Honey and silver for wound care, a brief review

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Key Point

With the emergence of antibiotic resistant bacteria in human and animals, honey and silver offer new possibilities for managing wounds and skin infections in horses. Using such topical products will decrease the need for using antibiotics hence minimizing the induction of resistance and improving stewardship.

Introduction

In companion and equine veterinary practice, antibiotics of human importance are commonly used. Due to use and overuse of antibiotics, bacterial resistance is an emergent problem in veterinary medicine and has led to an increased risk of therapeutic failure, higher costs, worse outcomes and public health implications.[1] With the intensification in pressures for more judicious use of antibiotics, finding effective alternative therapies for treating skin infections and wounds will improve the veterinarian's tool kit to care for patients as well as decreasing the need for the use of antibiotics. Furthermore the topical administration of substances to treat wounds are advantageous over systemic antibiotic administration because of lower treatment costs, achieving bactericidal concentration effects at the affected site and avoiding side effects of systemic antibiotic administration. [2]

The application of honey and silver for prophylaxis and treatment of wounds and wound infections dates back centuries, when it was used by ancient civilizations.[3]

For example in around 1650 BC the early Egyptians were the first to use honey for topical wound care. Silver has been known to be used for wound treatment since 69 B.C.[4] However in the 1940's with the advent of penicillin and further antibiotic class development, these therapies were forgotten. Due to the emergence of multi-resistant bacteria caused by the use and overuse of antibiotics in human and veterinary medicine, new interest has developed in the use of honey and silver for the management of wounds in humans and horses. [5-7]

In horses wound dehiscence rates for lower limb wound repair is as high as 74%, due to tension and infection, so it is common for these wounds to be left to heal by second intention. [2,8] Distal limb wounds are prone to excessive granulation tissue formation and prolonged healing because of greater wound retraction, slower rates and earlier cessation of wound contraction, and slower epithelization rates. [8] Therefore in horses the location of the wound influences healing, with lower limbs wounds having a higher complication rate compared to other locations in the body. [2]

Honey in wound care

There are many different types of honey that vary in constitution and quality. [9] The dissimilarities among honey stems from the kind of plant from which the nectar and pollen is collected, region of origin and method of production. [9]

The antibacterial effects of honey are due to its physical properties and the active ingredients it contains. [3,5,9] Honey has an osmotic effect (approximately 80% sugar), which dehydrates bacteria.[2] The pH of honey is acidic (3.2 – 4.5), hence inhibiting bacterial growth. Honey contains the enzyme glucose oxidase that transforms sugars into hydrogen peroxide which is bactericidal.[2,7]

The most common medicinal honey used is produced by bees foraging Manuka plans native of Australia and New Zealand.[9] Manuka honey has potent antibacterial activity against Gram-negative and Gram-positive bacteria. [8] This

non-peroxide, antibacterial activity has been attributed to methylglyoxal (MGO), and it is not affected by the tissue catalase activity.[3] MGO is one of the phytochemical factors with antibacterial activity within Manuka Honey and its concentration is closely related to the antibacterial activity. The non-peroxide antibacterial activity of Manuka Honey is referred to as the unique Manuka factor (UMF).[7,9] Manuka Honey antibacterial effect potency increases after 24 hours because MGO forms from the non-enzymatic conversion of dehydroacetone derived from the nectar of the Manuka flowers. [5,9]

The *in vitro* antibacterial effects of Manuka Honey depends on the bacterial species and the concentration of the honey. [5] Studies have demonstrated that honey has broad antibacterial activity against common equine pathogens including methicillin-resistant *Staphylococcus aureus*, as well as efficacy in preventing and eradicating biofilm. [2] The variety of antibacterial compounds present in honey act together to synergistically kill bacteria, therefore there is no evidence for the development of bacterial resistance. [2,9] It is important to maintain adequate concentration of an efficacious honey at the wound dressing interface in order to maximize its bactericidal effect. [9]

It is known that the acidic pH of honey induces local acidification of the wound promoting healing by increasing the release of oxygen from hemoglobin. [3] Furthermore, the acidic wound environment is less favorable for protease activity, decreasing the destruction of the matrix needed for tissue repair. The hyperosmolarity of honey also benefits wound healing because the osmotic effect draws water from the wound bed, creating an outflow of lymph which positively impacts healing. [3] Manuka Honey also contains antioxidants, flavonoids, phenolic acids and other enzymes, which are important determinants of its anti-inflammatory activity. [3,5,10]

Manuka Honey has been shown to have pro-inflammatory activities by increasing the production of cytokines in leucocytes that control angiogenesis and proliferation of fibroblasts and endothelial cells. [7,9] This activity is likely due to a

unique 5.8-kDa component found in Manuka honey which was shown to engage toll-like receptor 4 on monocytes to upregulate production of tumor necrosis factor alpha, interleukins 1ß and 6, and prostaglandin E-2, enhancing the inflammatory phase of healing.[8] Honey also upregulates the genes for matrix metallopeptidase 9 (MMP-9), a protease that detaches keratinocytes from the basement membrane to allow their migration during re-epithelialization. [3]

Silver in wound care

Silver metal (Ag) has no medicinal activity, but silver ion (Ag^+) has antimicrobial and cytotoxic effects against bacteria, viruses, yeast and fungi. [4] Another form of silver is its nanocrystalline form, Ag^0. [11] The metallic (Ag^0) and Ag^+ forms also can appear loosely attached with other elements such as oxygen or other metals and can form covalent bonds or complexes. [11]

Silver ions damage the bacterial cell wall by reacting with peptidoglycans, forming pores, increasing cellular permeability and causing death.[11] Silver ions also bind and disturb DNA affecting the microorganism replication cycle. [4,11] Another bactericidal mechanism is based on harming the respiratory chain, by interacting with thiol group-containing enzymes, such as NADH-dehydrogenase II in the respiratory system.[4,5] Similar to honey, the multiple targets that silver uses to cause microbial death makes the emergence of resistance a rare event and there is no direct evidence that silver resistance mechanisms confer cross resistance to antibiotics. [5] A study concluded that despite genetic evidence of resistance to silver, all bacteria tested were killed following a maximum of 48 hours of exposure to the dressings.[5,6] However the expanding use of silver in domestic, agriculture and industrial applications could in the future lead to the emergence of bacterial resistance due to environmental release of silver. [11]

Modern medicine uses medical grade forms of silver such as silver nitrate, silver sulfadiazine and colloidal silver. [11] Silver sulfadiazine (SSD) is widely used in

burn human patients as well as for treatment of different types of wounds in horses. [4] More recently nanocrystalline silver dressing and other formulations have been used for medical applications, incorporated into skin products and combined with Manuka honey. When Ag^+ is present in high concentrations within the wound it is toxic for keratinocytes and fibroblast interfering with the healing process.[4] Therefore newer silver formulations allow for the slow constant release of Ag+ within the wound, hence minimizing the deleterious effects of uncontrolled high Ag+ concentrations.

Effective Ag+ bactericidal activity requires a concentration of 30 to 40 ppm, hence the ideal silver containing dressing would maintain a sustained therapeutic level for several days of a concentration greater than 30 ppm but less than 60 ppm to avoid local toxicity. [4] Dressings containing nanocrystalline silver lead to a concentration of Ag+ within the wound bed of 70 ppm that is slightly above the toxic threshold. [4] Initially SSD releases very high levels of Ag+ (up to 3,176 ppm), which rapidity decreases to sub therapeutic concentration, causing tissue toxicity and lacking the ability for providing sustained release. [4] SSD is used for treatment of human patients with second degree burns; however it has been shown that it worsens outcomes in terms of infection and epithelialization, and increases the rate of hypertrophic scar formation. Furthermore in this setting it is less effective than Aloe vera, petrolatum gel and honey. [4]

Silver also exerts anti-inflammatory effects, although the exact mechanisms of action remain elusive. It has been proposed that the mechanisms for healing promotion are via inhibition of pro-inflammatory cytokine and increasing anti-inflammatory cytokines. [5,6]

Infected wounds

In people and horses, infection is one of the most common complications of wound healing despite the use of antibiotics and modern sterile techniques. In

people, wound infection accounts for considerable patient morbidity, discomfort and prolonged hospitalization. [10] Infection must be avoided in order for proper wound healing to occur. [10] The situation becomes worse in the case of antibiotic ineffectiveness due to resistant bacteria, and the use of antiseptics that cause tissue damage further slowing wound healing. [10] For example a study in horses evaluating the use of regional limb perfusion with amikacin failed to decrease the wound bioburden. [2]

Wound infections in the form of planktonic bacteria or biofilm negatively affect wound healing by depleting local micronutrients and oxygen, and producing toxins. [4] Bacteria in a biofilm form within the wound are exceedingly difficult to treat due to the resistance to antimicrobials conferred by the extracellular polymeric substance that covers the biofilm. A combination of surgical wound debridement and long-acting topical antimicrobials have been effective in humans to combat biofilm. [4] The ideal topical antimicrobial must be nontoxic to host cells, have broad spectrum antimicrobial activity and maintain constant concentrations within the wound until the infection has been cured. [4] Nanocrystalline silver satisfies the above requirements. Several randomized-controlled trials and systematic reviews have demonstrated that dressings that contain nanocrystalline silver are beneficial for wounds that have high bacterial counts and bad odor. Silver-containing dressings also have the advantage of requiring less frequent dressing changes than non-silver-containing dressings, leading to lower pain levels. [4]

Medical-grade honey is a valuable tool in the management of wounds. Honey has an acidic pH, which along with the generation of hydrogen peroxide gives it broad bactericidal properties. [4] Honey does no cause tissue damage and promotes healing, hence enhancing wound healing mechanisms and shortening the time needed for the wound to heal. [10] Studies have shown that human patients treated with honey had a significantly lower average duration of wound healing compared with those treated with SSD. [10] Manuka honey has an antibacterial

component that is a small water soluble molecule that is able to diffuse through the biofilm matrix. [3]

Wound management in horses

Wounds in horses, especially the ones affecting the distal portion of limbs, can undergo prolonged complex healing and may enter a non-healing state, having a negative financial impact and worsening the patient's outcome. [9] Similar to what occurs in people, wound infections are normally responsibly for delayed wound healing in horses. [9] Wound dehiscence is another common complication for normal wound repair in the distal limbs of horses. [2]

Despite the vast clinical evidence for using honey in wound care, there is a lack of protocol standardization for using honey in veterinary medicine, and in human medicine there is an absence of high quality controlled or randomized trials.[3,9]

An *in vitro* study showed that medical grade Manuka honey used commercially in wound products and dressings, and Manuka honey (UMF greater than 10) were able to inhibit growth of non-spore forming bacteria commonly involved in equine wound infections. [9] In a study the different types of tested honeys were effective at a concentration of 16% or less, much lower than is likely to occur at the surface of an infected wound treated with honey, even considering dilution by wound exudates. [9] In an equine randomized controlled clinical study intra-lesion application of medical grade honey significantly improved healing, lowered infection rates and improved veterinarian's satisfaction when compared to control horses. [2] In a study of horses where experimentally created surgical wounds on the distal limbs, it was shown that topically applied Manuka honey improved healing during the first 3 weeks of treatment. A potential downside of pure Manuka Honey is that at room temperature it assumes a fluid-like consistency, hence adhering poorly to wounds. Bandaging is necessary to enhance contact of Manuka honey with wounds on distal limbs, but prolonged bandaging has been

shown to negatively affect healing and produce excessive granulation tissue. Therefore, a Manuka honey gel application could be suitable for wounds that are not bandaged or cannot be bandaged. [7]

Discussion

Multidrug resistant bacteria is an emergent problem in veterinary and human medicine. The use of antibiotics prophylactically for the prevention of wound infections is an ethical concern and in some cases implies poor stewardship. [2] Therefore, using alternative therapies like silver and or honey, or combinations of both for the prevention and treatment of wound bacterial infections as well as improve healing, is an attractive alternative.

Using topical bactericidal products such as silver or honey, that aid with wound healing in lieu of systemic antibiotics will lead to decreased treatment costs, lower risk for secondary complication of systemic antibiotic such as colitis and improving treatment outcomes.

Despite evidence pointing towards beneficial effects of innovative therapies for wound care, further studies ideally with a multicenter design should be done in order to better determine the outcomes of horses being treating with topical medication. The formulation of honey or silver as well as application with or without a bandage also will require further investigation in order to find adequate protocols to improve patient outcomes.

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