INTEGRTIVE REVIEW ARTICLE

REVISTA ENFERMAGEM ATUAL IN DERME

USE OF HEMOGLOBIN SPRAY IN THE MANAGEMENT OF HARD-TO-HEAL INJURIES: AN INTEGRATIVE REVIEW

USO DE HEMOGLOBINA EN AEROSOL EN EL MANEJO DE LESIONES DE DIFÍCIL CICATRIZACIÓN: UNA REVISIÓN INTEGRADORA
INTEGRATIVA

UTILIZAÇÃO DE HEMOGLOBINA EM SPRAY NO MANEJO DE LESÕES DE DIFÍCIL CICATRIZAÇÃO: UMA REVISÃO INTEGRATIVA

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ABSTRACT
Introduction: Difficult-to-heal wounds are defined as any interruption in the continuity of body tissue that presents a more delayed healing process. It is known that insufficient oxygen is harmful and slows down the healing process. Therefore, the use of topical oxygen therapy has been implemented and it is important to know its benefits. Objective: To identify in the scientific literature the knowledge produced about the use of hemoglobin spray on difficult-to-heal wounds, in order to identify the benefits of its use. Methodology: An integrative review was carried out to answer the guiding question: "What is the scientific evidence for the use of hemoglobin spray for the management of difficult-to-heal wounds?". Works published between 2017 and 2022 from the following databases were included: PUBMED and BVS. Results: 9 articles that answered the guiding question were selected. It was identified that the topical hemoglobin spray was developed to assist in the treatment of wounds, providing oxygen directly to the injured tissue. Final considerations: Scientific evidence points to improvement in pain, management of exudate and slough, reduction in treatment time and improvement in the patient's quality of life.
Keywords: Wound Healing; Wounds; Stomatherapy.

RESUMEN
Introducción: Las heridas de difícil cicatrización se definen como cualquier interrupción en la continuidad del tejido corporal que presenta un proceso de cicatrización más retardado. Se sabe que la falta de oxígeno es perjudicial y ralentiza el proceso de curación. A raíz de ello se ha implementado el uso de la oxigenoterapia tópica y es importante conocer sus beneficios. Objetivo: Identificar en la literatura científica el conocimiento producido sobre el uso del spray de hemoglobina en heridas de difícil cicatrización, con el fin de identificar los beneficios de su uso. Metodología: Se realizó una revisión integradora para responder a la pregunta orientadora: "¿Cuál es la evidencia científica para el uso del spray de hemoglobina para el manejo de heridas de difícil cicatrización?". Los trabajos publicados entre 2017 y 2022 fueron incluidos en las siguientes bases de datos: PUBMED y BVS. Resultados: Se seleccionaron 9 artículos que respondieron a la pregunta orientadora. Se identificó que el spray tópico de hemoglobina fue desarrollado para coadyuvar en el tratamiento de heridas, aportando oxígeno directamente al tejido lesionado. Consideraciones finales: La evidencia científica apunta a mejoría del dolor, manejo del exudado y esfacelo, reducción del tiempo de tratamiento y mejora de la calidad de vida del paciente.
Palabrsa clave: Cicatrización de la Herida; Herida; Estomaterapia

RESUMO
Introdução: As feridas de difícil cicatrização são conceituadas como qualquer interrupção na continuidade do tecido corporal que apresenta um processo de cicatrização mais retardado. Sabe-se que a insuficiência de oxigênio é prejudicial e retarda o processo de cicatrização. Com isso, o uso de oxigenoterapia tópica vem sendo implementado e é importante saber seus benefícios. Objetivo: Identificar na literatura científica o conhecimento produzido acerca do uso de hemoglobina em spray em feridas de difícil cicatrização, a fim de identificar os benefícios de sua utilização. Metodologia: Realizou-se uma revisão integrativa para responder a questão norteadora: "Quais as evidências científicas do uso de hemoglobina em spray para o manejo de feridas de difícil cicatrização?". Foram incluídos trabalhos publicados no período de 2017 a 2022 nas bases de dados: PUBMED e BVS. Resultados: Foram selecionados 9 artigos que respondem à pergunta norteadora. Identificou-se que o spray de hemoglobina tópica foi desenvolvido para auxiliar no tratamento de feridas, fornecendo oxigênio diretamente ao tecido lesado. Considerações finais: As evidências científicas apontam para a melhora da dor, manejo do exsudato e do esfacelo, redução no tempo de tratamento e melhora na qualidade de vida do paciente.
Palavras-chave: Cicatrização de Feridas; Feridas; Estomaterapia.

REVISTA ENFERMAGEM ATUAL IN DERME

INTRODUCTION

Chronic wounds are conceptualized as any interruption in the continuity of body tissue that has a more delayed healing process, exceeding the duration of 1 month and a half [1]. There are also authors who consider that chronic wounds are those that do not have anatomical and functional integrity restored within 3 months [2]. The Wound Hygiene Consensus published in 2022 recommends replacing the term "chronic wound" with "hard-to-heal wound" so that the idea of chronicity is not associated with wounds, given that most have the potential for total healing.

Hard wound healing can be associated with various factors such as diabetes mellitus, nutritional changes, systemic arterial hypertension, pressure on bony prominences for long periods of time, venous and arterial insufficiencies, among others. Furthermore, late diagnosis and the chosen treatment also interfere with the healing process [1]. These injuries can cause great suffering for the patient, such as intense pain, emotional distress, reduced mobility, amputations and social isolation, as well as having an impact on family members [3].

The high complexity in managing such wounds generates high costs for health services, since prolonged hospitalizations, home care, complex treatments, and the use of adjuvant therapies are often necessary, not to mention the high recurrence rates [1]. However, despite the growing development of strategies and technologies related to the treatment of hard-to-heal wounds, the 2020 Wound Hygiene Consensus reiterates the importance of managing infection, observing the clinical signs that the wound indicates and balancing underlying diseases to positively favor the healing process.

It is known that sufficient oxygen availability is essential for effective wound healing, as it acts by providing energy and activating phagocytes that trigger the inflammatory response to tissue damage, as well as restoring blood vessels and connective tissue. This supply is altered by the edema, the microcirculation of the injured area and the contraction of vessels that occurs in the traumatized tissue, causing prolonged tissue hypoxia and, consequently, delaying the healing process [4].

Prolonged hypoxia is very damaging to tissue reconstruction. In order for treatment to be effective, in addition to all the new technologies offered by the industry, the local panorama of the wound must be evaluated, as recommended by the M.O.I.S.T. tool, which was developed to evaluate the local aspects of the wound involving analysis of moisture balance (M), oxygenation balance (O), infection control (I), support (S) and tissue management (T). This tool has not yet been validated, but it shows that there is a range of local treatment possibilities available to professionals that promote the rebalancing of the environment, favoring the healing process of hard-to-heal wounds [5].

Faced with the challenges of managing hard-to-heal wounds, the industry has developed studies and products aimed at improving the process of tissue reconstruction in these types of

REVISTA ENFERMAGEM ATUAL IN DERME

wounds, which repeatedly stagnate in the inflammatory phase of the healing process. Advanced therapies include high-tech dressings, low-intensity lasers, ozone therapy, negative pressure therapy and hyperbaric therapy [6]. In order to improve oxygenation of the wound bed, technologies have recently been developed that use blood components as an alternative for the treatment of complex injuries, including: Platelet Rich Fibrin (PRF), Platelet Rich Plasma (PRP) and, more recently, Topical Hemoglobin Spray.

Hemoglobin Spray delivers hemoglobin to the wound bed, where it binds to environmental oxygen, allowing it to diffuse into the wound bed tissue, reducing hypoxia and aiding the healing process [7].This technology is a resource that can be used as an adjunct to standard treatment, its use is recommended by the manufacturer every 72 hours, and promises to reverse prolonged hypoxia by helping to regulate oxygen availability in the wound bed, favoring angiogenesis, revascularization, connective tissue synthesis and infection resistance [8]. Accordingly, this technology can act on the progression of complex wound healing.

Therefore, since oxygen imbalance is a major obstacle to the healing of complex injuries due to its particularities in the epithelialization process, and the use of Hemoglobin Spray ensures that oxygenation in the wound is improved, it is necessary to ask, according to the guiding question: "What is the scientific evidence for the use of Hemoglobin Spray in the management of hard-to-heal wounds?", and gather evidence on the use of this technology, with the aim of identifying the knowledge produced on the use of Hemoglobin Spray in hard-to-heal wounds in the scientific literature, in order to identify the benefits of its use.

METHODOLOGY

This is an Integrative Review (IR) that synthesizes the experimental and theoretical literature published on platforms, in such a way as to obtain a broader understanding of a specific problem. In addition, it establishes current knowledge on a given issue, since it uses objects such as observation, investigation and synthesis of results on the theme in common and all corroborate for an improvement in the quality of the provided care conducted, in order to observe, investigate and synthesize results on the same theme, but from independent studies, collaborating for a possible favorable repercussion on the quality of the provided care [9].

This study aimed to elucidate the guiding question: "What is the scientific evidence for the use of Hemoglobin Spray in the management of hard-to-heal wounds?". To this end, data was collected from the PUBMED and VHL databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), LILACS (Latin American and Caribbean Literature on Health Sciences Information) and BDENF (*Base de Dados de Enfermagem*). The search was carried out between December 2022 and February 2023, by two experienced researchers,

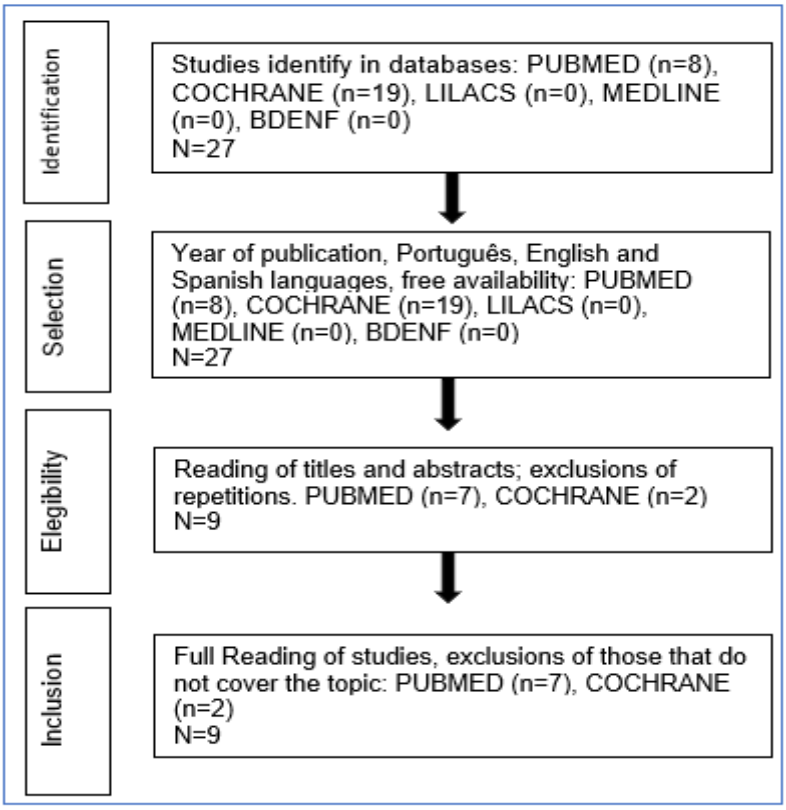
REVISTA ENFERMAGEM ATUAL IN DERME

using the Medical Subject Headings (MeSH): Wound healing, Wounds and Stomatherapy. In order to make the search more specific, it was necessary to replace the descriptor "Hemoglobin" with the keywords "Hemoglobin Spray" and "Topical Hemoglobin", separated by the Boolean "AND" with the following crossings: "Topical haemoglobin" AND "Wound healing" and "Haemoglobin Spray" AND "Wound". In PUBMED, English language descriptors will be used, checked in MeSH.

The adopted time frame was the last five years (2017 to 2022), and the inclusion criteria were studies available in full, in English, Portuguese and Spanish, which addressed the topic of complex wound healing using blood components. The exclusion criteria were book chapters, preprints and unavailable articles. Finally, a selection process was carried out by blinded researchers, as well as a guiding researcher, in order to resolve differences regarding the permanence or exclusion of the journal as an answer to the guiding question. The articles found within the established criteria are displayed in the flowchart (Figure 1).

Initially, a search was carried out for the title and abstract of the articles, and 8 and 19 articles were found in the PUBMED and COHCRANE databases, respectively. After analyzing them, one article was excluded from the PUBMED database because it did not answer the guiding question. In COHCRANE, 17 were excluded for being duplicates and for not answering the question that guided the study.

Figure 1 - Article selection.



REVISTA ENFERMAGEM ATUAL IN DERME

RESULTS AND DISCUSSION

Nine articles that answer the guiding question about the use of Hemoglobin Spray for the management of hard-to-heal wounds were selected. Of these, three are clinical studies [10,11,12], three systematic reviews [13,14], two literature reviews [8,15,16] and one pharmacoepidemiological study [17]. All studies were held in the American continent and the authors are predominantly nurses, physicians and surgeons. Thus, the articles were distributed in Table 1.

Table 1 - Articles included in the integrative review with the search strategy

Título	Autor/Ano	Tipo de estudo	Objetivo do estudo	Idioma	Resultados
Cost-effectiveness of adjunct haemoglobin spray in the treatment of hard-to-heal wounds in a UK NHS primary care setting	Elg, et al. 2019[10]	Avaliação Clínica Comparativa.	Avaliar o custo-efetividade do spray de hemoglobina tópica como terapia adjuvante no tratamento de feridas de difícil cicatrização em um ambiente comunitário do Serviço Nacional de Saúde (NHS) do Reino Unido.	Inglês	Os resultados desta avaliação apoiam o uso de spray de hemoglobina tópica como adjuvante ao tratamento padrão em feridas difíceis de. Nessas feridas, o spray tem o potencial de restaurar o processo de cicatrização, reduzir os tempos de cicatrização e reduzir os custos de curativos.
Assessment of clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of sloughy wounds	Hunt, et al. 2018[11]	Estudo de efetividade clínica que avalia tecnologias no ambiente real.	Investigar os efeitos da administração facilitada de oxigênio na assistência ao paciente com melhor cicatrização de feridas e redução da dor, bem como determinar os efeitos específicos do spray de oxigênio/hemoglobina nos níveis de esfacelo e exsudato.	Inglês	Os resultados mostraram que a adição de spray de hemoglobina adjuvante ao tratamento de feridas alcançou resultados clínicos positivos, reduzindo o exsudato e esfacelo da ferida dentro do complexo processo multifacetado de cicatrização de feridas.
Oxygenation Status in Chronic Leg Ulcer After Topical Hemoglobin Application May Act as a Surrogate Marker to Find the Best Treatment Strategy and to Avoid Ineffective Conservative Long-term Therapy	Petri, et al., 2017[12]	Ensaio clínico com 49 pacientes.	Determinar se mudanças na oxigenação tecidual podem ser medidas após a aplicação tópica de hemoglobina em feridas crônicas e avaliar os achados em termos de estratégias terapêuticas.	Inglês	Os achados sugerem que o uso do spray de hemoglobina pode aumentar a oxigenação local na ferida e a SatO2 pode ser quantificada, e isso acelera a cicatrização. O grupo em que foi utilizado o spray as feridas reduziram e a esclerose tecidual também foi diminuída, quando comparados com o grupo que não utilizou a tecnologia. A terapêutica acertada pode reduzir tempo de cicatrização, reduzir custos e aumentar qualidade de vida para pacientes que sofrem com úlceras na perna.

REVISTA ENFERMAGEM ATUAL IN DERME

Systematic review of the efficacy of topical haemoglobin therapy for wound healing	Hu, et al. 2020[13]	Revisão sistemática.	Fornecer uma visão científica abrangente da eficácia, escopo, reações adversas e precauções necessárias da terapia tópica de hemoglobina, incluindo evidências pré-clínicas e clínicas.	Inglês	A terapia de hemoglobina local pode promover com segurança e eficácia a cicatrização de feridas crônicas e de difícil cicatrização, além de apresentar vantagens como, eliminação de esfacelos e alívio da dor.
Hemoglobin spray as adjunct therapy in complex wounds: Metanalysis versus standard care alone in pooled data by wound type across three retrospective cohort controlled evaluations.	Elg, Hunt, 2018[14]	Revisão Sistemática	Avaliar o benefício alcançado utilizando hemoglobina em spray, em diferentes tipos de feridas, adjunto ao tratamento padrão.	Inglês	Espera-se que a adoção do spray de hemoglobina como adjuvante ao padrão de tratamento de lesões de difícil cicatrização, alcance benefícios de cura substanciais para os pacientes, visto que a melhora da cicatrização foi observada na primeira semana após a aplicação.
Granulox—The Use of Topical Hemoglobin to Aid Wound Healing:A Literature Review and Case Series From Singapore	Loh, et al. 2021[8]	Revisão de literatura e série de casos	Explorar o uso de um spray de hemoglobina, como um adjuvante no tratamento de feridas crônicas, relatar os resultados de uma revisão da literatura avaliando a eficácia do tratamento tópico hemoglobina tanto na cicatrização de feridas quanto no alívio dos sintomas e, finalmente, fornecer exemplos de casos.	Inglês	De acordo com os achados da literatura em questão sobre o uso do Granulox, a mesma concorda com a evidência clínica de que o Granulox é um adjuvante eficaz que promove a cicatrização de feridas crônicas e diminui os sintomas da ferida do paciente.
Radiation ulcer treatment with hyperbaric oxygen therapy and haemoglobin spray: case report and literature review	Winaikosol, et al. 2020[15]	Revisão de literatura.	Explorar a eficácia de uma combinação de oxigenoterapia hiperbárica e spray de hemoglobina no tratamento de úlceras por radiação.	Inglês	O estudo conclui que uma combinação de oxigenoterapia hiperbárica e spray de hemoglobina pode ser eficaz como tratamento de curta duração para úlceras de radiação.
Shifting the distribution curve for healthcare resource use through topical oxygen therapy for wound healing	Alves, et al. 2022[16]	Revisão de literatura.	Revisar e consolidar o material publicado disponível e avaliar o potencial do adjuvante tópico, spray de hemoglobina, na cicatrização de feridas.	Inglês	Sugere-se que a adoção do spray tópico adjuvante de hemoglobina pode efetuar mudanças na curva de cicatrização de feridas, movendo-a à esquerda reduzindo o tempo de cicatrização. Além disso, a implementação dessa tecnologia é realizada maneira fácil e sustentável em populações que necessitam de tratamento de feridas.
Topical application of haemoglobin: a safety study	Holzer, et al. 2019[17]	Estudo de segurança farmacoepidemiológico ou Estudo transversal.	Determinar se há risco de inalação ao usar o spray de hemoglobina.	Inglês	Os resultados do estudo em questão mostram que o uso do spray de hemoglobina é um produto seguro e não há risco de inalação de concentrações perigosas do produto, nem de formação de partículas finas durante a aplicação do

REVISTA ENFERMAGEM ATUAL IN DERME

					produto.

Topical Hemoglobin Spray was developed to help treat hard-to-heal wounds, most of which have a hypoxic bed, by supplying oxygen directly to the injured tissue. Prolonged hypoxia is generated due to increased metabolic demand at the site of the injury, whether due to damaged microcirculation, diffusive restrictions due to edema, poor blood circulation or oxygen consumption by bacterial biofilm [8].The topical application of Hemoglobin Spray aims to generate an increase in local oxygen, facilitating the reversal of hypoxia, being an adjunct therapy to the standard treatment of wounds that are hard to heal, offering greater chances of epithelialization due to the reduction in microbial colonization and a decrease in the formation of crusts [18].

The authors[10] developed a clinical evaluation that resulted in a significant improvement in oxygen diffusion rates in hard-to-heal wounds, when using Hemoglobin Spray, and the etiologies of the wounds were diverse such as vasculogenic, pressure injury, diabetic wound, trauma, among others. The study evaluated two groups of 50 people each, where the control group had the standard treatment and the intervention group used the standard treatment plus the use of Hemoglobin Spray, and it was observed that the patients in the intervention group already in the first week of treatment obtained a 26% greater reduction in the injured area when compared to the control group. After 26 weeks, the rate of complete epithelialization in the intervention group was 90%, while it was 38% in the group without the spray, which corroborates the importance of effective nutrition in the wound bed in the healing process.

In this sense, the authors[11] conducted a study that evaluated the efficacy of using Hemoglobin Spray in wounds with a large amount of slough, which is considered a barrier in the wound healing process, since its presence favors an increase in the microbial load of the injury and also favors the formation of biofilm. A sample of 200 patients with infected injuries was evaluated, and the results were also seen in the first week of use, where the reduction in the amount of slough was 67% in the patients who were using Hemoglobin Spray and only 8% in the control group. This study also assessed the amount of exudate present in the wound, resulting in a significant reduction of 94% in the intervention group.

This finding is in line with a review carried out by authors[14], where it was observed that the use of Hemoglobin Spray as an adjuvant in the treatment of hard-to-heal injuries of different etiologies leads to a shorter treatment time, a significant reduction in slough and pain, a substantial reduction in the wound and helps to improve the quality of life of the patient. The

REVISTA ENFERMAGEM ATUAL IN DERME

researchers ratify the importance of involving the patient in the treatment, given the ease of application, as well as the fact that costs are reduced with shorter treatment times [14].

In addition, there were patients who stopped using Hemoglobin Spray early of their own free will, before finishing the treatment, and the exudate returned significantly. Regarding the level of pain, as the weeks of treatment went by, the infection was managed and the patients reported that the pain was reduced more quickly in the group using Hemoglobin Spray [11]. It is important to note that this technology is an adjuvant therapy, i.e., it is a technology that accelerates the tissue repair process. Therefore, patients should continue to care for their injuries on a daily basis and professionals should carry out the cleaning process recommended by the consensus.

All the benefits evidenced by the aforementioned studies correlate with the advantages of maintaining a continuous supply of oxygen to facilitate and promote wound healing, as advocated in the M.O.I.S.T. tool, where the letter O equates to oxygen balance and aims to improve tissue perfusion and local oxygenation in the wound bed [5]. This is because oxygen plays an important role in various processes, including migration and replication of fibroblasts, production of collagen fibers, stimulation of angiogenesis, antimicrobial activity of leukocytes and macrophages, proliferation of endothelial cells, neovascularization, epithelialization, i.e., it is directly related to the epithelialization process [19].

Accordingly, there is also a reduction in public health costs in relation to the total treatment of patients, since the epithelialization of injured tissue occurs more quickly. Thus, the number of nursing consultations is reduced, as is treatment time, the risk of hospitalization is greatly reduced when wounds are properly managed and the risk of infection is reduced (HUNT et al., 2018[11]). At the end of the evaluation, a 37% reduction in health service spending on wound treatment was identified, so it is possible to identify that the use of Hemoglobin Spray has a good cost-benefit ratio that can promote savings in nursing costs, drug costs, costs related to surgical procedures and, consequently, savings in public spending [11].

A clinical trial carried out by authors[12] points out that oxygen saturation at the wound site improved from 60% to 71% in 20 minutes after topical application of Hemoglobin Spray, which interferes with improved healing and entails a significant reduction in pain. In this study, it was possible to understand the need for an individual evaluation of each wound, as a group of people did not progress with the proposed treatment, and the evaluation revealed the need for surgical intervention due to the serious condition of the injury. Nevertheless, in the patients who responded to the treatment, it was concluded that the use of topical therapy helps to reduce wound healing time, reduce costs and improve the quality of life of the affected patients [12].

REVISTA ENFERMAGEM ATUAL IN DERME

A systematic review by authors in 2020[13] shows that Topical Hemoglobin Therapy is safer and simpler because it does not depend on the damaged vascular system to supply oxygen to the wound. It also highlights that, in a hypoxic wound, hemoglobin sprayed on the wound binds to oxygen in the surrounding air and transports it to the base of the wound, from where it diffuses into the cells at a rate that depends on the differential partial pressure of oxygen between the wound bed and the air. This process is repeated continuously, as hemoglobin is not consumed, creating a continuous cycle of oxygen transportation. In addition, it makes a comparison with hyperbaric oxygen therapy, which is also an adjuvant in the treatment of injuries, and there is a benefit to this type of oxygen therapy when compared to hyperbaric, since it needs a specific environment and suitable machinery for its use, while the spray technique provides self-care of the injury by the professional and even by the patient himself/herself due to the practicality of its use [13].

A review carried out by author and his collaborators in 2021[8] presented an analysis of studies conducted in several different locations that point to Hemoglobin Spray as a powerful adjuvant due to its high wound healing rates. In addition, five cases of patients with hard-to-heal wounds were analyzed, where they achieved complete healing in 3 months, using standard therapies plus the use of Hemoglobin Spray every 3 days [8]. This fast and effective healing process was also evidenced in another study, where they analyzed the evaluation of the use of topical oxygen therapy together with hyperbaric oxygen therapy and complete epithelialization occurred in 15 weeks [15]. Both authors point to the need to develop randomized controlled studies for further evidence on the use of Hemoglobin Spray.

In 2022[16], research by authors showed that health resources can be saved when strategies are implemented to promote rapid wound healing [16]. Therefore, proper treatment with cleanliness, ideal coverings and powerful adjuvants reduces the frequency of dressing changes and decreases the time needed to apply the dressing. In addition, the correct handling of the wound means that the need for dressing changes in health services is reduced and does not occur on a daily basis, allowing more time for professionals, which further increases savings for public coffers [20].

Furthermore, a pharmacoepidemiological safety study was carried out by Holzer[17], with a view to identifying the risks of inhalation when using this spray to ensure the safety of both the patient, who can use this technology at home, and the professional, who uses this spray in offices. The safety study is important because a cleaning agent was recently condemned by the Brazilian Health Regulatory Agency (ANVISA, as per its Portuguese acronym) for posing an inhalation risk and affecting health. The evaluation of Hemoglobin Spray made it possible to identify that no dust, nanoparticles or aerosols were formed during use of this spray, and the concentrations of particles generated

REVISTA ENFERMAGEM ATUAL IN DERME

during use were below the permitted concentrations of inhalable and respirable fractions. There is therefore no risk of inhaling dangerous concentrations of the product or of fine particles forming during application [17].

FINAL CONSIDERATIONS

This review synthesized the best evidence on the use of Hemoglobin Spray in hard-to-heal wounds. It was found to be an effective and convenient adjuvant for the treatment of these wounds, which can be considered in non-healing wounds that have failed conventional therapy. The benefits of improving pain, managing exudate and slough, reducing treatment time and improving the quality of life of the patient should be highlighted.

This research aggregates scientific evidence that supports the use of this new technology in the treatment of wounds, especially those that are hard to heal, and identified that its use is safe and effectively intensifies the healing process. In addition, its role in preventing wound infection should be emphasized, whether for treating infected wounds or those with biofilm and slough. Cleaning the wound and making the right choice of dressings associated with the use of Hemoglobin Spray can lead to a reduction in costs for the health system and promote a better quality of life for individuals suffering from wounds that are hard to heal.

It is important to underline the limited number of robust studies published on the topic, with studies with a limited number of participants. It is therefore extremely important to carry out new research that expands the use of this technology to all types of wounds and considers its cost-benefit and applicability, in order to give greater scientific basis to the use of the technology.

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Declaration of conflict of interests
Nothing to declare.

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