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Revision Article

SUCROSE IN INFECTED WOUNDS: A SCIENTIFIC BASIS AND SPECULATIONS

SACAROSE EM FERIDAS INFECTADAS: FUNDAMENTAÇÃO CIENTÍFICA E ESPECULAÇÕES

SACAROSA EN HERIDAS INFECTADAS: BASE CIENTÍFICA Y ESPECULACIONES

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Sucrose use in wound treatment is a common practice that seems to promote tissue healing and reduce microbial load. The objective here was thus to analyze the scientific evidence through an integrative review to determinate indications and contraindications for use of sucrose in the form of granulated, brown (unrefined muscovado sugar) and/or refined sugar in infected wounds and thus assist the professional in clinical decision-making. Ten studies published in full articles were selected, from the period 2002 to 2012 and indexed in the PubMed, Cinahl, Lilacs and Cochrane databases. Considering the analysis of studies, mostly experimental in the animal model, sugar's effectiveness in tissue repair was verified, as was positive modulation in the inflammatory response. To elucidate the mechanisms or action of sucrose in the wound, further clinical trials are recommended in order to standardize the concentration, volume and frequency of sucrose in changes of wound dressings.
Descriptors: Sucrose; Wound Healing; Sugar.

O uso de sacarose na terapêutica de feridas é uma prática comum que parece favorecer a cicatrização tissular e reduzir a carga microbiana. Objetivou-se, desta forma analisar as evidências científicas por meio da revisão integrativa a fim de determinar a indicação e contraindicação do uso da sacarose (nas apresentações de açúcar cristal, mascavo e/ou refinado) em feridas infectadas e assim auxiliar o profissional na tomada de decisão clínica. Selecionaram-se 10 estudos publicados na íntegra, no período de 2002 a 2012 e indexados no PubMed, Cinahl, Lilacs e Cochrane. Considerando a análise dos estudos, em sua maioria experimentais no modelo animal, verificou-se a efetividade do açúcar na reparação tecidual e modulagem positiva na resposta inflamatória. Com vistas a elucidar os mecanismos ou ação da sacarose na ferida, recomendam-se ensaios clínicos adicionais para padronizar a concentração, volume e periodicidade da sacarose nas trocas de coberturas.
Descritores: Sacarose; Cicatrização; Açúcar.

El uso de sacarosa en el tratamiento de heridas es una práctica común que promueve la cicatrización de tejidos y reduce la carga microbiana. El objetivo fue analizar las evidencias científicas mediante la revisión integradora para determinar la indicación y contraindicación del uso de sacarosa (azúcar cristal, marrón y/o refinado) en heridas infectadas y ayudar al profesional en la toma de decisiones clínicas. Seleccionaron 10 estudios publicados, de 2002 a 2012, indexados en PubMed, Cinahl, Lilacs y Cochrane. Teniendo en cuenta el análisis de los estudios, principalmente en modelos animales experimentales, se verificó la eficacia de azúcar en la reparación tisular y modelaje positiva de las respuestas inflamatorias. Con el fin de dilucidar los mecanismos de acción de sacarosa en la herida, se recomiendan ensayos clínicos adicionales para normalizar la concentración, el volumen y la frecuencia de sacarosa en el cambio de las coberturas.
Descriptores: Sacarosa; Cicatrización de Heridas; Azúcar.

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INTRODUCTION

Wound therapy challenges scientific-technological advances, mobilizing researchers' attention in the attempt to implement measures which advance healing and impede colonization and the occurrence of infection. The issue involves a complex process, which still has controversies regarding the clinical and physiological aspects linked to the therapeutic basis[1].

Historical documents describe the use of sugar in wound therapy, such as the Edwin-Smith Papyrus which deals with injuries sustained in wars in Ancient Egypt, as well as in World War I with Russian soldiers. However, there are other substances containing sugars, such as molasses and syrup, used by the Indians of Peru, Chile and Colombia in treating infected wounds, which seem as a result to reduce the use of antibiotics[2].

Sugar has a bacteriostatic and bactericidal action due to the high osmolarity of the syrup which forms some hours after its application on a wound[2-3]. Honey also has bactericidal action due to the composition of formic, malic and lactic acid, which give it an acid pH, making the environment unfavorable to the development of microorganisms[3]. Nevertheless there seems to still be a shortage of clinical evidence for the use of these substances.

There is consensus among the professionals regarding the difficulties of control of microbial proliferation in wounds[4-5], including adherence, colonization, and formation of biofilm, among others[6-8]. As a result, the rise in bacterial resistance associated with the formation of biofilm, transformed the entire field of the understanding of microbiology in wounds[8]. The microbial biofilm is a complex community of bacteria, aggregated and incorporated within an extra-cellular matrix, or within extra-cellular polymeric substances[5,9-11].

There is the concept of infected wounds – those lesions with microbial presence corresponding to $\geq 10^6$ per gram/tissue, purulent secretion or exudate, or the progressive loss or devitalisation of tissue, resulting in difficulty in the healing process. In this group, an acute inflammatory bacterial process is present, with or without purulent secretion, as well as when there is perforation of the viscera[12]. Following the trauma, the organism's immediate response is inflammation, with the classical symptoms appearing, such as redness, heat, pain and loss of function[12]. In this way, the immunological and coagulation systems are activated, as well as autolytic debridement of the lesion and the healing. In this regard, the inflammatory or exudative phase generally lasts 4 to 5 days, possibly rising in the event of infection, a foreign body or lesion caused by the dressing, or should there be inadequate energetic or nutritional intake. This fact may weaken the patient and increase the healing time, that is, tissue repair[12-13].

Although the tissue repair is a systemic process, it is necessary to improve the local conditions through appropriate topical therapy with a view to better healing results in the shortest length of time possible. The arsenal for topical wound therapy is highly diversified, requiring the health professional to have a grounding in scientific studies on the physiology of tissue repair, as well as indications, contra-indications, advantages and disadvantages; and the identification and elimination of infectious processes, among other similar principles[14-15].

In addition to cleaning and debridement, another important principle of topical wound therapy is occlusion with wound covers[12,14-16]. The covers are also termed dressings, although this term is no longer appropriate, as it encompasses the technique of "curing". In general, the procedure involves the removal of the old covering, cleaning, debridement, and the putting-on of the new covering.

The purpose of this study was to analyze the scientific evidence by means of an integrative review, so as to determine the indication and contra-indication of the use of sucrose (in the forms of granulated sugar, brown sugar - unrefined muscovado sugar- and/or

refined sugar) in infected wounds; and to assist the health professional in clinical decision making.

METHOD

This is an integrative review based on experimental and non-experimental studies, which advances a comprehensive understanding of sucrose's action in infected wounds. This technique in its turn brings together and summarizes relevant publications on a delimited issue or question, in a systematic and ordered way, contributing to the deepening of knowledge – and thus elaborates conclusion in regard to a particular area of the study[17-18]. In this regard, considering the clinical implications of the microbial presence in wounds, and the variety of therapeutic options, the question is: "What are the indications and contra-indications regarding the use of sucrose in infected wounds?"

The inclusion criteria was studies on sugar in infected wounds published in the last 10 years (2002-2012) and indexed in the PubMed, Cumulative Index to Nursing and Allied Health (CINAHL), the Latin-American and Caribbean Health Sciences Literature (LILACS) and Cochrane VHL databases (Chart 1).

Chart 1 - Scientific production from 2002 to 2012 on the use of sucrose in infected wounds, according to the different databases.

Database	Descriptors	Articles	
		Found	Selected
Pubmed	wound healing and sucrose and sugar	20	6
	honey and wound healing	1	1
Lilacs	wound healing and sucrose and sugar	2	1
	cicatrização and sacarose and açúcar	2	0
Cinahl	wound healing and sucrose and sugar	5	2
	honey and wound healing	1	0
Cochrane	wound healing and sucrose and sugar	3	0
Total		33	10

Consequently, cross-referencing of descriptors was used: *cicatrização/açucar/sacarose*, wound healing/sugar/sucrose and *cicatrización de heridas/ azúcar/ sacarosa* in the period December 2012 to January 2013. For the search for articles obtained in the Health Sciences Descriptors (DeCs) and MeSH there was the combination of key-words 'granulated sugar', 'brown sugar' and 'refined sugar'. Articles were selected by their titles and abstracts, and when these showed conformity with the investigatory question and inclusion criteria, they were evaluated in full. In addition, for the analysis of the studies included in this review, the following levels of evidence were used: I- Systematic reviews or meta-analysis of Randomized Controlled Clinical Trials (RCCT); II - RCCT; III - CT without randomization; IV - control-case or cohort studies; V - systematic reviews of qualitative studies; VI - single descriptive study and VII- opinion of specialists and editorials[19].

Articles related to infected wounds treated exclusively with honey or other healing compounds with essential fatty acids (EFA) and povidone-iodine (PI) were excluded.

RESULTS

Considering the interest in seeking clinical evidence for supporting the use of sucrose in infected wounds, the articles were initially categorized as human or involving experiments in the animal model. In this regard, there were a total of 33 articles in the different databases, of which 10 were eligible for thorough reading with methodological rigor and criticality. Chart 2 presents the summary of the results obtained (a, b, c).

Chart 2a - Scientific production on the use of sucrose in infected wounds, by objective, method, principal results, conclusion and level of evidence

N	Objective	Method	Principal results	Conclusion	Level of evidence*
1[20]	To assess the inflammatory reaction in wounds treated with sugar and essential fatty acids (EFA), healed by secondary intention in rats.	Controlled randomized experimental trial	There was no significant difference between the groups.	There was no difference in the inflammatory reaction of cutaneous wounds treated with sugar and EFA healed by secondary intention.	II
2[21]	To summarize in the scientific literature the use of sugar, papain and papaya and essential fatty acids in wounds.	Editorial	Shortage of RCCT and comparative statistical data. Difficulty in the evaluation of the sugar's action, due to the variety of forms (sugar and sugar paste). Absence of standardization in changing dressings, as well as wound irrigation.	Further RCCT are necessary to evaluate the efficacy and adverse effects of the natural products. It queries the availability of other options which are cheaper.	VII
3[22]	To clarify the mechanisms of efficacy of sugar with povidone-iodine (PI)) at 3% (U-PASTATM), according to keratinocytes and fibroblasts.	Experimental study (*in vitro)*	Sugar and PI paste raised the synthesis of fibroblast collagen, and also acted in wounds as antibiotic agents.	Sugar and povidone-iodine paste increased the synthesis of fibroblast collagen.	III

*Melnik BM, Fineout-Overholt E, 2005.

Chart 2b - Scientific production on the use of sucrose in infected wounds, by objective, method, principal results, conclusion and level of evidence

N	Objective	Method	Principal results	Conclusion	Level of evidence*
4[23]	To determine the efficacy of paste of sugar with povidone-iodine (PI) in the healing process in cutaneous ulcers infected with MRSA in diabetic rats.	Experimental study	Sugar and PI accelerated the re-epithelialization and reduced the microbial load of cutaneous ulcers infected with MRSA.	Sugar and PI are efficacious for topical use in cutaneous ulcers in diabetics.	III
5[24]	To verify the possibility of sugar as a nutritional signal that regulates the production of toxins in gas gangrene in *C. perfringens.*	Experimental study	High concentrations (0.5% to 3%) of sugar produced significant regulation, dose-dependently, in alpha-toxin (PLC) and theta-toxin (PFO) during the complete growth cycle of *C. perfringens*.	It demonstrated that sugar regulates the production of tissue degradation by the PLC and PFO toxins, which are essential to the development and progression of gas gangrene.	III
6[25]	To evaluate infected venous wounds treated with sugar paste	Case study	In two weeks, it reduced the odor, pain, exudate and signs of infection. The wound bed had 50% granulation tissue.	Sugar paste is efficacious in bacterial infection and pain reduction in venous ulcers, as well as contributing to healing.	VI

*Melnik BM, Fineout-Overholt E, 2005.

Chart 2c - Scientific production on the use of sucrose in infected wounds, by objective, method, principal results, conclusion and level of evidence

N	Objective	Method	Principal results	Conclusion	Level of evidence*
7[26]	To evaluate the effect of saline solution ($NaCl^-$), sugar and medium chain essential fatty acids and triglycerides (EFA-TG) in cutaneous wounds experimentally induced in rats.	Controlled randomized experimental study	Sugar allowed an increase in inflammatory cells between the 3rd and 7th day, and a reduction on the 14th day, as well as better healing conditions.	Demonstration of the therapeutic advantages of sugar in relation to the EFA-TG and saline solution in the treatment of acute cutaneous wounds in rats.	II
8[27]	To compare efficacy between honey and sugar in dressings of colonized wounds.	Randomized clinical trial	Improvement in healing ($3.8cm^2$/week) and reduction in the pain during the changing of dressings with the use of honey (86% of 22 patients).	Honey is more effective than sugar, as it reduces the bacterial contamination and the pain when dressings are changed, as well as favoring the healing process.	II
9[28]	To analyze the progressive treatment with sugar in 16 pressure ulcers (PU) in chronically-ill patients.	Experimental non-randomized study	Application of the sugar treated seven PUs and improved the others in regard to the clinical tissue characteristics (reduction of edema and exudate).	Sugar has antibacterial and healing properties, with inactivation of fetid odor and edema. This also reduced costs in the treatment.	III
10[29]	To determine the antimicrobial efficacy (*in vitro*) of three types of sugars, as well as to conduct a randomized clinical pilot study to develop a protocol.	Experimental study (*in vitro*)	The tests demonstrated that the sugar inhibits the bacterial growth and substantially reduces both odor and pain.	It aims to develop a randomized clinical trial protocol (RCT) and suggests the efficacy of the sugar in cleaning the wound, as well as its safety in patients with diabetes mellitus type II.	III

*Melnik BM, Fineout-Overholt E, 2005.

Regarding the year, most of the studies were undertaken between 2000 and 2010 (80%) and the others in 2011 (10%) and 2012 (10%); thus one may observe a concern with the investigatory question, that is, with analyzing sugar's effect on healing and on reduction of microbial load in infected wounds, mainly verified in experiments in the animal model.

According to the results presented in Charts 2a to 2c, the present study evaluated, in the various concentrations (0.01; 0.1 or 1M) of sugar that there were neither benefits nor harm in the formation of granulation tissue in an animal model involving experimental randomized wounds[20]. In the studies of other researchers there is reflection about the genuine efficacy of the direct application of sucrose in wounds, considering the variety of mixtures of sugar with other antiseptic substances such as povidone-iodine, essential fatty acids, and honey[21].

Overall, it is possible to infer that there is consensus among randomized controlled experimental studies (RCES) regarding the effectiveness of sucrose in infected wounds; however, there is a gap in relation to the possibilities regarding concentration of use, frequency of changes of dressings, and the toxicity or not of sugar associated with other antiseptics, as well as the absence of comparative statistical data between the research subjects in these RCTs[20,22-24].

It was verified that nurses had difficulty in choosing to use sugar, whether it was granulated, refined or brown in the treatment of infected wounds, as

well as in indicating other complementary or alternative therapies[21]. Also considered is the role of the Internet, that does not always supply reliable information on what to evaluate in the application to the wound bed, product concentration and frequency of changes of dressings. Although there are some studies which substantiated the efficacy of sucrose in the forming of granulation tissue and re-epithelialization, as well as in the reduction of infection and fetid odor in tissue lesions, there is still a need for more knowledge of this issue through clinical trials[20,22-28].

DISCUSSION

In the literature evaluated, most of which was experimental in the animal model, both notable tissue repair and positive modelling in the inflammatory response were verified with the use of sucrose[20,22,25,28,30].

It should be noted that in the presence of a tissue lesion, the physiological process of healing is universal, with a sequence of physical, chemical and biological reactions. This series of prominent and dynamic reactions, whether inflammatory, fibroblastic or of maturation, aims for reconstitution in the tissue continuity through the ideal temperature, hydration, appropriate conditions of oxygenation, and nutrients[3,31-32]. When healing is delayed, deficiency or inexistence of obstruction of the wound occurs, thus extending the physiological period of healing[12].

It is considered that healing is intimately related to the patients' metabolic profile, as there is a delay in the process of tissue repair and development of infection in individuals with chronic non-transmissible diseases or extremes of age, whether associated or not with co-morbidities. This fact is corroborated in the study in which patients with complete surgical dehiscence with evisceration, as well as a picture of serious malnutrition and advanced age, presented delays in the healing process, and bacterial infection in 60% of the cases identified[3].

It must be considered that sucrose has bactericidal action, as in the presence of formic, malic and lactic acid, it exhibits an acid pH and an environment which is unfavorable to the development of microorganisms[3]. In this regard, sugar was efficacious for the treatment of infections, due to the inhibition of bacterial growth; greater intake of nutrients for the cells; activation of macrophages; acceleration of debridement of the devitalized tissue and greater collagen synthesis[22,33].

One can add one *in vitro* study[29] with a variety of forms of sugar (demerara, beetroot sugar and granulated cane sugar) to determine the Minimum Inhibitory Concentration (MIC) regarding 18 bacteria (gram positive and negative), using different concentrations (0.38-25%). Thus, they verified that these were effective in the inhibition of bacterial growth and safe to use with patients with diabetes mellitus type II.

At the same time, specialists investigated the use of sucrose and honey, evidencing that honey favors healing through cell division, the synthesis and maturation of collagen, in the epithelialization of the wound and its acidity (pH<4), which in its turn allows bacterial lysing through activation of the macrophages[27,34]. In one descriptive and comparative study, on the healing effects of honey in patients with septic surgical wounds, it was verified that this eliminated colonized microorganisms, as well as treating and healing other septic wounds, irrespective of where they were located[27].

Given the diversity of antiseptics used in infected wounds, an experimental randomized study[20] was held, in the animal model, regarding the inflammatory response of post-surgical cutaneous wounds treated with sugar and essential fatty acids (EFA) and it was ascertained that there were no differences in the

investigatory response between the substances used. However, it was verified that the sugar and the EFA contribute to the repair and restoration of the tissue's permeability barrier due to stimulating peroxides produced from the substrates of the sugar and EFA[20,26].

It is added that researchers[23,33] conducted experimental studies, in the animal model, with a paste containing sugar and povidone-iodine (PI) in order to ascertain its healing action in cutaneous ulcers with *Staphylococcus aureus*, and evidenced its anti-inflammatory (reduction of edema, exudate and local pain) and antimicrobial efficacy. It should be noted that some bacteria[35] produce toxins which are lethal to tissue, for example *Pseudomonas aeruginosa* which liberates pyocyanine (a substance which triggers alterations in cellular respiration and toxicity 30 times greater than an antiseptic solution). *S. aureus*, on the other hand, liberates the alpha toxin (λ) which causes alterations in cellular respiration, as well as a dermal lesion.

In one editorial study[21], the issue was evaluated reflexively through evidence-based-practice (EBP) and it was evidenced that the sugar reduces odor in wounds, facilitates debridement, and accelerates the forming of granulation tissue and epithelialization, among other benefits. Nevertheless, the majority of eligible studies are experimental without randomization and/or group control, while the others are descriptive or case studies. It is added that only one study obtained a representative sample, and, some of the others selected from the EBP did not present statistically-significant data regarding the sample, that is, the research subjects. In addition to this, the application of sugar variety, as a result of its direct application in a paste (mixture of sugar with other antiseptics) making it arduous to analyze the efficacy of the sugar itself. The well-known divergence between the frequency of changing the dressing and irrigating the wound also stands out, as well as the continuance of the doctor's decision in the use of sugar in wound therapy.

Sucrose, whether presented as refined sugar, granulated sugar or brown sugar (unrefined muscovado sugar), or as paste or honey, evidenced an effective antimicrobial action due to the hyperosmolar formation where it was applied, minimizing the fetid odor in infected wounds, and accelerating the healing process.

As a result, it is necessary to examine, in particular in the scientific literature, the standardization of protocols with povidone-iodine and hydrogen peroxide with sugar (paste) in the effective reduction of microbial load and cytotoxic effects in the fibroblasts in tissue repair, as the gap in relation to variation and/or absence of concentration and volume of sugar used in the wound bed and the frequency of changing dressings is evident.

CONCLUSION

In the light of the literature analyzed, it is noted that there is a need for greater investment in controlled randomized clinical studies, such that it may be possible to genuinely clarify not only aspects of antimicrobial activity of alternative therapies, but also aspects of the healing time, the form and concentration of use, the frequency of changing of dressings and the clinical action in injured tissue.

COLLABORATIONS

Rossi GO, Cabral DB, Shimura CMN and Andrade D contributed to the conception, analysis, interpretation of data, editing of the article, and the final approval of the version to be published.

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