What’s New and Innovative in Wound Management: Problems and Solutions

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You can positively influence repair by selecting appropriate wound-management techniques, but first, you must understand the basic mechanisms underlying repair to better judge the validity of available therapies. Author’s address: Département de Biomédecine Vétérinaire, Faculté de Médecine Vétérinaire, Université de Montréal, C.P. 5000 St-Hyacinthe, Québec J2S 7C6, Canada; e-mail: christine.theoret@umontreal.ca. © 2006 AAEP.

1. Introduction
Traumatic wounds are challenging and often labor intensive for both horse owners and equine practitioners. A retrospective study of horses with traumatic wounds recently determined that primary closure was successful in only 24% of horses in which it was attempted.1 To compound the problem, repair of wounds by second intention is subject to numerous complications that compromise outcome in the horse, including chronic inflammation, poor contraction, development of exuberant granulation tissue (proud flesh), and slow epithelialization.

Wound repair begins the moment a cellular barrier is broken and follows a predictable pattern of synchronized and interrelated phases including the inflammatory phase, the proliferative phase, and the remodeling phase (Fig. 1).2

The estimated market share of wound-care products for humans was over $3,000,000,000 in 2005.3 This reflects the number of available products, many of which are exempted from stringent FDA testing as a result of their topical (as opposed to systemic) use. Although it is imperative that novel alternatives in wound management be offered to equine practitioners faced with this daily task, many commercially available products have not been rigorously evaluated and rely heavily on anecdotal evidence. Furthermore, one must bear in mind that because of the unique nature of wound repair in the limbs of horses, therapies beneficial to other species may not apply to the horse. The purpose of this in-depth review is to reflect on the new concepts and materials that have arisen from recent investigations into the physiology of wound repair in this species.

2. Therapy During the Inflammatory Phase
This is the phase during which the practitioner can exert the greatest influence. Inflammation is essential to protect against infection as well as to initiate the repair process. Through release of multiple cytokines and growth factors, the macrophage is attributed a key role in the transition between inflammation and repair. Paradoxically, excessive or prolonged inflammation may contribute to the pathogenesis of a number of diseases characterized by fibrosis and/or scarring (for example, the development of exuberant granulation tissue on the distal aspect of the limb of the horse). It has been shown
experimentally that inflammation in horses is weak but protracted\(^4\) and that horse leukocytes produce fewer reactive oxygen species essential to bacterial killing.\(^5\) They also produce lower levels of other mediators required to reinforce the inflammatory response and to induce tissue formation and wound contraction.\(^5\) In view of these facts, it may be wise to facilitate a strong, early inflammatory response to injury.

Debridement is an important step in the initial treatment of a wound, particularly when necrosis, exposed cortical bone, or frayed tendons are present; it can be achieved through surgical, enzymatic, wound dressing, laser, and biosurgical means. Debridement of non-viable tissue reduces the duration of the inflammatory phase. After thorough debridement, it is advisable to dress the wound briefly in an effort to accelerate biological processes. Bandaging can be combined with topical therapy to enhance the inflammatory response.

Wilmink et al.\(^6\) recently investigated the use of a protein-free dialysate of calf blood\(^a\) in deep wounds of horses. In the first 4 wk after injury, Solcoseryl stimulated repair by provoking greater inflammatory response, faster contraction, and faster formation of granulation tissue. Subsequently, it inhibited repair by delaying epithelialization and prolonging inflammation. The author recommends its use in the treatment of deep wounds during the initial phase of repair by second intention; treatment should cease when epithelialization predominates.

Dart et al.\(^7\) examined the efficacy of a hydrogel\(^b\) on second intention wound healing in horses. Hydrogels are made from materials such as gelatin or polysaccharide that are cross-linked with a polymer to form a sheet or gel. By enhancing the moisture content of necrotic tissue and increasing collagenase production within the wound, hydrogels facilitate autolytic debridement. Contrary to expectations, the hydrogel investigated in this study did not produce beneficial effects on healing of small full-thickness skin wounds on the limb of horses. A b,1–4 acetylated mannan,\(^c\) commercially available as a hydrogel, is likewise touted to enhance macrophage activity; it seems beneficial in the management of dog foot-pad wounds\(^b\) but has not been investigated in the horse.

A general strategy for improving wound repair may be through any molecule that can recruit or activate macrophages during the acute inflammatory phase. The trend of applying sugar or honey to open wounds dates back a long time and has recently acquired some scientific merit.\(^9\) Both products are chemoattractant for tissue macrophages and when applied to contaminated or infected wounds, may have antibacterial properties. Indeed, the stimulatory effect of honey may be imparted through up-regulation of various inflammatory cytokines within monocytes.\(^10\) Both sugar and honey have been shown to enhance fibroplasia as well as epithelialization. A synthetic form of sugar, Maltodextrin N.F.,\(^d\) is commercially available. On application, Intracell works by mixing with wound exudate to form a semi-permeable barrier, and thus, it maintains moisture while protecting the wound from environmental contaminants. Furthermore, it attracts endothelial cells, fibroblasts, and epithelial cells to minimize scarring and reduce the incidence of proud flesh. Although anecdotal evidence is encouraging, no scientific studies have been conducted to evaluate the efficacy of natural or synthetic sugar in the management of horse wounds.

Ketanserin,\(^e\) a serotonin receptor, is the active ingredient in Vulketan gel. Macrophage activation may be suppressed by serotonin present in the early inflammatory phase; ketanserin antagonizes this serotonin-induced suppression and thus, allows a strong and effective inflammatory response to occur within wounds. This should translate into a superior control of infection and a better orchestration of

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\(^a\) Protein-free dialysate of calf blood
\(^b\) Hydrogel
\(^c\) Acetylated mannan
\(^d\) Maltodextrin N.F.
\(^e\) Ketanserin

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Fig. 1. Phases of wound repair.
the later phases of repair when growth factors released by the activated macrophage play an important role. Vulketan gel was clinically tested against an antiseptic and a desloughing agent in equine limb wounds. Vulketan gel was 2–5 times more likely to result in successful closure, because it reduced infection and the development of exuberant granulation tissue. Many wounds located on the distal limb of horses exhibit signs of chronic inflammation, regardless of whether or not they are infected. Chronic wounds seem to be “stuck” at some critical stage of repair, probably during inflammation or cell proliferation. Current emphasis of chronic wound management focuses on three main issues: (1) identification of the obstruction to healing, (2) removal of the obstruction by debridement, (3) creation of a favorable environment at the wound site. Suggested therapy for chronic wounds includes a combination of proteinase inhibitors and anti-inflammatory agents followed by the application of growth factors. An oxidized regenerated-cellulose (ORC)/collagen dressing has been developed for wounds that have not progressed beyond the inflammatory phase. It is designed to modify the chronic wound environment by decreasing the activity of key matrix metalloproteinases (MMPs) in the wound fluid. A study in diabetic rats found faster epithelialization of wounds treated with ORC/collagen than with hydrocolloid dressing alone; this was accompanied by higher wound proteinases (MMPs) in the wound fluid. A study in diabetic rats with topical application of TGF-β improves wound repair in a variety of species, especially in models of chronic, impaired wound healing. A study by Steel et al.21 tested the recombinant growth factor, found to be effective in laboratory animals, on full-thickness wounds located on the limb of horses. There were no beneficial effects on total amount of granulation tissue and epithelialization area or on clinical assessments of wound biopsies. Conversely, Ohnemus et al.22 achieved promising results by topically applying the anti-fibrotic isoform TGF-β3 to wounds on the limbs of horses. Granulation tissue had a healthier appearance and did not become exuberant in treated wounds, despite the use of bandages. Numerous companies now promote products based on their bioactive molecule (cytokine/growth factor) content. For example, an all-natural, equine-specific wound healant is currently marketed in the United States. The company claims that a gel containing activated platelets and their released growth factors induces wound repair in injuries previously deemed untreatable.23 Because application of a single growth factor does not mimic natural processes and should not improve healing unless impairment was caused by the relative lack of that single protein, a cocktail approach, such as motivating the use of platelet-rich plasma, might indeed impart benefit. Along those same lines, we recently accelerated wound repair in diabetic rats with topical application of elk velvet-antler extracts.24 Velvet antler contains various growth factors and a soluble extract that stimulates dermal fibroblast growth in vitro. According to the premise that slow growth of dermal fibroblasts from equine limbs may contribute to the poor healing characteristics of wounds of the distal aspect of the limbs of horses, we suggest that this extract may be an economical adjunct to the treatment of full-thickness wounds in this location on horses.
Therapy During the Remodeling Phase
We recently investigated the efficacy of a silicone-gel dressing in the treatment of proud flesh in limb wounds of horses. This therapy is successful in reversing hypertrophic scarring in human burn patients, apparently by exerting pressure on the microvasculature of the scar and altering levels of various growth factors, notably pro-fibrotic TGF-β. The anoxic fibroblasts undergo apoptosis rather than proliferating and secreting ECM. In our study, the silicone-gel dressing surpassed a conventional dressing in preventing formation of exuberant granulation tissue and improving tissue quality in horse wounds. Microvessels were occluded significantly more often in wounds dressed with the silicone gel.26 Thus, we recommend integrating the silicone dressing into a management strategy designed to improve the repair of limb wounds in horses.

Tissue engineering is used to develop methods for the repair and restoration of injured or missing body parts. ECM is at the heart of most scaffold-based therapies, because it represents a collection of molecules organized in a three-dimensional ultrastructure, unique for each tissue/organ. The components are principally collagen, proteoglycans, glycoproteins, and growth factors secreted by resident cells that provide, in addition to the structural framework, a source of information that contributes to cell phenotype and behavior.27 ECM does not cause perfect regeneration but will accelerate wound closure and improve tissue quality. The healed, remodeled tissue is associated with differentiated cell and tissue types with minimal scar tissue.

A natural biocompatible collagen matrix derived from porcine small-intestinal submucosa or urinary-bladder submucosa and containing a plethora of proteins and growth factors is available to veterinarians. A recent study determined that porcine small intestinal submucosa offers no apparent advantage over a non-biological dressing for treatment of small, granulating wounds of the distal limb of horses.28 Indeed, no differences were detected in the rate of wound healing in wounds dressed with the silicone dressing versus control wounds.26 Thus, we recommend integrating the silicone dressing into a management strategy designed to improve the repair of limb wounds in horses.

References and Footnotes


a Solcoseryl Solco Basle Ltd, Birsfelden, Switzerland.
b Solugel, Johnson & Johnson Medical Products, Markham, Canada L3R 0T5.
c Carravet Veterinary Products Laboratories, Phoenix, AZ 85067.
d Intracell Macleod Pharmaceutical, Fort Collins, CO 80525.
e Vulketan gel, Janssen Animal Health, Beerse, Belgium.
f Promogran, Johnson & Johnson Medical Products, Markham, Canada L3R 0T5.
g Lacerum BeluMedX, Little Rock, AK 72212.
h Cicacare, Smith Nephew, Hull, UK HU3 2BN.
i Vet BioSIST, Cook Veterinary Products, Bloomington, IN 47404.
j ACell Vet, Jessup, MD 20794.
k Carrasorb, Carrington Laboratories, Irving, TX 75038.