Use of biological products in the healing process of skin lesions

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ABSTRACT

Research in the chemical and techno-pharmacological sector has allowed the use of medical devices based on biological products in the various phases of the tissue repair process of acute and chronic wounds. Neem and St. John's Wort oil, Aloe vera, essential fatty acids are applied to the wound only after non-vital tissue has been removed and in the absence of biofilm and/or infection. Honey, on the other hand, is used in the debridement phase thanks to its biological-natural properties and the ability to draw water from the tissues surrounding the lesion, thus allowing the detachment of the non-vital tissue from the wound bed (autolytic debridement). In the presence of biofilm or wound infection, the only indicated debridement is surgical. The study evaluated the possibility of using the autolytic properties of honey on lesions even in the presence of biofilm or local infection, demonstrating how such use is possible especially in patients in whom surgical debridement is contraindicated.

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Introduction

Research in the chemical and techno-pharmacological sector has allowed the use of medical devices based on biological products in the various stages of wound bed preparation.

The term Wound Bed Preparation (WBP) indicates the set of wound management procedures with the aim of removing obstacles to the repair process and accelerating the endogenous healing processes. The cornerstone of the WBP is the T.I.M.E. acronym that includes the procedures to be applied in the therapeutic management of the lesion.

The products of biological derivation can be used in the different phases of the T.I.M.E.[1]

Neem and St. John's wort oil, aloe vera, essential fatty acids and honey are used in the management of Chronic Skin Lesions (CCL).

Some of these products, Neem and St. John's wort oil, aloe vera, essential fatty acids are applied to the wound only after removing the factors hindering healing such as the presence of non-vital tissue, the presence of biofilm or infection.

Honey can be used in the presence of non-viable tissue due to its debridement action on the wound bed.

The removal of non-vital tissue from the wound bed (debridement) is a fundamental step in the tissue repair process.

Non-viable tissue provides an excellent substrate for bacterial growth, increases the risk of infection, prolongs the inflammatory phase, delays progression to the proliferative phase, hinders neoangiogenesis, and forms a mechanical barrier to contraction and impedes re-epithe-

lialization.[2]

The removal of non-vital tissue can be performed through different debridement methods: surgical, mechanical, autolytic, enzymatic, biological.

The choice of the type of debridement is influenced by various parameters: the care setting, the type of lesion, the state of the lesion, the operator's experience and the patient's conditions.

In relation to the debridement to be used, different medical devices can be chosen: hydrogels and hydrocolloids in the autolytic debridement, collagenases in the enzymatic one, *Lucilia Sericata* larvae in the biological one.

The use of honey can be framed as a bio-autolytic debridement in relation to its biological-natural properties and the ability to draw water from the tissues surrounding the lesion thus allowing the detachment of non-vital tissue.

It is well known that in the presence of biofilm or infection of the wound, the only debridement indicated is surgical but, in this study, we wanted to evaluate the ability of honey to carry out a debridement on the bottom of the wound even in infected ulcers, taking into account the antibacterial properties some honey.[3]

The aim of the study was to evaluate the possibility of using honey in the wound debridement process even in the presence of signs of significant bacterial load.

Materials and Methods

19 patients affected by cutaneous ulcerative lesions of different etiology were enrolled: venous, decubitus and iatrogenic for a total of 25 lesions, 6 patients having multiple lesions.

Of the 25 injuries, two were pressure injuries, located on the heels, while the two iatrogenic ones were located in the elbow crease and the upper third of the leg, in correspondence with the tibial crest.

The presence of local clinical signs of increased bacterial load or biofilm were not exclusion criteria.

For the diagnosis of local infection (biofilm), the following clinical signs were evaluated: the non-progression of the wound edges, an excess of serous-corpuscular exudate and a friable, often overabundant and bright red granulation tissue.

Lesions of ischemic genesis were excluded, for which it was decided to refer them to vascular surgery centers for possible revascularization.

Lesions were included in the study which, according to the Falanga score, in relation to the presence of granulation tissue and non-vital tissue, belonged to classes D (absent), C (less than 50%), B (between 50 and < 100 %) (Table 1).

Of the 25 lesions treated, according to the Falanga score, 12 were classified as D, 10 as C and 3 as B.

There were 12 lesions with objective signs of localized infection/biofilm.

The dressing procedure involved cleansing the wound and the perilesional skin with a Polyhexanide and Betaine-based solution, applying medical honey-based gel (Figure 1) or a honey-based dressing with alginate (Figure 1) to the wound base (Figure 2), protection of the perilesional margins with 10% zinc oxide cream, non-ad-

Table 1. Lesions examined and Falanga score.

Score	Granulation	Non-vital tissue	Exudate	N. ulcers
A	100%	Absent	-	-
B	50-99%	+	Partially checked	3
C	<50%	+	Not checked	10
D	Absent	+	-	12

Figure 1. Application of honey on the ulcer bed.

Figure 2. Alginate and honey dressing.

herent eudermic secondary dressing and sterile gauze in the wounds where the gel was applied.

The honey used in the study was that derived from Leptospermum, known as Manuka honey, in different types of preparation: gel containing 100% honey, gel containing 80% honey and 20% beeswax, dressing in calcium alginate and honey.

The dressing was performed every 24 hours while the assessment of the lesion, according to the Falanga score, was performed every 7 days.

In venous ulcers, a multilayer, multicomponent compression bandage with short-stretch bandages was prepared.

Results

By applying Manuka honey to the wound bed, it was possible to obtain the disappearance of non-vital tissue in 22 wounds (88%) (Figure 3, 4 and 5). In the remaining three lesions (12%) the treatment was interrupted due to the onset of burning which was not tolerated by the patient.

Figure 3. Biofilmed ulcer.

Figure 4. Application of dressing in alginate and honey.

Discussion

Biologically active, natural substances are increasingly used in the treatment of acute and chronic skin lesions.

Some of these such as Neem oil and Hypericum Perforatum are used, thanks to their biological properties, to stimulate cell proliferation once the lesion has been debrided.[4]

The regenerative properties of these elements would be linked to a component, hyperforin, an important active ingredient that promotes wound healing, thanks to its action on fibroblasts, on the proliferation and differentiation of keratinocytes.

The proliferative phase of the cellular repair process is preceded by one in which it is necessary to debribe the lesion to prepare the wound bed.[5]

Debridement is a fundamental moment of the tissue repair process and refers to the removal of bioburden from the wound bed, margins and perilesional skin.[6]

The choice of debridement must take into account the care setting, the wound bed, the condition of the perilesional skin, the patient's pain threshold, the emotional condition and the general conditions of the patient.[7]

Enzymatic debridement is performed in patients with wounds in which surgical debridement is not an available option or is contraindicated such as in patients using anticoagulants. Enzymatic debridement with collagenase is one of the most commonly used techniques in clinical practice.

In autolytic debridement, products with a dual mode of action are used: they can donate water to dehydrated wounds or recall liquids from surrounding tissues.

Hydrogels and hydrocolloids have a moisturizing effect which leads to swelling of the necrotic tissue and fibrin patina, facilitating its detachment.

Other products have an autolytic effect through the pos-

Figure 5. Application of product consisting of 80% honey associated with waxes and natural oils.

sibility of recalling liquids from the surrounding tissue thanks to the high sugar content which favors the balancing of liquids (hydration) from an area with a higher concentration to a drier area.[8]

Fluids are drawn to the surface from deeper tissues and this osmotic effect helps reduce edema (inflammatory state) while simultaneously allowing effective removal of devitalized tissues.

In general, this methodology is contraindicated in the presence of a significant bacterial load capable of delaying and/or blocking tissue repair.

In fact, the continuous presence of virulent microorganisms leads to a massive and persistent inflammatory response with the increase of cytokines with protease activity, which combined with the reduced activity of growth factors contributes to damage the host organism through a competition for the availability of oxygen and a release of toxins, causing local necrosis.

Enzymatic debridement, with collagenase, or autolytic, with hydrogels and hydrocolloids, is contraindicated in wounds with a high and significant bacterial load as it takes longer than surgical debridement, which is much faster.

In many situations, such as in patients taking anticoagulants or in particular healthcare settings, surgical debridement is not feasible and therefore there is a stalemate.

In the aforementioned situations it is possible to use honey-based products thanks to its antibacterial, anti-inflammatory and antioxidant properties.[9]

The use of honey for autolytic debridement even in the presence of significant bacterial load is due in the presence of bacteriostatic and bactericidal factors.

The antibacterial activity of honey is linked to several elements.

The pH of honey can limit and inhibit the growth of microorganisms. The pH value, between 3.2 and 4.5., depends on organic acids, inorganic ions, such as phosphate and chloride, ionized minerals and its botanical source (nectar and honeydew).[10] An alkaline pH (between 6.2 and 7.8) favors bacterial proliferation. Acidic pH, on the contrary, inhibits microbial growth, stimulates the bactericidal action of macrophages, reduces protease activity, increases fibroblast activity and activates growth factors such as TGF-β.[11]

The antibacterial activity of honey is further enhanced by the presence of hydrogen peroxide, lysozyme, phenolic acids, methyl glycoxal and defensin 1.[12]

The formation of hydrogen peroxide is determined by the relative levels of glucose oxidase, an enzyme which oxidizes glucose to gluconic acid and H_2O_2.[13] Hydrogen peroxide is responsible for the production of free radicals, which cause oxidative damage to bacterial cell walls. The catalase enzyme can block the activity of hydrogen peroxide as it breaks it down into oxygen and water. The antibacterial activity is however supported thanks to the presence of methylglycosal (MGO).

The concentration of methylglycosal which oscillates between 100mg/kg) and 900mg/Kg determines the greater or lesser antibacterial and immunomodulatory activity.[14]

Defensin binds to the membrane of target microorganisms in the form of multimeric pores leading to lysis of the target cell, also inhibiting the synthesis of RNA, DNA and proteins.[15]

The antibacterial activity of honey has been demonstrated in several human pathogens, including *Escherichia Coli*, *Enterobacter aerogenes*, *Salmonella typhimurium*, *Streptococcus aureus*.

In view of the antibacterial activity of honey, lesions with clinical signs of biofilm and local infection were included in the study, supported by studies demonstrating inhibition of bacterial growth using honey-impregnated discs or incorporating honey into agar plates.[17]

The type of non-vital tissue and the amount of exudate influenced our choice of technique and products used.

In lesions with dry, hypoexuding eschar, a gel containing 100% completely hydrophilic honey was applied to the lesion.

In the lesions with fibrin and/or slough, a product consisting of 80% honey associated with natural waxes and oils was used to give greater viscosity to the product.

In the presence of highly exuding lesions, a dressing consisting of honey and calcium alginate fiber was used, the latter capable of guaranteeing better management of the exudate.

In all wounds the margin and periwound skin was protected with 10% zinc oxide cream.

In the wounds with gel application, a non-adherent, eudermic secondary dressing plus sterile gauze was then applied.

In the wounds where the disposable medical device consisting of honey and calcium alginate was chosen, no secondary dressing was applied.

In 22 wounds, wound debridement was completed. In lesions with clinical signs of local infection, a reduction and progressive disappearance of the same was observed.

This result is to be related to the ability of honey to penetrate the biofilm and perform a bactericidal action on the microorganisms present on the wound bed.[18,19]

Three patients stopped the treatment due to the onset of unbearable burning.

It is known that the use of bee products for the production of cosmetics and medicines can lead to the occurrence of allergic reactions. Honey allergy is very rare but sometimes causes an IgE-mediated hypersensitivity reaction.[20]

Conclusions

The organic-biological characteristics of honey allow it to be used in the various phases of the T.I.M.E.

In the proposed study, its effectiveness in preparing the wound bed was evaluated, even in cases with local clinical signs of biofilm and a significant increase in the bacterial load.

It was not the objective of the study to evaluate the efficacy of honey in the proliferative phase but many studies have been published in the literature that support the efficacy of honey in the management of wounds related to the improvement of granulation and re-epithelialization considering the anti-inflammatory and antioxidant activity.[21]

The use of honey is, therefore, a low-cost topical therapy with an important potential for healing chronic skin lesions in relation to its debridement, anti-inflammatory and immunostimulant activity.

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