

USE OF AMNIOTIC MEMBRANE IN WOUND HEALING: INTEGRATIVE REVIEW

Uso da membrana amniótica na cicatrização de feridas: revisão integrativa

Uso de membrana amniótica en curación de heridas: revisión integrativa

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ABSTRACT

Objective: To identify in the literature the use of the amniotic membrane in wound healing. **Method:** integrative review where the descriptors were applied: “wounds”, “amniotic membrane” and “healing” to the databases Latin American and Caribbean Health Sciences, Medical Literature Analysis and Retrieval System Online and Cumulative Index for Nursing and Allied Health Literature, between January and February 2019. **Results:** eighteen articles were selected which supported the construction of two thematic categories. It has been shown that the amniotic membrane has the ability to decrease exudate and adhesions, reduce local pain and act as a substrate for tissue growth. **Conclusion:** amniotic membrane is an effective alternative for wound treatment. More in-depth studies are needed to increase the knowledge of the health team and contribute to the advancement and strengthening of stomatherapy practices.

Descriptors: Wounds, Amniotic membrane, Wound healing, Health technologies, Stomatherapy.

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RESUMO

Objetivo: Identificar na literatura o uso da membrana amniótica na cicatrização de feridas. **Método:** revisão integrativa onde aplicou-se os descritores: "feridas", "membrana amniótica" e "cicatrização" às bases de dados Literatura Latino-Americana e do Caribe em Ciências da Saúde, *Medical Literature Analysis and Retrieval System Online* e *Cummulative Index to Nursing and Allied Health Literature*, entre Janeiro e Fevereiro de 2019.

Resultados: foram selecionados 18 artigos os quais embasaram a construção de duas categorias temáticas. Evidenciou-se que a membrana amniótica possui capacidade para diminuir o exsudato e adesões, reduzir a dor local e agir como um substrato para o crescimento de tecidos. **Conclusão:** a membrana amniótica constitui-se alternativa eficaz para o tratamento de feridas. Faz-se necessário o desenvolvimento de estudos mais aprofundados a fim de ampliar o conhecimento da equipe da saúde e contribuir para o avanço e fortalecimento de práticas em estomatoterapia.

Descritores: Feridas, Membrana amniótica, Cicatrização de feridas, Tecnologias em saúde, Estomatoterapia.

RESUMEN

Objetivo: Identificar en la literatura el uso de la membrana amniótica en la cicatrización de heridas. **Método:** revisión integradora donde se aplicaron los descriptores: "heridas", "membrana amniótica" y "curación" a las bases de datos Ciencias de la Salud, Análisis y Recuperación de Literatura Médica de América Latina y el Caribe Sistem Online e índice acumulativo de literatura de enfermería y salud aliada, entre enero y febrero de 2019.

Resultados: se seleccionaron 18 artículos que apoyaron la construcción de dos categorías temáticas. Se ha demostrado que la membrana amniótica tiene la capacidad de disminuir el exudado y las adherencias, reducir el dolor local y actuar como sustrato para el crecimiento del tejido. **Conclusión:** la membrana amniótica es una alternativa efectiva para el tratamiento de heridas. Se necesitan más estudios en profundidad para aumentar el conocimiento del equipo de salud y contribuir al avance y el fortalecimiento de las prácticas de estomatoterapia.

Descritores: Heridas, Membrana amniótica, Cicatrización de heridas, Tecnologías sanitarias, Estomatoterapia.

INTRODUCTION

Wound healing is defined as a tissue repair process that consists of replacing the injured tissue with new tissue. This process involves the regeneration of specialized cells, the formation of granulation tissue and the reconstruction of tissue which is triggered in phases and supported by biochemical mediators.¹

The concern with wound care is an old one. Over the centuries, various products were applied to wounds in order to heal them. Thus, the advances and discoveries that have occurred in the health area have influenced the improvement of this treatment to achieve better results and in the shortest possible time.²

To that end, numerous technologies have been developed in dressing coverings, in order to maintain, in

the wound bed, an environment conducive to rapid tissue repair with little or no sequelae. To be considered ideal, coverings must have good adhesion, resist movement, not be cytotoxic, maintain physiological humidity, remove excess exudate, allow gas exchange and thermal insulation, provide defense against infections, be easily available, simple to handle and low cost.³

The amniotic membrane (MA), the inner layer of fetal membranes, was one of these technologies, developed and tested as a covering, proving to be effective in improving healing in burns, ulcers and eye injuries. Amnion, because it has characteristics of stem cells, has properties of plasticity and self-renewal which are based on the ability to stimulate the epithelialization process, prevent apoptosis and restore the epithelial phenotype, in addition to reducing the inflammatory process and having an antimicrobial action.⁴

Thus, based on the premise that adequate assistance and the use of effective dressings and dressings must be provided, this review aims to identify, in the literature, the use of the amniotic membrane in wound healing, aiming to contribute to advances in the area of stoma therapy that provide recovery from injuries in patients, as well as quality of life.

METHODS

Integrative literature review, based on the theoretical framework of Mendes, Silveira and Galvão, developed in six stages: 1) establishment of hypothesis or research question, 2) sampling or search in the literature, 3) definition of the information to be extracted or categorization of the studies, 4) evaluation of studies, 5) interpretation of results and 6) synthesis of knowledge or presentation of the review.⁵

The guiding question was elaborated from the acronym PICO, defining P = population: "patients with wounds", I = interest: "use of the amniotic membrane" and Co = context: "healing". Thus, the following research question was elaborated: what is the use of the amniotic membrane in wound healing?⁶

The inclusion criteria were articles of primary studies indexed in the databases described, published until 2018, in English, Portuguese and Spanish and related to the research theme. Monographs, dissertations, theses and qualitative studies were excluded.

The bibliographic survey was carried out in January and February 2019 in the electronic databases Medical Literature Analysis and Retrieval System Online (MEDLINE via PubMed®), Cumulative Index to Nursing and Allied Health Literature (CINAHL-Ebsco) and LILACS bibliographic index (Latin American Literature in Health Sciences) via Virtual Health Library (VHL).

The controlled and uncontrolled descriptors were selected by consulting the terms of the Medical Subject Headings (MeSH), Descriptors in Health Sciences (DeCS) and List of Headings of CINAHL Information Systems.

The search expressions were created using the Boolean operators “OR” and “AND”. Different search strategies were chosen, due to the peculiarities of the bases. The search syntax is described in **Chart 1**.

Chart 1: Controlled, non-controlled descriptors and search expressions used to retrieve the articles. *Teresina, PI, Brazil, 2019*

| MeSH e List CINAHL | | |
|----------------------------------|---|---|
| P | DC | Wounds and Injuries; |
| | DNC | Wounds and Injuries; Wounds; Wound |
| I | DC | Amnion |
| | DNC | Amnion; Amniotic Membrane |
| Co | DC | Wound Healing |
| | DNC | Wound Healing |
| Search expression | ((((("wounds and injuries"[MeSH Terms]) OR ("wounds and injuries") OR "wounds") OR "wound")) AND (((("amnion"[MeSH Terms]) OR "amnion") OR "amniotic membrane")) AND (("wound healing"[MeSH Terms]) OR "wound healing") | |
| Search expression LILACS via BVS | ((MH "Wounds and Injuries") OR "wounds and injuries") AND ((MH "Amnion") OR "amnion") AND ((MH "Wound Healing") OR "wound healing") | |
| DECS | | |
| P | DNC | Ferida; Feridas |
| | DC | Âmnio |
| I | DNC | Âmnio; Membrana Amniótica |
| | DC | Cicatrização |
| Co | DNC | Cicatrização; Cicatrização de Feridas |
| | Search expression | (tw:((tw:(ferida) OR (tw:(feridas)))) AND (tw:((mh:(âmnio)) OR (tw:(âmnio)) OR (tw:(membrana amniótica)))) AND (tw:((mh:(cicatrização) OR (tw:(cicatrização)) OR (tw:(cicatrização de feridas)))) |

Chart subtitle: DC (Controlled Descriptor); DNC (Uncontrolled Descriptor).

Source: direct research, 2019.

The Evidence Level was classified by the Oxford Center for Evidence-based medicine - Levels of Evidence.⁷ The data were extracted using a specific instrument. The results were presented in a descriptive way and the critical analysis allowed the construction of two categories: 1) Histological and biochemical aspects of the amniotic membrane in the healing process and 2) Effectiveness of using the amniotic membrane as a biological dressing.

RESULTS AND DISCUSSION

It was found that the theme has a recent nature in the literature, comprising the largest number of publications in 2017 with six (33.3%) articles. As for the country of publication, there was greater expression for the United States of America (USA) with five (36%) articles. Regarding the methodological approach, the most frequent was the randomized controlled study with eight (44.4%) productions, classified as level of evidence 1B. The main conclusions pointed to the effectiveness of the amniotic membrane in the treatment of injuries. Other relevant information is listed in the following table (**Table 1**):

Table 1. Distribution of publications according to article, year, country of publishing, methodological approach, level of evidence and main conclusions. *Teresina, PI, Brazil, 2019*

| Selected articles | Year and country of publishing | Methodological approach and level of evidence | Main conclusions |
|-------------------|--------------------------------|---|---|
| A ⁸ | 2017/Brazil | Randomized controlled trial / 1B | Intense inflammatory reaction, preventing graft nutrition. |
| A ⁹ | 2017/ Brazil | Randomized controlled trial / 1B | Increased anal fistula recovery rate. |
| A ¹⁰ | 2014/ Brazil | Randomized controlled trial / 1B | Increased angiogenesis during granulation. |
| A ¹¹ | 2013/Uruguay | Observational study / 2C | Tissue regeneration and reepithelialization. |
| A ¹² | 2013/Australia | Randomized controlled trial of lower quality / 2B | Promoted reepithelialization and angiogenesis. |
| A ¹³ | 2015/ Netherlands | Randomized controlled trial / 1B | Promotion of healing and pain relief. |
| A ¹⁴ | 2017/ Netherlands | Randomized controlled trial of lower quality / 2B | Decreased plasma leakage and bacterial count. |
| A ¹⁵ | 2017/USA | Case report / 4 | It protected the wound while promoting angiogenesis and healing. |
| A ¹⁶ | 2015/ Netherlands | Randomized controlled trial / 1B | It was unable to inhibit bacterial growth in vitro. |
| A ¹⁷ | 2017/ USA | Expert opinion / 5 | Better understanding of proteins, cytokines, growth factors. |
| A ¹⁸ | 2015/ USA | Randomized controlled trial / 1B | Increase in epithelialization factors. |
| A ¹⁹ | 2014/Australia | Expert opinion / 5 | It allowed a better adjustment to the user's particular needs. |
| A ²⁰ | 2017/USA | Case reports / 4 | They play an important role in the reconstruction of injuries. |
| A ²¹ | 2018/USA | Case reports / 4 | Treatment can significantly accelerate healing in wounds of different etiologies. |
| A ²² | 2016/UK | Case reports / 4 | There was timely closure of the wounds |
| A ²³ | 2010/Australia | Observational study / 2C | Safe dressing, promoting epithelialization. |
| A ²⁴ | 2014/Australia | Randomized controlled trial / 1B | The application can decrease scarring and increase patient satisfaction. |
| A ²⁵ | 2012/UK | Randomized controlled trial / 1B | It reduced the size of the wound in the initial stage of the healing process. |

Source: direct research, 2019.

Histological and biochemical aspects of the amniotic membrane in the healing process

AM has numerous biologically active factors that have the function of promoting cell proliferation and differentiation, in addition to having antimicrobial functions, probably due to the presence of elements such as interferon, lysozyme, transferrin, progesterone, immunoglobulin 7S and globulin B1c / B1a, antifibrotic, low antigenicity, due to the absence of certain surface antigens on epithelial cells, anti-inflammatory action, ability to reduce exudate, adhesions and local pain. These properties suggest that it can be used as a biological dressing.^{9,14,16-21}

It works as a substrate for tissue growth because it has numerous growth factors and promoters of healing, such as: the epidermal growth factor, vascular endothelial, keratinocytes, basic fibroblasts, alpha and beta transformers, interleukin-8 (IL-8), angiogenin (ANG), dipeptidyl peptidase IV (DPPIV / CD26), serine protease inhibitor, is also known as plasminogen activator inhibitor type 1 (PAI - 1), insulin-like growth factors (IGF), binding

proteins (IGFBPs) and others.^{14,19-20}

It presents essential hyaluronic acid that facilitates cell migration, as well as some anti-inflammatory and immunosuppressive properties and nitric oxide, derived from endothelial nitric oxide synthase that plays a crucial role in maintaining vascular integrity and remodeling.^{13,17,19}

Type IV, V and VII collagens and other fibrous protein components provide a structural framework to support proliferation and regeneration. These tissues also contain factors that modulate the immune response, control inflammation, inhibit the production of matrix metalloproteinases, support angiogenesis, promote the production of extracellular matrix and assist in tissue remodeling.^{13,17,19}

Efficacy of using the amniotic membrane as a biological dressing

AM has been used as a wound dressing for over 100 years. Being used in different organs, for example, many surgeons have evaluated its effectiveness in burns or in the reconstruction of the corneal epithelium or in gastrointestinal tract surgeries.^{12,16,18}

Other studies have evaluated the effectiveness of skin lesions, which are expensive for the health system. According to a study where 20 patients were treated, all wounds closed in approximately 9.9 weeks. When applied to diabetic foot ulcers, they closed on average in 11.8 weeks and in venous leg ulcers in 9.2 weeks. No adverse events were observed secondary to its application, which shows a safe and effective treatment option.^{9,12,16,18,21,26}

The methods commonly used for their preparation and storage directly influence their effectiveness. The most used are cryopreservation at -80 ° C with 10% dimethyl sulfoxide, preservation in glycerol at 4 ° C, freeze drying and irradiation, dehydration and decellularization. Obviously, such processing can affect cell viability and influence the cytokine profile in the prepared samples.^{12,13,15,17,20-22}

The use in clinical applications may be associated with the risk of infection. Several methods have been developed for donor serological screening, microbiological testing and preparation, sterilization and long-term storage of ammonia samples.¹³

Recently, a system has been identified to gently process, sterilize and dry the placental tissue obtained from pregnant women tested and submitted to cesarean delivery. This patented process is used to create a dehydrated human amnium membrane that can be stored at room temperature for up to 5 years. Preservation in glycerol minimizes the risk of disease transmission, using the strong antiviral and antibacterial activity of such concentration, and its clinical efficacy is maintained.^{13,15,17,21}

Decellularization is designed to better preserve the natural biomechanical structure of the fabric, scientifically controlling moisture levels versus traditional heat cooking or freeze drying (freeze drying) systems, avoiding the use of aggressive chemical rinses or crosslinking agents. In

addition, while some amniotic membranes are marketed as “immuno-privileged”, based on the natural properties of the placentas, the de-culturalized allografts have been shown to be able to suppress an active immune response in vitro, which is essential in the modulation of inflammation, reducing the risk graft rejection and failure.¹⁶

In relation to injuries, the main concerns are the speed of healing and pain relief. However, the cost must also be taken into account, especially in developing countries. A study carried out in the United States compared five types of dressing materials. The cost of treatment ranged from 0.014 to 0.155 dollars for each square centimeter treated. The amniotic membrane of a placenta measuring 400 to 500 cm² costs only about \$ 3. Thus, the cost of treatment with AM is lower, and it still has numerous advantages for promoting healing and pain relief.^{12,26}

Despite being considered hospital waste, having a low cost and containing numerous healing properties, its large-scale production is hampered by legal and religious issues that limit its supply, in addition to the way of preparation and storage reduce its use.^{13,17,20}

Among the limitations of this study, the limited number of researches and studies at the national level stands out, making it difficult to recognize the practice, application and effectiveness of the properties of using the membrane in the country. Another is that most of the studies found are of an experimental character, with animals as the control group. Therefore, studies like this contribute to stimulate biotechnological development, studies and research in Brazil that support the development of effective and cost-effective coverings and / or dressings for the treatment of injuries.

CONCLUSIONS

The amniotic membrane is an excellent natural temporary substitute for the skin, histologically privileged with antimicrobial, antifibrotic, anti-inflammatory, anti-adhesive, analgesic factors and with a high capacity to stimulate reepithelization.

This study contributes to the advancement of practices in stomatherapy by reiterating the importance of the development and application of quality, efficiency and low cost products that allow advances in treatment, recovery and quality of life for patients with injuries. It is suggested to elaborate more studies on this theme, in order to raise awareness and expand the knowledge of the health team.

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