Topical Management of Chronic Wounds

The treatment and management of wounds represent some of the earliest recorded attempts at medical care. Topical treatment of wounds and remedies for infection are recorded as far back as 1650 B.C. The Edwin Smith Surgical Papyrus (which in itself is a copy of an even older document) mentions the use of honey, lint, and grease for the treatment of wounds. During his time as a practitioner in the 4th and 5th centuries Hippocrates described pouring wine or vinegar into wounds to prevent infections.[1] Though some of these ancient treatments are still in practice in one form or another in modern times, there have been many developments in wound treatment as our understanding of wound repair and infection has improved. In this clinical review we will discuss active ingredients commonly used to facilitate wound healing and evaluate what data current exists to support their efficacy.

Wound healing consists of three general steps: inflammation, proliferation, and maturation.[2] Inflammation can last up to 3 days in healthy patients. This stage includes the clotting cascade (platelet aggregation, adhesion, and release of thromboxane, prostaglandins, and other healing factors) followed by vessel dilation to allow other components to reach the wounded area. The immune system including white blood cells like leukocytes, phagocytes, and macrophages migrate to the site of injury where they work to prevent infiltration by microbes and clean up cellular debris resulting from damage to the site.[2] Proliferation, the next stage, happens immediately following inflammation stage and can last up to 4 weeks. During this stage fibroblasts and endothelial cells migrate to the edge of the wound, granulation - the new formation of blood vessels and connective tissue - begins, and epithelialization on the wound surface commences. At the end of this process of collagen synthesis and deposition there is generally a red, puckered scar.[2,3] Maturation, also sometimes called the remodeling stage, is the stage during which granulation tissue is replaced with collagen and elastin. Generally, wound management occurs primarily in the inflammation and proliferation phases. After the maturation phase, the focus tends to be on mitigation and management of scars and scar tissue.[2,3] This clinical review will discuss treatment at these steps in the context of ulcers, abrasions, sores, and other minor injuries or wounds. Larger or deeper wounds may require sterile treatments, and such wounds are not addressed in this review.

Different wound types can require different treatments, but generally the treatment consists of removing necrotic tissue if necessary, keeping the wound moist but avoiding maceration, determining the appropriate dressings or topical treatments needed to manage the wound, and preventing infection, or if one has already manifested, treating infection. Additionally, if the wound was caused by ongoing conditions, such as can be the case with pressure ulcers, management of risk factors such as sedentary time or excessive time in one position can be important. In this newsletter we will be primarily focusing on active ingredients used for wound healing, rather than specific dressings or debridement.

Common active ingredients used for the topical management of wound healing include aloe vera, calcium channel blockers (such as nifedipine), pentoxifylline, misoprostol, phenytoin, and topiramate. Some emerging agents such as naltrexone, are also being studied for their potential utility. Wound healing preparations also frequently include antibiotics or ingredients for pain management.

Aloe Vera promotes wound healing via vasodilation, antimicrobial effects, enhanced collagen synthesis in granulation tissue, and reduction of inflammation.[2,4,7] There is a plethora of small-scale study and animal trial data to support the wound healing capabilities of aloe vera both as a direct extract and from powder concentrate products. High quality trials on aloe vera are more limited, but one randomized double-blind controlled trial comparing aloe vera powder 0.5% in gel form to placebo found statistically significant improvements in epitheliazation time and accelerated healing in skin graft donor-site wounds.[11] One

placebo-controlled study in rats compared saline solution to 25mg/ml and 50mg/ml aloe in gel form applied for 10 days. A dose-dependent increase in collagen was observed in the lesions treated with aloe vera. Rats treated with aloe vera also had decreased scar tissue and better skin elasticity compared to controls.[5] An in vitro study evaluating the efficacy of aloe vera gel against herpes simplex virus found concentrations ranging from 0.2-5% all to have significant inhibitory effect on viral replication.[8] Aloe Vera powder extracts have also been studied for potential wound healing capabilities. One study in rats on aloe vera 2% powder extract in a gel found an aloe vera gel product combined with amniotic membrane significantly enhanced burn wound healing both in vitro and in vivo.[9] Another study evaluating the effect of aloe on healing anal fissures tested aloe powder 0.5% in a cream applied three times daily for 6 weeks found statistically significant healing by the end of the first week as compared to the control group.[10]

Calcium channel blockers such as nifedipine and verapamil have also been studied topically for wound healing. These agents are thought to help in part by inducing local vasodilatory effects, improving blood flow to wounds resulting in improved healing time.[12] Additionally, calcium channel blockers increase the production of nitric oxide (NO) which plays a role in the regulation of collagen synthesis, angiogenesis, and extracellular matrix formation.[14] Several cases in humans including one case in a 43 year old woman with diabetes who applied 8% nifedipine gel twice daily resulting in accelerated healing of an open wound on her foot and another in which a boy undergoing multiple surgeries for club foot demonstrated increased healing associated with the application of 2% nifedipine gel twice daily.[12] More recently, higher quality evidence in the form of a randomized, double-blind placebo controlled trial on patients with stage I or II pressure ulcers evaluated nifedipine 3% topical ointment twice daily for 14 days vs placebo. The study found even at just 7 days the nifedipine group had a statistically significant decrease in pressure ulcer size as compared to the placebo group and this effect persisted through the end of the study (day 14).[13]

Verapamil, a common topical option for management of scarring, has also been studied as a topical option for wound care. One study of verapamil HCl 1mg/g gel compared to silicone gel and control over a 14-day period in mice found that verapamil treated mice had increased capillary and vessel formation compared to the control and silicon alone groups as well as faster wound healing overall. Interestingly, the silicon gel group did note increased expression of wound healing markers over the control group as well.[14] Another animal trial in rats looked at verapamil 5% gel applied daily for 15 days compared to control (vehicle only) and a no treatment group. Density of collagen and wound closure rate was significantly faster in the verapamil group as compared to the control or no treatment groups.[15]

Another common ingredient that works by effecting blood flow to the wounded site is pentoxifylline. Pentoxifylline has been studied both topically and orally for wound healing. It is thought that pentoxifylline enhances blood flow to wounded area via several mechanisms including increased deformability of red blood cells, reduced vasoconstriction, and reduced blood viscosity.[16] One randomized double-blind, placebo-controlled trial of 112 critically ill patients with stage I or II pressure ulcers found that pentoxifylline 5% ointment applied twice daily for 14 days significantly improved the severity and size of pressure ulcers as compared to placebo.[17] Another trial comparing pentoxifylline 10% topical gel once daily for 14 days compared to a control group for treatment of stage II or III pressure ulcers found the pentoxifylline group had statistically significant higher rates of complete wound healing than control as well as significantly decreased wound size at both the one and two week timepoints.[18]

The mechanism of phenytoin for wound healing has not been fully elucidated. It is known that oral phenytoin can cause tissue proliferation (one of the side effects seen with this medication is gingival hyperplasia). Topical phenytoin appears to promote granulation, inhibit collagenase (thereby increasing collagen synthesis), decrease pain and inflammation, and perhaps even have something of an antimicrobial effect.[21] One study in patients with chronic venous ulcers evaluated a phenytoin 4% lotion product and found that once daily application resulted in statistically significant faster wound healing and higher rates of complete wound closure after 8 weeks compared to a control group. Side effects in the treatment group were mild and consisted of a burning sensation at the site of application for about 7% of patients.[19] Another study looked at the impact of topical phenytoin solution on pyoderma gangrenosum, a

chronic ulcerative skin disease. The study evaluated the impact of topical phenytoin 2% solution once in patients with treatment resistant pyoderma gangrenosum over four weeks. Treatment with phenytoin was found to result in complete resolution in four of six patients after four weeks and partial resolution was noted in the remaining two.[20]

Phenytoin has also been studied in combination with other ingredients for wound healing, such as misoprostol. Misoprostol is a synthetic prostaglandin E1 analog typically used for facilitating the healing of mucosal injuries such as stomach ulcers associated with nonsteroidal anti-inflammatory (NSAID) use. Prostaglandin is thought to play a mucosal cytoprotective role and modulate inflammation.[22] In addition to the data establishing its benefit for mucosal injury, some limited studies have looked at topical use for healing other types of wounds as well. One study of misoprostol 0.0024% in combination with phenytoin 2% gel in mice found that over a period of 9 days this treatment significantly reduced wound area as compared to a control group.[23] One case study evaluated the effect of phenytoin 3%, misoprostol 0.0024% gel (0.2mL applied twice daily for wound healing) and nifedipine 10% in PLO (0.6mL applied twice daily) in a 65 year old woman with a diabetic foot ulcer. Significant healing was noted at 2 weeks after application and by week 17 the patient was completely healed.[24]

Animal studies evaluating naltrexone HCl have also suggested a potential benefit for wound care. Naltrexone is thought to block the opioid growth factor receptor regulatory pathway. Overexpression of this pathway, which is common in patients with diabetes, has been shown to be associated with downregulated cell proliferation and slow wound healing.[25] One study of naltrexone 0.03% applied topically once daily found benefit as early as 48 hours in the treatment group and nearly complete wound closure by day twelve.[25] Studies in fish (specifically vieja maculicauda) also showed significantly improved wound healing with naltrexone HCl 0.04% ointment applied every 3 to 4 days for 35 days.[26] Currently, there are no clinical trials in humans, though, at least one case study reported efficacy of topical naltrexone topically for wound healing.[27]

Other active pharmaceutical ingredients that have shown promise in animal trials include arginine and topiramate. Similar to calcium channel blockers, arginine increases total NO and vascular endothelial growth factor (VEGF). Though not focused on wound healing, a study investigating the impact of 12.5% L-arginine HCl cream applied to the feet twice daily for two weeks vs placebo found measurable increases in blood flow to application areas.[31] Poor blood flow is a major factor in slowed healing in patients with diabetes, making this a promising finding. A study in mice comparing oral L-arginine HCl (1g/kg twice daily) to topical L-arginine 20% applied once daily found both groups to heal significantly faster than the control groups, though, the systemically treated group did see greater benefit.[32] Topiramate has also been shown in animal studies to increase angiogenesis and decrease inflammation.[33] A study looking at topiramate 2% applied once daily for 14 days found increased signs of wound healing in the treatment group based on various markers of inflammation.[34] Further studies in humans are needed to confirm the potential benefit of topiramate for wound healing.

Topical antibiotics are sometimes included in wound care preparations as well, though, their use is in some ways controversial. A meta-analysis comparing topical antibiotic treatment to no topical antibiotic treatment concluded that it was likely that topical antibiotics did reduce the risk of surgical site infection, though, the number needed to treat to prevent a single surgical site infection was 50.[28] Though the overall data suggests a relatively large number needed to treat for infection prevention, some studies on particular antibiotics are more promising. Specifically, metronidazole has been studied as a potential treatment for improving wound odor. One study evaluated 24 patients with malodorous malignant wounds and found that the application of 0.8% metronidazole daily significantly reduced odor associated with these wounds within four days of application.[29] Metronidazole has been found to improve odor associated with other types of wounds as well. Case reviews regarding the impact of metronidazole 0.75% or 1% applied two to three times daily on pressure ulcers have noted resolution of almost all cases of wound odor withing two to seven days.[30]

Formula ID	Formula
FA-13756	Phenytoin Sodium 5% - Nifedipine 2% Ointment
FA-13743	Metronidazole 2% - Lidocaine HCl 2% - Phenytoin Sodium 5% - Aloe Vera 0.2% Ointment
FA-13752	Pentoxifylline 5% - Lidocaine HCl 2% - Phenytoin Sodium 5% - Aloe Vera 0.2% Ointment
FA-12785	Metronidazole 2% - Phenytoin 5% - Lidocaine 3% - Misoprostol 0.0024% Ointment
FA-13758	Vancomycin HCl 0.33% - Lidocaine HCl 2% - Phenytoin Sodium 5% - Aloe Vera 0.2% Ointment
FA-13730	Lidocaine HCl 2% - Phenytoin Sodium 5% - Aloe Vera 0.2% Ointment
FA-24147	Verapamil HCl 1% Anhydrous Gel (Nourisil)

API and Range	
Aloe Vera[2-11]	0.5-2% Aloe Vera Powdered Extract applied up to three times daily or 2.5-5% Aloe Vera Extract
Arginine HCl[31]	Data is limited, 12.5% topical arginine HCl applied twice daily has been found to improve blood flow in diabetic patients
Metronidazole[29,30]	0.75-1% applied once to twice daily
Misoprostol[23,24]	Studied at 0.0024% twice daily in animal trials and case studies
Naltrexone HCl	Animal studies have evaluated 0.03-0.04% applied once daily or just once every three to four days
Nifedipine[12,13,24]	Studied at a wide range of concentrations 2-10% applied twice daily
Pentoxifylline[17,18]	5-10% applied once to twice daily
Phenytoin[19,20,24]	2-4% applied once two twice daily
Topiramate[34]	Data is limited, 2% applied once daily in animal studies
Verapamil HCl[14,15]	Data is limited, 0.1-5% applied once daily in animal studies

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