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Optimal Support of Wound Healing: New Insights

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Abstract
Background: The ultimate goal of wound healing following minor injury is to form a tissue regenerate that has functionality and visual appearance as close to the original skin as possible. The body's physiological response to any wound is traditionally characterised by three distinct steps: inflammation, proliferation and remodelling. ***Summary:*** New insights suggest that the three phases overlap (and even occur in parallel) in both time and space in the wound, necessitating a clinical approach that targets each stage simultaneously to ensure rapid repair and wound closure without further complications. Ingredients that exhibit activity across each of the three phases, such as dexpanthenol, are of value in the context of minor wound care and scar management. ***Key Messages:*** In addition to treatment and ingredient selection, it is also important to consider broader clinical best practices and self-care options that can be used to optimise the management of minor wounds. An individualised approach that can account for a patient's unique requirements and preferences is critical in achieving effective wound recovery.

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An Introduction to the Wound-Healing Process: A Complex Interplay

Superficial damage to the skin occurs frequently for a variety of reasons. The process of wound healing, in which the skin barrier recovers and closes following injury, is traditionally described as occurring over three sequential phases: inflammation, proliferation, and remodelling [1, 2]. Inflammation, the first stage of wound healing, follows initial haemostasis and is essential for the recruitment of the innate immune system, which helps to defend the body from invading pathogens and remove dead tissue [1, 3]. During the proliferation stage, the wound surface recovers through re-epithelialisation, collagen synthesis, extracellular matrix (ECM) formation, and restoration of the vascular network [1, 3]. In the third and final remodelling phase, regenerative processes are downregulated and replaced by reorganisation of the connective tissue and the initiation of the contractile response [1, 3]. In previous years, these phases were generally viewed as three distinct steps that occurred sequentially; however, more recent insights suggest that this traditional thinking is outdated. Rather, wound healing proceeds via a complex mechanism that starts immediately after skin injury, with the three phases overlapping (and even occurring in parallel) in both time and space in the wound [1, 3].

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The body's physiological response to wound healing, which comprises these three overlapping stages, ensures that wound closure occurs as quickly as possible to prevent further damage or infection [1]. Disruption of these physiological processes can result in the formation of complex wounds with healing disturbance, failure of or delayed wound closure, chronic wounds, and subsequently, excessive scar tissue, hypertrophic scars, or keloids [1, 3]. Hypertrophic scars are generally raised, red or pink in colour, and sometimes pruritic [4], as opposed to the more trivial fine-line scars that can be observed at the endpoint of mammalian tissue repair following superficial injury [5]. Keloids form when scars invade adjacent healthy tissue, and rarely regress over time [6]. The formation of keloids is a complex and poorly understood process that is influenced by several factors, including a patient's race, genetic disposition, and the location of their injury [7]. As well as significant physical impairment, the consequences of such disruptions to the wound-healing process can place a heavy burden on the quality of life of patients, along with a significant psychological impact that is often underestimated [8].

The body's natural response to skin injury can be supported through clinical intervention, the ultimate goal of which is to resolve the wound to form a tissue regenerate that has functionality and visual appearance as close to the original skin as possible within a reasonable timeframe [9]. Because formation of a "scarless" wound requires the involvement of stem cells, accomplishing this goal can be very difficult to achieve in practice, and is feasible only in instances of superficial epidermal injury [10]. By contrast, wounds that involve substantial parts of the dermis and dermal blood vessels typically heal with a scar that can be aesthetically unpleasant, depending on size and body region [5].

Clinical practice to support wound healing varies considerably [11]. As each wound is different, management strategies should be adapted on a case-by-case basis, depending on the type of wound observed [12]. For example, some wounds are associated with a risk of infection, whereas others are not (e.g., those that are induced during a planned minor medical procedure in a sterile environment) [11]. However, this distinction is not always reflected in clinical practice. As few guidelines exist for the management of wounds, significant variation is observed in their treatment and care. In a UK community survey of more than 3,000 patients, substantial variation was observed in the care of complex wounds, which was attributed to underuse of evidence-based practices and overuse of practices not supported by robust clinical evidence; in light of these findings, the authors highlighted the need to invest in wound-healing strategies that have a strong scientific basis, and conversely deprioritise those that are supported by little to no evidence [13]. In addition, the vast number of treatment options available for acute wounds may also contribute to this lack of clarity in management strategies, as well as the number of individuals involved in wound care, including healthcare professionals and the patients themselves [11].

The overall objective of this article is to provide an overview of the latest insights into the wound-healing process and discuss how these insights can be effectively translated into clinical practice. Moreover, several strategies exist to improve wound-healing outcomes, with this article focusing primarily on the well-studied pantothenic acid analogue dexpanthenol as a means to optimise the management of minor wounds.

New Insights for Managing Wounds

To reflect the complex interplay that comprises the three phases of wound healing occurring concurrently, approaches to wound management should target different aspects of each phase simultaneously. This strategy should therefore involve:

- Protection from infection.
- Protection from free radicals.
- Modulation of inflammation.
- Support of cell proliferation and acceleration of migration.

Protection from Infection

Unless a wound is induced in a sterile environment (such as during surgery), there is some risk of wound infection, depending on several exogenous factors. These include an individual's general health status, whether or not they suffer from an underlying condition that affects immune competency, tissue viability in the area surrounding the wound, time to treatment or access to healthcare, and the species and quantities of bacteria contaminating the wound site [14]. While the skin's own microbiome and antimicrobial lipids and peptides can protect healing tissue from disease-causing microorganisms and can accelerate the wound-healing process [15, 16], wound infection leads to tissue damage and an impaired immune response, which can further delay wound healing [9].

A biofilm, defined as a group of surface-adherent bacteria that are encased in and protected by a self-produced extracellular polymeric substance, exhibits reduced susceptibility to antimicrobial agents, as well as the body's own immune response [17]. Biofilms can form in wounded tissue exposed to bacteria within 8 h and can become associated with deep-seated and difficult-to-treat wound infections [17, 18]. Biofilm formation impairs the immune response by blocking neutrophil access to the wound site, delays re-epithelialisation, and hinders the development of granulation tissue [17]. These individual mechanisms collectively result in significant delays in the wound-healing process.

Protection from Free Radicals

Reactive oxygen species (ROS) are produced after skin injury and exhibit broad activity during the wound-healing process that helps to prevent or minimise wound infection [19]. ROS are able to act as secondary messengers for both immune cells and non-lymphoid cells required at the wound site, facilitate effective tissue repair, regulate angiogenesis, and can prevent pathogen colonisation [19]. However, excessive ROS release can damage healthy epithelial cells and interfere with wound repair [19, 20]. Therefore, it is important that ROS levels are carefully regulated throughout the wound-healing process in order to provide effective protection without exhibiting a detrimental effect on healthy tissue.

Modulation of Inflammation

Balance is also critical in the context of the inflammatory phase of wound healing. Inflammation is a natural response of the body's immune system and an essential first step in initiating the healing process [21]. For example, interleukin (IL)-6, a cytokine with both pro- and anti-inflammatory properties, has been shown to play a critical role in the wound-healing process, with knock-out mice deficient in IL-6 exhibiting impaired leukocyte infiltration, re-epithelialisation, angiogenesis, and collagen accumulation, and thus reduced epidermal barrier repair [22, 23]. Wound healing involves a complex and sensitive balance between activation and inhibition of inflammation that needs to be adjusted based on the local microenvironment within the wound [21]. Because inflammation is intimately linked to the extent of scarring, it requires careful modulation [21]. Although scar formation is a normal physiological response to deep injury of substantial parts of the dermis and intradermal blood vessels, chronic inflammation results in excessive and unbalanced cellular proliferation and collagen deposition, which can lead to unrestrained scar tissue formation [1, 21, 24, 25]. Maintaining this delicate balance is therefore of paramount importance in successful wound healing.

Following skin injury, platelets encounter exposed collagen and other elements of the ECM, triggering the release of clotting factors, essential growth factors, and cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β) [26, 27]. These growth factors are key regulators of cellular functions, including proliferation, migration, and differentiation. Following haemostasis, neutrophils infiltrate the wound site and initiate phagocytosis to remove foreign materials, potential pathogens, and damaged tissue. As part of this inflammatory phase, macrophages are also recruited to maintain phagocytosis, as well as releasing further PDGF and TGF-β [27].

The production of several key components of the ECM, such as collagen and fibronectin, is promoted through the activity of PDGF and TGF-β_1, a specific isoform of TGF-β [28]. Conversely, matrix metalloproteinases (MMPs), enzymes that are released from fibroblasts, macrophages, and neutrophils during tissue growth and turnover, promote collagen degradation [28], with MMP3 likely to be essential for wound re-epithelialisation through its role in wound contraction [29]. While TGF-β_1 inhibits the synthesis of MMPs, epidermal growth factor, when released by macrophages and platelets, stimulates MMP secretion [28]. Effective modulation of these components is critical when the healing process transitions from inflammation to proliferation and remodelling.

The correlations between elevated TGF-β_1 and wound healing impairment and the formation of hypertrophic scars are well established. Loss of TGF-β_1 signalling has been observed in chronic, non-healing wounds [30, 31], and hypertrophic scar tissue, as well as fibroblasts extracted from it, have been shown to produce more TGF-β_1 mRNA and protein than fibroblasts derived from normal skin [32]. As well as elevated TGF-β_1 expression, hypertrophic-derived fibroblasts exhibit prolonged expression of the TGF-β receptors compared with normal skin [32]. The stimulatory effects of TGF-β_1 on the expression of the ECM components and its inhibitory effects on the expression of MMPs in fibroblasts leads to the accumulation of excessive collagen fibres within the wound sites, and subsequently, the formation of hypertrophic scars [28].

Support of Cell Proliferation and Migration

As inflammation resolves and infection risk is mitigated, wound healing transitions to proliferation to initiate wound closure, barrier repair, and restoration of the vascular network [3]. Increased proliferation and migration of different cell types involved in wound healing and re-epithelialisation, including fibroblasts and keratinocytes, ensures that wound healing occurs efficiently [3, 21]. Keratinocytes secrete structural proteins to rebuild the basement membrane of the ECM, whereas fibroblasts play a central role in the formation of granulation tissue, which close the wound and provide a structural platform for cell adhesion, migration, growth, and differentiation as the wound proceeds to the final stages of repair [3].

Dexpanthenol: A Vehicle for Translating New Insights into Practice

Wound Management before Wound Closure

Protection from Infection

Where there is risk of wound infection, cleansing and disinfection with an antiseptic is an important first step in the treatment of minor wounds [11]; this should be completed as soon as possible after the time of wounding and continue until the risk of infection is mitigated. However, because some antiseptics can cause damage to healthy tissue, they should only be used in instances where a wound is at risk of becoming infected [33]. Use of a mild antiseptic in the correct concentration in conjunction with preparations containing compounds that promote epidermal keratinocyte proliferation may help to counterbalance these effects and help protect healthy tissue. Dexpanthenol, a precursor and alcohol analogue of D-pantothenic acid, can aid in restoring the skin barrier [34] to prevent disease-causing microorganisms reaching the dermis and subcutaneous tissue.

Protection from Free Radicals

The body needs to tolerate the free radicals that fight infection, while concurrently protecting itself from their harmful effects. Dexpanthenol may aid this process by decreasing the production of ROS and minimising tissue damage. An in vitro experiment found that both panthenol and pantothenic acid inhibited nicotinamide adenine dinucleotide phosphate-dependent ROS production in human skin fibroblasts [35]. Panthenol comes in two enantiomers, D and L [36]. Only D-panthenol (dexpanthenol) is biologically active; however, both forms have moisturising properties [36]. The upregulation of the cytoprotective, anti-inflammatory protein HO1 (a product of HMOX-1) after panthenol or pantothenic acid treatment was also reported, and a functional assay showed a post-treatment decrease in the formation of ROS [35]. However, data demonstrating the effect of dexpanthenol on ROS in vivo are currently lacking and dexpanthenol, panthenol, and pantothenic acid have not been compared directly, so further research is required to draw more definitive conclusions around this activity.

Modulation of Inflammation

As inflammation must be carefully regulated throughout the wound-healing process, compounds that support the body's own modulatory processes are of value in wound-healing preparations. Dexpanthenol can alter the expression of both pro- and anti-inflammatory genes, so they can support the body's natural response as it regulates inflammation following injury. The gene expression data from both in vivo and in vitro studies indicate that treatment with dexpanthenol, or calcium pantothenate, upregulates the expression of genes that function across the three phases of wound healing, including the pro-inflammatory cytokines IL-6 [37] and IL-1α [38], and HO-1 [35]. Data from IL-6 knock-out models have demonstrated an important role for IL-6 in wound healing [22], and the upregulation of IL-6 in dexpanthenol-treated human skin biopsies further confirms this critical role [37]. Increased expression of the *MMP3* gene is also of particular interest in the context of the overlap of the inflammatory and proliferative stages of wound healing, as the MMP3 protein is involved in re-epithelialisation and fibroblast recruitment, initiation of wound contraction/angiogenesis, and the downregulation of inflammatory mediators in macrophages [39, 40]. After skin injury, *MMP3* levels decrease [41], but this effect may be counteracted by topical treatment with dexpanthenol-containing ointment, which has been shown in vitro [38]. Dexpanthenol may therefore contribute to the modulation of the inflammatory phase of wound healing. However, further in vivo studies are required to fully elucidate the complex gene expression patterns associated with dexpanthenol use.

Support of Cell Proliferation

Dexpanthenol supports the body's natural response to injury by initiating the proliferation of cells involved in wound healing and re-epithelialisation [42]. The addition of a medium containing 0.1% dexpanthenol to traumatised skin constructs led to the regeneration of epider-

mal cells and the formation of new cellular layers within 1 week, as assessed histologically [43]. In the medium-only control, a further decline in the structure of the multi-layer equivalent was observed, indicating that, in an artificial skin construct model, dexpanthenol can support the proliferation stage of wound healing [43]. In another study by Schmitt et al. [44], standardised lesions were induced with a non-sequential fractional ultrapulsed CO_2 laser in a full-thickness in vitro model of the non-keratinised mucous membrane. Unlike other studies, dexpanthenol and other proliferation-enhancing additives were removed from the culture medium in order to clearly discern the effect of the dexpanthenol-containing topical ointment [44]. In the dexpanthenol-treated group, wound closure was enhanced compared to the untreated controls, as assessed histologically [44]. Microarray and real-time qRT-PCR analysis showed a >1.5-fold upregulated expression of genes associated with wound healing, such as *CXCL10*, mucin protein family genes, and a retinoid acid receptor responsive gene *(RARRES1)* [44].

Culturing human keratinocytes in pantothenic-deficient medium suppressed their proliferation and reduced the expression of keratinocyte growth factor mRNA, compared with a control medium [45]. This suggests that pantothenic acid may promote the synthesis of keratinocyte growth factor and the proliferation of keratinocytes [45]. Furthermore, calcium pantothenate enhances the proliferation and migration of human dermal fibroblasts, as shown using in vitro skin models [35]. As part of human dermal fibroblast studies, dexpanthenol has also demonstrated a positive effect on wound healing by activating proliferation, increasing the rate of migration, and stimulating intracellular protein synthesis [35, 46]. Proliferation of dermal fibroblasts and keratinocytes is a key component of wound healing, responding to the inflammatory process and restoring the integrity of the skin barrier [47]. Measurement of the diameter of laser-generated lesions and visual evaluation of their appearance showed significantly improved re-epithelisation and appearance with a dexpanthenol-containing ointment at days 1, 2, and 5 when compared with petroleum jelly [48]. However, this study was not blinded, and further clinical studies are needed to confirm the effects seen in vitro. In another study, use of a dexpanthenol mouthwash or gel three times daily did not significantly alter the dimensional change of denture-induced lesions [49]. Whilst the formulations used in this study may not have been optimised for the oral environment, nevertheless the existence of conflicting clinical data is highlighted.

Preparations containing dexpanthenol may expedite wound healing and reduce the time to wound closure, which is important in reducing transepidermal water loss (TEWL) and minimising the risk of infection [42].

Proactive Scar Management after Wound Closure

The use of occlusive silicone-based products for scar management is recommended following wound closure; these products provide hydration and prevent excessive collagen deposition by reducing inflammation [50]. A single-group, single-centre, open-label pilot study assessed the efficacy of a silicone-based panthenol-containing formula, with concurrent use of a massage ball, in improving the appearance of hypertrophic scars [51]. Subjective and objective assessment of hypertrophic scar healing after 8 weeks of treatment showed an improvement in scar appearance and skin hydration, in addition to a reduction in discomfort and TEWL [51]. However, the contribution of panthenol to scar management in this study cannot be easily distinguished. Use of a silicone-based anti-scar product is recommended for up to 1 year after wound closure to enable TEWL to recover to the levels observed prior to skin injury [50, 52]. This proactive approach to scar management is preferred to reactive treatment of fully developed hypertrophic scars or keloids [4].

Dexpanthenol increases lamellar lipid mobility and enhances fluidity in the lipid bilayers of the skin throughout the three phases of wound healing, which may also contribute to hydration of a fresh scar [42]. An experimental study with excised porcine skin reported that dexpanthenol treatment increased the molecular mobility of a number of the stratum corneum lipids and protein segments, enabling the stratum corneum to adopt properties of a hydrated skin, even in dehydrated conditions [53]. Dexpanthenol is thought to interact with lipid segments of the extracellular lamellae and protein residues in the corneocytes in the stratum corneum, thus compensating for reduced hydration by maintaining (or increasing) molecular fluidity [53]. A randomised, double-blind, placebo-controlled study assessed the efficacy of two topical formulations of dexpanthenol on epidermal barrier function [34]. After 7 days of dexpanthenol treatment, stratum corneum hydration was significantly improved and there was a significant reduction in TEWL [34]. TEWL is a marker of skin barrier disruption [54], which is a superficial wound. This study supports the favourable impact of dexpanthenol on superficial, epithelial wound healing and hints to increased epidermal hyperproliferation and differentiation and increased epidermal lipid synthesis, both necessary for repair.

Although not required for the management of minor wounds, other strategies may need to be adopted for the management of hypertrophic scars, such as pressure garments, topical corticosteroid injection, radiation, excision, and laser therapy [4].

Other Key Considerations for Optimal Wound-Healing Support

In addition to selecting treatments (or indeed ingredients) that act on the three stages of wound healing simultaneously, it is also important to consider best practices in wound management that facilitate rapid skin recovery without complications.

All wounds, regardless of size, severity, location, and cause, should be treated as soon as possible following skin injury. Early intervention can support the rapid onset of the body's natural response to wounding. Moreover, bacterial infections can develop into biofilms rapidly, so the speed of clinical intervention must correspond to this [55].

As part of the effort to optimise the clinical support for all wounds, it is important to show special consideration for certain patient groups, such as individuals with diabetes. High glucose levels have been associated with an increased risk of wound infection in humans and animal models [56, 57]. The impaired wound healing observed in people with diabetes is associated with a multitude of factors, including afferent and efferent neuropathy, vascular disease, and foot deformities [58, 59].

The potential psychological impact of scar tissue formation on patients is also an important consideration. Although often trivialised, scars can be associated with anxiety and depression, loss of self-esteem, stigmatisation, and disruption of daily activities, placing a heavy burden on an individual's quality of life [50]. This is of particular importance in scenarios in which hypertrophic scars and keloids are located in areas that are visible, such as the head, lower arms, or lower legs [8].

Influence of pH on Wound Healing

Finally, the broader characteristics of topical preparations used to manage minor wounds, such as pH, must also be considered. Maintaining an acidic pH in the stratum corneum is of paramount importance for preserving epidermal barrier homeostasis, the regulation of cytokine signalling, and effective wound healing [60, 61]. In chronic wounds, a more alkaline pH is observed, so topical acidic preparations are of value in supporting the natural wound-healing process by normalising the skin pH and restoring the skin barrier [61, 62]. Because wound healing is a complex process that can be influenced by several factors, a topical preparation's pH and its other properties may modify the microenvironment of the wound (i.e., acceleration of healing and prevention of further infection). The pH of healthy skin is acidic at its surface [62], which supports the body's natural wound-healing process by inhibiting the growth of pathogenic bacteria, as well as reducing proteolytic activity and promoting the growth of fibroblasts [62]. However, wounding causes the deeper, more alkaline layers of the skin (pH 7.4) to become exposed, creating a microenvironment that supports the colonisation by pathogenic bacteria, which require a pH >6 to grow effectively [61, 62]. Therefore, wound-healing preparations with a lower pH present a targeted approach that supports the natural wound-healing process [62].

Conclusion

New research into the process of wound healing (across inflammation, proliferation, and remodelling) has highlighted the importance of intervention at all three phases, with multiple simultaneous actions required as soon as possible after injury, continuing until wound closure and beyond. Wound management preparations should actively modulate the three phases of wound healing, and several strategies exist that can support the body's natural processes, including use of dexpanthenol. In vivo and in vitro data suggest that dexpanthenol may assist wound healing in all three stages by modulating inflammation, supporting cell proliferation, and protecting against infection and free radical damage. Dexpanthenol supports the remodelling phase and contributes to the prevention of scarring through its hydrating properties. However, additional data from systematic studies in humans is required to fully elucidate the mechanism of action of dexpanthenol and support its efficacy in wound healing. If there is risk of a wound being infected, an antiseptic should be used as soon as possible after injury, ideally in combination with a compound that promotes epidermal keratinocyte proliferation, such as dexpanthenol; this should be continued until wound closure to reduce the risk of wound infection. Present guidelines for the management of wounds do not recommend the use of supplementary products to increase wound healing. Updated guidelines to educate clinicians, pharmacists, and patients on these new insights may be required.

Key Message

Wound management preparations should actively modulate the three phases of wound healing.

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J.M.B., M.G., and E.P. made substantial contributions to the conception of this article, drafted and critically revised it for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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