraisal Checklist for Randomized Controlled Trials. This tool provides a set of 13 questions aimed at verifying whether the study followed practices that minimize biases and systematic errors, such as adequate randomization, allocation concealment, blinding, identical treatment between groups, use of intention-to-treat analysis, and appropriate statistical methods. Thus, it measures the robustness of the design and conduct, helping to

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judge the reliability of the conclusions [14]. Critical appraisal of methodological quality for Non-Randomized Clinical Trials will utilize the JBI Critical appraisal checklist for quasi-experimental studies (non-randomized experimental studies). This tool provides a set of nine questions aimed at verifying whether the study followed methodological rigor, which can provide greater reliability in the results presented [14].

Two tools will be used to assess the risk of bias analysis: one for randomized clinical trials and another for non-randomized trials.

For the first situation, randomized clinical studies, the Cochrane Risk of Bias 2 (RoB 2) will be used, composed of five domains, where each domain has a set of signaling questions, each with five possible answers [16].

For non-randomized clinical trials, the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool will be employed, which assesses seven bias domains; five possible answers and five judgments [17].

The risk of bias regarding the certainty of the evidence will be assessed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering five criteria: “risk of bias”, “inconsistency of results”, “indirect evidence”, “imprecise estimates”, and “publication bias”. This assessment will allow the confidence in the evidence to be classified as high, moderate, low, or very low [14].

Data Synthesis

The synthesis of results will be qualitative and quantitative. Initially, the results will be analyzed qualitatively, describing the characteristics of the included studies and their main results. Subsequently, meta-analysis models will be performed to compare the results of the intervention groups with the MFLA and its comparators, the clinical protocols.

For categorical outcomes, relative risk combination models will be used using the DerSimonian & Lair method. The results of each group from each article will be combined into a single measure using the inverse variance method to define the weights of each study.

The pooled effect estimate represents a weighted average of all studies, and the confidence interval calculation for this measure considers both intra- and inter-study variability. The weight of each individual study will be defined in inverse proportion to its variance, a method that gives greater weight to those with larger samples and less weight to those with smaller samples.

The inverse variance method will be used, and fixed or random effects models will be employed depending on the heterogeneity test result.

Heterogeneity among the results will be tested using the I^2 test, and when significant ($p<0.05$), random effects models will be used. When not significant, fixed effects models will be used.

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Publication bias will be analyzed using Egger's test, considering it significant when p<0.05.

The results will be presented with the summary measure obtained, its 95% confidence intervals, and Forestplots. For this analysis, the meta [18] package will be used in the R 4.1.0(19) environment.

Assessing the certainty of the conclusions

After review, it will be assessed whether the results are fully aligned with the PICO strategy and whether the conduct of the study corresponds to what was previously recorded in this protocol, without any alteration in the search strategies, in order to minimize possible biases in the selection of articles.

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No databases were generated in this study. The information presented is described in the body of the article.

Authorship Criteria (Authors' Contributions)

Milena Pereira contributed substantially to the conception and/or planning of the study; to the acquisition, analysis and/or interpretation of the data; as well as to the writing and/or critical review and final approval of the published version.

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Mariana Tyska Peroni contributed substantially to the acquisition, analysis and/or interpretation of the data.

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Conflict of Interest Statement

Nothing to declare.

Scientific Editor: Ítalo Arão Pereira Ribeiro. Orcid: https://orcid.org/0000-0003-0778-1447