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Topical Use of Phenytoin for Promoting of Wound Healing in Equines

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Abstract

The aim of this study was to evaluate the effect of topical phenytoin therapy (spray) on the wound healing in equines. The study was divided into two parts, experimental and clinical parts; 1) Experimental part, to evaluate the effect of topical phenytoin therapy (spray) on cutaneous incisional wound healing in donkeys. Six donkeys were subjected to cutaneous square incision 3x3 cm made over the skin of the back of the animal, three wounds on each animal, these wounds were divided into three groups one in each group, (the group consisted of six wounds, one in each animal). Group A, treated with phenytoin spray (HEALOAL) ^{R}; Group B, treated with antibiotic spray (Bivatracin) ^{R} and Group C, untreated control group. The treated groups received daily topical application of the spray until that day the wounds were closed completely. For computation of the percentage of wound healing, the area of the wound was measured in all groups (A, B and C) at the beginning of the experiments and every 3 days until the day of complete healing, day 18,21&27 consequently. Tissue specimens were collected from the wounded area after complete healing for histopathological investigations. The percentages of wound healing were calculated after measurement of the area of the wound. Significant differences in wound closure times between the treated and untreated groups were detected in days 9,12 and 15 days after the start of treatment. There were no significant differences in wound closure times between the treated groups. All wounds treated with PHT spray healed significantly faster than the other untreated wounds. The histopathological results showed improvement in the wound architecture of the group treated with PHT compared to those treated wounds with antibiotic spray and untreated group. 2) Clinical part, was performed by topical application of PHT spray on 25 clinical cases suffering from different varieties of skin wounds, after obtaining confirmative results for the effect of topical application of PHT on promoting healing of the wounds of equines in the experimental part. The result of gross examination had revealed that these wounds were not contracted, uniform healing with reduction of the wound healing time. It is concluded that phenytoin has little significant effect on the rate of wound healing, but has a promoting effect on the healing of wounds.

Introduction

Wound in animals are a common and frequent reason for seeking veterinary attention. Many different varieties of trauma result in skin injury

in animals. The animals' body is usually capable of closing these wounds spontaneously to restore its protective function as a barrier and maintain homeostasis. Wound healing, the result of a complex tissue repairing process consists of several processes, including cell migration, tissue proliferation, differentiation and formation of new extracellular matrix **(5).** Delay in healing may occur with large wounds or impaired tissue viability and express a significant clinical problem that resulted enhanced scarring. Healing is often considered as complete when a wound is epithelialized, the way in which wounds are managed affect the rate of healing, the time to return normal function and the final cosmotic appearance **(19) and (10).**

All cutaneous wounds heal by two independent processes, contraction and epithelialization. Wound contraction reduces the perimeter by centripetal movement of dermis and epidermis and occurs as long as the contractive forces of the wound myofibroblasts exceed the reactive forces of the surrounding skin on the wound edge **(16) and (19)**. Epithelialization is the process that keratocytes proliferate and migrate to cover the surface of the cutaneous defect. The sum of these processes determines the rate of wound healing. Wound healing is a dynamic process, so a primary goal should be management of local factors to provide an environment that promotes acceptable wound healing. Requirements for this include microcirculation for oxygenation and nutrition, moisture, increased temperature, neutral to slightly acidic pH, and a bacterial population less than 10^5 organisms per gram of tissue **(28), (35) and (43).** In addition to, wound healing is divided into three phases: inflammatory phase, proliferating, and remodeling **(22).** During the initial response to injury, platelet accumulation provides chemotactic attraction through platelet derived growth factor. Macrophages and other leukocytes are activated and infiltrate the wound. This initial inflammatory phase of wound healing including debridement of necrotic tissue and foreign debris is crucial for initiation of the repair phase **(36) and (37)**. Once this macrophage directed phagocytosis clears the tissue debris, perivascular pleuropotential mesenchymal cells differentiate into fibroblasts and myofibroblasts. These cells produce collagen, protein polysaccharide, and glycoprotein ground a process which reaches a peak around the fifth day after wounding **(5) and (34).** During the proliferative phase of wound healing rapid reduction in

wound size is due to contraction of actin containing myofibroblasts. The rates of contraction vary according to wound location on the horse **(45)**. Contraction ceases when epithelialization is complete or when tension in the surrounding skin exceeds the exertion by the myofibroblasts **(38) and (31)**. Optimally, second intention wound healing contracts rapidly during the rapid healing phase, approximately days 14 through 35 in a horse, to minimize amount of epithelialization, which is often referred to as the scar epithelium (**16) and (44).** The difference in wound contraction appears to be determined by local environments such as oxygenation, moisture, temperature rather than by inherent contraction capacity of the cells **(43).**

The persistence of inflammation contributes to longer healing times in the horse **(8) and (18).** Earlier research, demonstrated that horses have inherent dermal and subcutaneous precursors predisposing them to exuberant granulation tissue formation **(6).** Exuberant granulation tissue delays healing by inhibiting wound contraction and subsequent epithelialization and eventually resulting in a larger scar (**12), (16) and (19).**

In attempts to reduce exuberant granulation tissue formation, application of topical medications either alter the wound environment by suppression of opportunistic bacterial infection, reduction of mitotic activity or promotion of epithelialization through fat-soluble vitamin supplementation **(42) and (10).**

Topical medications should provide a specific desired effect during the appropriate stage of healing. Most of these topical medications have a stimulatory effect on the fibroblasts resulting in increased collagen synthesis; stimulate angiogenesis and enhancing rate of epithelialization **(38) and (21).**

Phenytoin (PHT) was firstly used in human as an effective control of convulsive disorders. Also PHT has been used in healing of wounds and pressure ulcers in human being **(32), (29), (24),** (**3), and** (**2).** Clinical study in human was first showed that pretreatment with oral PHT enhanced healing of the periodontal wound **(26).** PHT was used in other studies and investigations acceleration for healing of different types of wounds in human **(25) and (39)** and in arrhythmic heart in horses **(9).** PHT is related to the barbiturates in chemical structure (but has a five–membered ring), though it does not cause sedation and is non-habit forming. PHT may