The use of fatty acids in wound care: an integrative review of the Brazilian literature

UTILIZAÇÃO DOS ÁCIDOS GRAXOS NO TRATAMENTO DE FERIDAS: UMA REVISÃO INTEGRATIVA DA LITERATURA NACIONAL

UTILIZACIÓN DE ÁCIDOS GRASOS EN TRATAMIENTO DE HERIDAS: REVISIÓN INTEGRAL DE LA LITERATURA NACIONAL

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ABSTRACT

The objective of this study was to characterize the Brazilian scientific production on the topical use of fatty acids in wound care, and to describe the effects of its administration in this process. This integrative literature review included articles indexed in Lilacs and BEDENF databases. Data collection was carried out in December 2010 using controlled descriptors and without publication date limitations. The sample consisted of nine articles, mostly concerning animal models and the use of different fatty acids mixtures. Due to the lack of randomized clinical trials in human beings and the limitations of this review, it is not possible to generalize that essential fatty acids have a positive effect on the healing process or have antimicrobial effects on wound healing. Therefore, it is necessary to conduct studies of higher methodological rigor, comparing the different formulas available with fatty acids and their effects on the healing process.

DESCRIPTORS

Fatty acids, essential
Wound healing. Triglycerides
Helianthus
Nursing research

RESUMO

Os objetivos deste estudo foram caracterizar a produção científica nacional da utilização tópica de ácidos graxos no tratamento de feridas e descrever os efeitos da sua ação nesse processo. Trata-se de uma revisão integrativa da literatura indexada nas bases de dados LILACS e BEDEnf. A coleta de dados ocorreu no mês de dezembro de 2010, com descritores de assuntos controlados e sem delimitação de período de busca. A amostra constitui-se de 09 artigos, sendo, a maioria conduzida em modelos animais e utilizando diferentes composições de ácidos graxos. Diante da escassez de estudos clínicos randomizados controlados em humanos e as limitações desta revisão, não se pôde generalizar, na prática clínica, que os ácidos graxos essenciais influenciam o processo de cicatrização positivamente ou possuem ação antimicrobiana. Assim, há necessidade de realização de pesquisas com maior rigor metodológico comparando as diferentes fórmulas disponíveis contendo ácidos graxos e sua influência no processo cicatricial.

DESCRITORES

Ácidos graxos essenciais
Cicatrização de feridas
Triglicerídeos
Helianthus
Pesquisa em enfermagem

RESUMEN

Se objetivó caracterizar la producción científica nacional sobre utilización tópica de ácidos grasos en tratamiento de heridas y describir los efectos de su acción en tal proceso. Revisión integral de literatura indexada en bases de datos LILACS y BEDEnf. Datos recolectados en diciembre 2010 con descriptores de asuntos controlados, sin límite en período de búsqueda. Muestra constituida por nueve artículos, la mayoría efectuada en modelos animales y utilizando diferentes composiciones de ácidos grasos. Ante la escasez de estudios clínicos randomizados en humanos y las limitaciones de esta revisión, no se puede generalizar en la práctica clínica que los ácidos grasos esenciales influyan positivamente en el proceso de cicatrización o posean acción antimicrobiana. Por lo tanto, existe necesidad de investigar con mayor rigor metodológico comparando las diferentes fórmulas disponibles conteniendo ácidos grasos y su influencia en el proceso de cicatrización.

DESCRIPTORES

Ácidos grasos esenciales
Cicatrización de heridas
Triglicéridos
Helianthus
Investigación en enfermería

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INTRODUCTION

Vegetable oils are used to treat wounds, mainly in Latin America[1]. These oils have an abundant amount of fatty acids, namely oleic, linoleic, and linolenic. Most studies that address the use of fatty acids and healing have been performed in South America, mainly in Brazil, and only a few are published in international journals[2].

Fatty acids form a class of compounds that have a long hydrocarbonate chain and a carboxyl-terminus group. They have three main functions: they compose the biological membrane structures; function as precursors of intracellular messengers; and are oxidizers, in this case, generating adenosine triphosphate (ATP).

Since the early 1970's, studies have demonstrated the effects of fatty acids on the immune response. These metabolites interfere in several steps of the inflammatory process, such as vascular contraction, chemotaxis, adhesion, leukocyte extravasation, cellular activation and death, and most of these events occur through arachidonic acid derivatives, namely prostaglandins, leukotrienes, thromboxanes and lipoxins[2].

Several types of fatty acids exist, but in terms of wound treatment, the most important are the linoleic and linolenic acids. They are not synthesized by mammals because they do not possess the delta 9-desaturase enzyme, thus they are referred to as essential fatty acids (EFA)[3].

EFA products for wound treatment contain one or two EFA, added to other substances such as vitamin A, vitamin E and soy lecithin, or they integrate medium-chain triglyceride (MCT) formulations. The structure of the latter is predominantly comprised of fatty acids with eight carbons (caprylic), ten carbons (capric), six carbons (caproic), and twelve carbons (lauric acid). The triacylglycerol of the capric and caprylic acids deserve special attention as esters. Because they are classified as medium-chain triglycerides, they are useful as a nutritional source, solvent, medium, and stabilizer of oral, topical or parenteral products. They can be used for the treatment, as well as the prevention of, ammoniacal dermatitis and pressure ulcers, forming a protective barrier on the skin and impeding maceration, besides being important in cellular inflammation processes, providing relief after the first application and boosting local cellular nutrition, in addition to having a great capacity for tissue regeneration[4]. All these components work in a way that increases the immune response, thus accelerating the inflammatory process and, consequently, stimulating the healing process through angiogenesis and epithelialization, facilitating the entrance of growth factors into the cell[5].

Studies have shown that, besides EFA, soy lecithin and vitamins A and E also contribute to the process of tissue repair. The vitamins A and E have antioxidant properties and they protect the cellular membrane from the effect of free radicals. Soy lecithin, besides being a protective agent, maintains tissue hydration and helps in the skin healing process[6-7].

Linoleic acid (LA) plays an important chemotaxic role for microphages, and it is fundamental in the expression of the components of the fibrinolytic system (regulates the production of collagenase). It favors autolytic debridement in the wound bed because it contributes to the production of metalloproteins, inducing granulation and accelerating the healing process. It has been observed that LA is capable of inhibiting the growth of *Staphylococcus aureus*, affecting protein synthesis, cell wall, nucleic acids, and cellular membranes during cell division[8-11].

LA is the lipid found in greatest quantities in the epidermal layer. It is important in fat transport, helps maintain the integrity of the epidermal permeability barrier and accelerates healing processes. This substance acts as a modulator of the cellular membrane, protecting the lesion and acting as a local immunogen; it protects the skin against chemical and enzymatic agents, as well as from the maceration action of moisture, diuresis and feces. Because it is a lipid that forms a natural impermeable barrier on the skin, it acts as an important tissue restorer because it promotes chemotaxis and angiogenesis by maintaining the moistness of the environment and accelerating the tissue granulation process. Furthermore, it also protects the skin against *Staphylococcus aureus,* regulates the permeability of the water barrier of the skin and provides local cellular nutrition[5,10-13].

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In Brazil, the EFA commercial products available for wound treatment include the following: Dersani® (Saniplan), Curatec® AGE (LM Farma), Repitelin® (Biolab), Dermosan® (Sunny Day), AGE Cremer óleo® (Cremer), AGEDerm® (Helianto Farmaucêutica Ltda), Lin'Óleo® (V Declair), Primoderm® (LC produtos Naturais com Calêndula) and Supriderm® (LC produtos Naturais com Calêndula).

The formulation of Dersani® is as follows: Capric acid, caprylic acid, caproic acid, lauric acid, linoleic acid, lecithin, retinol palmitate, tocopherol acetate and alpha-tocopherol. Curatec® AGE is a product rich in EFA, also containing medium-chain triglycerides: MCT, linoleic acid, oleic acid, caprylic acid, capric acid, lauric acid, palmitic acid, myristic acid, stearic acid, retinol palmitate (vitamin A), tocopherol acetate (vitamin E) and soy lecithin. The formulation of Repitelin® is: wheat germ oil, triglycerides of caprylic/caproic acid, retinol palmitate (1,000,000UI/g), tocopherol acetate, butylhydroxytoluene, soy lecithin, mineral oil, phenoxyethanol, and sunflower oil. Dermosan® lists the following ingredients: capric acid, lauric acid, linoleic acid, caprylic acid, caproic acid, palmitic acid, my-

ristic acid, soy lecithin, vitamin A and vitamin E. AGECremer óleo® consists of: essential fatty acids (EFA), vitamins A and E, soy lecithin and Andiroba oil. AGEderm® contains: essential fatty acids from polyunsaturated vegetable oils, linoleic acid, soy lecithin, and triglycerides of capric, caprylic, lauric and caproic acids enriched with vitamins A and E. Lin'Óleo® contains: unsaturated essential fatty acids. Primoderm® AGE lists the following ingredients: sunflower, calendula, wheat germ, and olive oils, shea butter, soy lecithin, and vitamins A and E. Finally, Supriderme® AGE contains: sunflower, calendula, wheat germ oils, soy lecithin, and vitamins A and E.

EFA are indicated for treating all types of skin lesions, such as pressure ulcers, venous stasis ulcers, with or without infection, as well as to prevent pressure ulcers and other skin problems[5,11]. However, it should be outlined that not all commercial products containing EFA are indicated or permitted for treating wounds or broken skin. Hence, health care professionals must observe if the product is classified under the Brazilian National Health Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA) as Class III, i.e., a medical health product, thus permitted to be used on skin lesions.

Regarding the use of EFA in wound treatment, a systematic literature review[14] spanning the period from 1970 to 2006 found that, as far as national scientific production is concerned, few publications have been produced. In view of this fact, and considering that EFA is widely used in wound treatment in Brazil, an interest emerged to identify if more national studies regarding this issue have been produced. Therefore, contrary to what other authors say: *information was produced to support the choice options of using this substance*, the evidence obtained from this review, which is not characterized as systematic in essence, does not permit any generalization regarding indications for use of EFA to treat wounds in human beings, as the recommendations were mostly obtained from animal studies and with substances, mediums and concentrations containing EFA, many of which are not available in Brazil.

OBJECTIVE

To characterize the national scientific production regarding the use of fatty acids to treat wounds and describe their effects on this process.

METHOD

This is an integrative scientific literature review, whose method permits the inclusion of empirical and theoretical literature, with one of its main advantages being the possibility of combining data from different study designs[15].

The following guiding question was used to develop the integrative review: What is the Brazilian scientific production regarding the effects of the topical application of fatty acids on the treatment of chronic and acute wounds in animal and human models?

The bibliographic survey was performed in December of 2010, through an online search of the Latin American and Caribbean Literature on Health Sciences (LILACS) and Nursing Database (BEDENF). It should be highlighted that an additional survey was performed considering the references found in the selected articles. The search period of these databases was not restricted.

The search was performed using Health Science Descriptors, combining in the basic form on the LILACS and BEDENF: essential fatty acids and dressings; dressings and linoleic acid; linoleic acid and wound healing; wound healing and essential fatty acids; essential fatty acids and triglycerides; fatty acids and wound healing; fatty acids and wounds and injuries; triglycerides and healing; Helianthus and wound healing.

Articles were included and analyzed using the following criteria: articles indexed on the previously described databases; written in Portuguese, English, or Spanish; and addressing the topical application of fatty acids on wounds in animal and human models. Articles were excluded if they were narrative literature reviews; studies that used more than one topical agent on the same wound; case studies; studies that used topical fatty acids for wound prevention; editorials; letters; and studies published in the form of abstracts, dissertations and theses.

Data collection was performed using an adapted instrument[16] comprised of: data regarding the journal (name, year, volume, number, original language, country); the researcher (name, workplace and graduation); and the article (title, year and place the study was performed, scope, sample, the performed interventions, results, analyses and conclusions). Two researchers evaluated all of the obtained studies, and when there was any disagreement, a third researcher read the article and discussed with the first two.

RESULTS

Eleven articles were identified, nine of which were selected after the analysis, performed according to the methodology.

In order to analyze the studies, a description was obtained considering the following: author, sample, scope, type of wound, methodology and outcome, which will be presented below.

Regarding the analyzed studies, two were published in the 1990's and seven after the year 2000.

In terms of the study design, five (55.6%) were randomized studies performed on animal models (rats), three (33.3%) were randomized human studies, and one (11.1%) was a descriptive comparative animal study (sheep).

There were a total of 46 authors, with a mean of 5.1 authors per article. Regarding their profession, there was a variety of professional areas involved: 16 (34.8%) physicians, nine (19.6%) medical students, six (13%) nurses, four (8.7%) pharmacists, biologists and veterinarians (each), two (2.2%) biomedical professionals and two (4.3) nursing students. The analyzed studies were published in six different journals.

It should be highlighted that only one study reported that the company provided the product used in the study, while the others did not mention any funding sources, including the pharmaceutical industries responsible for the production of the described products, or any possible conflict of interests.

DISCUSSION

In searching for national articles on the selected databases, it was realized that there is a scarcity of published studies regarding the use of essential fatty acids (EFA) for treating wounds. This fact is not surprising, as other authors[1,8] have already pointed out this issue, despite this substance being widely used in Brazil for the prevention and treatment of wounds.

In Brazil, the use of medium-chain triglyceride essential fatty acids (TG-EFA) became popular in 1994[17], when clinical effects were observed in the prevention of pressure ulcers.

In this review, it was determined that there was a higher concentration of studies starting in the year 2000 (77.7%), likely due to the dissemination and supply of medium-chain triglycerides (MCT) in the market, with or without EFA.

The number of authors per article varied between one and eight, with a predominance of physicians, medical students and nurses (34.8%, 19.6% and 13%, respectively). It was also found that most authors worked in positions connected to higher education.

Wound care is mainly performed by the nursing team; however, wound care should not be limited to this professional area, as it should be implemented within an interdisciplinary perspective.

Because of the nature of the studied theme, from the ethical point of view, the recommendation to use (or not to use) a certain product for wound treatment should be based on a theoretical framework, no longer used empirically. For this reason, experimental studies are fundamental. To do this, nurses must know how to obtain, interpret and integrate the evidence from studies in order to help in the decision-making process regarding the nursing care that is delivered to patients and their family members[18]. Therefore, it is necessary that nursing professionals think about these issues, not only considering scientific principles, but also the Professional Practice Law that determines, among other duties, that the professional must preserve the integrity of the clients. This includes not using any products that could represent any level of threat to their health[19].

Below, each analyzed study is described, with the purpose to outline their characteristics and weaknesses, thus allowing for a better understanding and synthesis of the results.

The first study(20) aimed at evaluating the evolution of skin wounds in rats treated with Agarol® (composed of mineral oil, phenolphthalein and agar-agar), and Triglyceril® (a product constituent of EFA). The 25 rats were randomly divided into three groups: Group C (control): 9 animals, the dry occlusive dressing was changed daily after cleansing with a 0.9% NaCl solution; Group A (Agarol®): 9 animals, the dressing was changed daily and Agarol® was applied after cleansing with isotonic NaCl saline solution; and Group T (Trigliceril®): 9 animals, the dressing was changed daily and Trigliceril® was applied after cleansing with isotonic NaCl saline solution. The wounds of all animals were protected with an occlusive dressing. The groups were evaluated for a period of 14 days. On the third postoperative day, the use of Agarol® and Trigliceril® did not show any evidence of histological alterations in the healing process. On the seventh day, however, it was observed that the inflammatory reaction in the wounds treated with Agarol® was less than in the wounds treated with Trigliceril®; on the other hand, these results were similar to the control group. In addition, on the seventh day an acute inflammatory reaction occurred only in the group treated with Trigliceril®; on the fourteenth day, however, all groups were similar. When the granulation tissue was analyzed on the seventh day, it was observed that there was more granulation tissue in the Agarol® group compared to the control and T groups. Furthermore, compared to the control group, the T group showed a greater amount of granulation tissue i.e., Trigliceril® apparently conditioned the reduction of the amount of granulation tissue, whereas Agarol® had the opposite effect. There was no significant difference regarding neovascularization between group A and group C. The same was observed between groups A and T. However, when group T was compared with group C, the former presented less neovascularization, which suggests that Trigliceril® delayed the neovascularization process. On the fourteenth day, no interference from these substances was observed on the healing process.

The previous study results are contradictory in terms of the literary concept of this product (Trigliceril®), as it is indicated for the purpose of accelerating cellular mitosis, stimulating angiogenesis and acting as a chemotactic agent for the cells involved in the entire tissue repair process. The concentration of EFA was not described.

A randomized clinical trial[21] with 27 cardiac patients (clinical and surgical) aimed at testing the effectiveness of

MCT with EFA (15% linoleic acid) as therapy for stage II and III pressure ulcers. The study was performed on two groups of cardiac patients: group I: (n=14) using MCT with EFA; group II: (n=13) using PVPI. It was observed that with the solution of MCT with EFA there was a reduction of 8 cm^2 in the total ulcer area in the first week (p=0.003), while with PVPI there was a 1 cm^2 increase in the first week. From the first to the third week there was a 22.7 cm^2 reduction of the area using MCT with EFA, whereas with PVPI the area increased 7 cm^2. It was confirmed that the MCT solution with EFA is effective compared to the conventional solution, as the ulcer size actually increased after its application.

This study does not clarify how subjects were randomized, the frequency of dressing changes, secondary coverage or other clinical characteristics of the wounds and the biochemical parameters during the treatment. Another issue, from an ethical perspective, concerns the absence of reports regarding the interruption of the PVP-I treatment, considering it increased the area of the wounds.

Another study[11], randomized, multicenter, double-blind and placebo-controlled, involving 100 patients with chronic ulcers of differing etiologies (venous, diabetic and stage IV pressure ulcers), was performed with the objective of verifying the capability of linoleic acid (LA) to stimulate the formation of granulation tissue and heal chronic wounds, and also to evaluate the collateral effects and the patients' tolerability of the treatment. The patients were randomized into two groups: G1: 50 patients-63 ulcers treated with LA enriched with vitamins A and E; G2: 50 patients-65 ulcers received a placebo. The wounds were jet-cleansed with a normal saline solution and covered with gauze soaked in LA or placebo, which were changed once a day. The wound area was measured (mm^2) and the percentage of area reduction was calculated by subtracting the final area from the initial area, multiplying by 100 and dividing by the initial area. A significant difference was found in the wounds treated with LA regarding the development of granulation tissue and healing ($p < 0.001$). Among the ulcers treated with LA, 100% granulated within two weeks and 90.4% healed completely. Among those treated with placebo, 1.5% presented granulation tissue on the fourth week and only 1.5% healed. No severe collateral effect was observed except for mild bleeding of the granulation tissue in 44% of the LA group; however, the treatment was well tolerated.

Nevertheless, it is worth highlighting that the previously described study does not clarify the randomization method, nor does it mention the placebo substance that was used. Furthermore, it does not describe other wound evaluation methods besides the percentage of area reduction and biochemical parameters of the patients before being divided into groups.

In the fourth study, using a comparative-descriptive design, the researchers[22] demonstrated the effects of the topical application of sunflower oil on wound treatment, using eighteen sheep. The animals were divided into groups of six, according to the observation period, prospectively (7, 14, and 21 days). Two surgical wounds (4 cm^2) were made in the thoracic region of the animals, near the scapula; the right wounds were treated with sunflower oil with a high concentration of linoleic acid (65%) and the left wound (control) was treated with sterilized Vaseline; both wounds were kept occluded. The wounds were washed every 24 hours with a 0.9% saline solution and new rayon gauze soaked in sunflower oil or Vaseline was placed over each wound. This procedure was repeated for 7, 14, and 21 days for the first, second and third groups, respectively. Tissue biopsies of the postoperative wounds were performed on the 7th, 14th and 21st days, and subjected to clinical and histopathological evaluations. The results showed that the topical application of sunflower oil accelerated the healing process on the 7th and 21st days, reducing the area and increasing the contraction of the wounds ($p<0.05$). The granulation tissue developed faster on treated wounds compare to the control group, thus allowing the conclusion that the topical use of sunflower oil accelerated the healing process because it promoted the acceleration of the development of granulation tissue and epithelialization.

This study highlights that the LA concentration was high (65%), a fact that may have contributed to the positive results of wound healing. This concentration was either not used or omitted in the articles analyzed in the present study. Another characteristic omitted in the study was the LA composition; it was made of sunflower seeds and nothing else is mentioned regarding elements that could have been added to this substance. It was observed that wound healing was faster with the topical application of sunflower oil, accelerating the formation of granulation tissue, compared to the topical application of Vaseline. The referred author may have reached this result due to the fact that his control group was tested with a solution that is known to have no healing properties (Vaseline) and, therefore, could have included another group using gauze soaked in a saline solution and keeping it moist.

In another comparative experimental study[23] regarding the effect on skin healing in 24 rats, medium-chain triglycerides and sunflower oil were used. Three groups were randomized and established according to probability: group C – control (n=8): 0.9% NaCl; group MCT – medium-chain triglycerides: (n=8); and group SFO- the sunflower oil group: (n=8). The wounds were moisturized every day with the products. The microscopic characteristics were analyzed regarding the type of inflammatory reaction and the predominant type of cell, granulation, neovascularization, fibrosis intensity, and re-epithelialization during the 3rd, 7th and 14th days. A notable reduction in acute inflammation (neutrophils) was observed during the 3rd postoperative (PO) day compared to the control group. Regarding tissue granulation, it was observed to be

in early development on the 7th PO day, and no significant difference was found between the groups. Neovascularization was noted in all animals in the MCT group between the 3rd and the 14th PO day. This process was severe in only 12.5% in the SFO and MCT group, and only on the 14th PO day. This event was absent in 37.5% of the cases in the SFO group, and 12.5% in the control group, but moderate in most cases in the MCT group (37%) and severe in 25%, noted on the 3rd PO day. Fibrosis was not observed in the control group, and only a small amount of fibrosis occurred in 87.5% of the cases in the MCT group, and 50% in the SFO, on the 3rd PO day. On the 14th PO day, severe fibrosis was observed in most cases in all groups. Re-epithelialization was progressively extensive in the three groups late on the 3rd PO day. After the 7th day, no significant difference was observed between the SFO and MCT groups. The obtained results demonstrated that the medium-chain triglycerides as well as the sunflower oil alter the healing process in a positive way, despite the fact that the fibrosis they cause is more severe than in the control group.

In the previously described study, the authors are unclear about whether the dressings were occlusive or if they only moisturized the wounds with the products. Moreover, they do not describe the concentration and the commercial brand of the sunflower oil and MCT. In view of these unclear data, the results must be interpreted with caution, because a previously reported study [20] using MCT demonstrated an increase in the inflammatory reaction on the 7th postoperative day.

Another experimental study[24] aimed at evaluating the inflammatory reaction present in wounds made on the backs of 96 male Wistar rats, which healed by secondary intention and were treated using sugar and MCT-EFA. The animals were distributed into three groups of 32, comprising the sample. On each animal, the wound was covered with an occlusive dressing using the referred products, and were changed daily at the same hour of the day. In group A (control), a sodium chloride solution of 0.9% was applied on the wounds; in group B sugar was applied, and an EFA solution was applied on the animals in group C. No significant difference was observed between the groups. The results were equivalent in terms of the inflammatory response modulation of the studied animals, and there was no significant difference in the inflammatory reaction during the healing of wounds treated with sugar and EFA compounds.

A rat study[4] was conducted with the objective to evaluate the effect of the association of medium-chain triglycerides (caprylic, capric, capric and lauric acids), linoleic acid (essential fatty acid), vitamins A and E and soy lecithin (test product), by means of morphometric analysis, in 45 male Wistar rats, regarding the kinetics of repairing experimental skin ulcers. The animals were randomly assigned to 3 groups containing 15 rats each, Control group (saline solution 0.9%), Reference group (clostebol compound associated with neomycin sulphate) and Test group, which received daily topical therapy, from the 1st to the 12th PO day. The wounds were cleansed every day with a 0.9% saline solution. The wound areas were measured by digital planimetry on day zero, and on PO days 3, 7 and 12. Based on the wound area, it was also possible to calculate the degree of repair and the mean repair rate in a given period of time. On the 3rd day it was observed that the wound area increased in the reference group, and there was slight contraction in the control and test groups. On subsequent days, the repair process, measured by the repair degree variable, showed linear evolution, in such a way that on the 12th day, the repaired area achieved 77.95% healing of the initial ulcer area in the Control group, 78.40% in the Reference group, and 83.49% in the Test group, with no statistically significant differences. Similar values were found for the mean repair rates for the 12 days of treatment: 25.79 mm²/day in the Control group, 25.42 mm²/day in the Reference group and 27.38 mm²/day in the Test group. It was concluded that the compound in the Test group, applied topically on the experimental skin wounds of rats, did not accelerate the tissue repair process by secondary intention, although there was a slightly better effect compared to the test treatment.

Similar to other studies, there was no reference to the brand and composition of the products, or whether the wounds were exposed or received any secondary coverage. In addition, it was unclear which product was used in the control group.

A randomized patient study[25], which included seven men and one woman who had been cured of Hansen's disease and had been discharged from treatment, was performed with the objective of comparing the effects of a latex biomembrane (Biocure®) and an EFA-based product (Dersani®) on the microbiota of infected chronic wounds. There were a total of 19 wounds, which were randomly assigned into two groups, as follows: 11 wounds in group A (treated with Dersani®) and eight wounds in group B (treated with Biocure®). The assignment into groups was performed by a draw, using identical dark envelopes that were sealed and shuffled. When one patient had two or more wounds, two or more envelopes were drawn. An identification code was used for the wounds, with the purpose of maintaining confidentiality regarding the identity of the subject. The dressing was prepared daily by the same researcher, with the help of an assistant, and the wound was cleansed using saline solution 0.9% warmed to approximately 37ºC, using cotton gauze on tweezers, or jet cleansed depending on the type of tissue present in the wound bed. Both products were evaluated *in vitro* regarding the control bacteria (*Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 9027) and one representative for each bacterium was isolated from the wound by Agar diffusion. The following were identified: *Staphylococcus aureus* (50%), *Pseudomonas aeruginosa* (35.7%), *Proteus vulgaris* (8.2%), *Enterobacter aerogenes* (3.3%) and *Escherichia*

coli (2.7%). The results obtained *in vivo* suggest that Dersani® had a positive antimicrobial effect on *Enterobacter aerogenes,* while Biocure® had an effect on *Pseudomonas aeruginosa.* Furthermore, the *in vitro* results showed neither product had an effect on the microorganisms isolated from the wounds.

Some aspects of the aforementioned study should be outlined. The diagnosis of infection was performed considering clinical signs that were not described in the results and/or qualitative microbiological analysis. Although a standardized swab technique was used, an appropriate diagnosis of wound infection cannot be achieved by qualitative analysis. Furthermore, the authors conclude that the tested products have an antimicrobial activity against some bacteria, but the same result was not confirmed in the *in vitro* analysis. Therefore, it can be inferred that the products do not necessarily have this action *in vivo*, because skin microbiota can change due to several factors, including the cleansing technique and the method that the material from the wound is collected, as this procedure occurred during five different times, with seven-day intervals. Thus, it is possible that the microbiological material was not collected from the same location of the wound, and this could explain the fact that some bacteria were not recovered in certain intervals, hence the attribution of a possible microbial action to the tested products.

Despite the fact that the commercial presentation of Dersani® indicates the presence of a composition of EFAs, only linoleic acid is present in its formulation.

The final analyzed study[26] was performed with the purpose of evaluating the effect of applying a sodium chloride solution at 0.9%, crystalized sugar and MCT-EFA on experimentally induced wounds in Wistar rats. This sample was subdivided into three groups, A, B, and C, with 32 animals each. Each group was treated with one type of product: group A was determined as the control group, group B, sugar, and group C, MCT-EFA. The measurements were performed in four different time periods (3rd, 7th, 14th and 20th days) and consisted of determining the percentage of reduction of the wound area, cellular inflammatory reaction, collagen organization, and types I and III collagen density in the wounds. Healing occurred equally in the studied groups, i.e., no significant effects were observed in terms of wound area reduction (p=0.101) and collagen organization, or in regards to an inflammatory reaction between the MCT-EFA and the control group. However, sugar caused a positive modulation of the inflammatory reaction between the 7th and the 14th day. On the 20th day, there were no differences in the amounts of collagen types I and III between the tested groups. Wound healing occurred in the three groups. The sugar group presented a positive modulation of the cellular inflammatory response. No differences were observed in the amount of collagen types I and III upon completion of the experiment in the treated groups. However, the sugar treatment promoted an increase in acute phase inflammatory cells and, later, an increase in chronic inflammatory response cells (p<0.001). On the 20th treatment day, it was observed that in the MCT-EFA group there was a greater density of collagen type I, and a smaller density for type III collagen (p=0.0027) compared to control, but there was no significant difference between the sugar and MCT-EFA groups (p=0.098) or between the sugar and control groups (p=0.1104) on that day, thus demonstrating that the sugar treatment exhibited tendencies towards better healing conditions compared to the other products.

It is emphasized that in the previous study, the authors reported that the company provided the Trigliceril CM® used in the study. However, they do not mention the EFA concentration in the product.

After analyzing each study, we synthesized the effects of the tested products regarding their effect on wound healing: in two situations, a negative effect occurred as a result of using medium-chain triglycerides (MCT); one negative, one positive and no effect was observed when applying MCT+EFA; and three positive effects were observed with the use of LA. Finally, one questionable effect was observed regarding the action of MCT+EFA on the *in vivo* antimicrobial action.

In agreement with a previous review[14], in general, the methodology of the studies was not clearly described; there was a lack of details regarding how the evaluation of the described variables was conducted as well as the results (mainly in studies involving human beings), and the form of wound treatment was not clearly described or lacked information; for example, regarding the cleansing method, how the dressings were changed, and the secondary coverage used (if any).

It should be noted that in the analyzed studies, the formulations containing EFA varied considerably. This fact may have influenced the results. It is noticed that the EFA products available in Brazil contain several other substances in their composition. Therefore, it is not feasible to attribute any beneficial effects on healing exclusively to the presence of EFA. In addition to these characteristics, the studies do not make any explicit reference to the concentrations of the products and the brands that were used; hence, it is not possible to make any generalizations for their indication in clinical practice. Furthermore, it is also highlighted that the interpretation of further study results must be done with caution to allow for a homogeneous generalization of the use of fatty acids, considering that the different fatty acids, essential or not, included in these formulations have different concentrations and, in some cases, other emollient substances and vitamins may also be added.

It is emphasized that most of the studies analyzed in the present review were performed using animal models; therefore, these types of studies cannot serve as sources of evidence to be applied in clinical practice, but instead should be viewed as evidence that demonstrates the

need for the performance of randomized clinical trials in humans. Furthermore, the analyzed human studies are methodologically weak and do not, therefore, allow for generalized conclusions to be used in clinical practice.

The fact that the present study included only national articles from only two databases can be considered a limitation of this integrative review, because the publication of national articles in international journals indexed on other databases cannot be disregarded. This points to the need for systematic reviews using the *Cochrane* methodology with randomized clinical trials.

CONCLUSION

It is concluded that there is a scarcity of national studies, indexed on the referred databases, addressing the use of fatty acids for wound care. Most studies are experimental and were performed on animal models. Authors were mostly physicians, medical students and nurses.

Overall, the studies are methodologically weak considering the products that were used, as they fail to provide details regarding their composition, a fact that, considering the study sample, renders unfeasible the indication of the therapy for human beings regarding its positive effect on wound healing and/or antimicrobial action.

The study results do not present any contraindications or collateral effects from the use of EFA on wounds of animals and humans, which confirms the findings of another study [15]. However, the analyzed studies, mainly performed using animal models, are not appropriate to indicate EFA as an efficient therapy for wound healing in humans. On the other hand, the animal studies involving the effects of fatty acids on the immune system cells showed this substance plays an important immunomodulation role.

It should be highlighted that the lack of strong scientific evidence regarding the effects of EFA on wound healing does not mean that this substance is not effective in clinical practice; rather, there is a need for randomized clinical trials in humans to prove the possible benefit of this therapy on wound care, considering it is widely used in Brazil.

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