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Effectiveness of topical zinc oxide application on hypertrophic scar development in rabbits☆,☆☆

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ABSTRACT

Background: The etiology, biology, prevention and effective treatment of hypertrophic scars have not exactly been defined. Topical zinc oxide application was shown to be effective in the treatment of proliferative scars. We studied the effectiveness of topical zinc oxide ointment in the prevention of hypertrophic scar development by using the rabbit ear hypertrophic scar model.

Methods: Circular full-thickness skin excisions were performed on both ears of 10 rabbits. The rabbits were divided into two groups and topical 40% zinc oxide ointment was applied daily to one ear and the ointment base was applied as placebo to the other ear. Scar samples were taken in the 3rd week in group 1 and in the 6th week in group 2. All of the specimens were divided into two halves: one half for histopathologic/histomorphometric examinations and the other half for biochemical studies.

Results: Application of topical zinc oxide ointment decreased clinical scar hypertrophy scores significantly ($p = 0.017$) at 6th week in comparison with placebo. Topical zinc oxide also reduced nodule formation histopathologically at 6th week in comparison with placebo but this was not significant statistically ($p > 0.05$).

Conclusion: The findings of this study may have clinical implications on the management of human hypertrophic scars.

1. Introduction

Hypertrophic scars and keloids are important problems confronting clinicians. These scars cause both subjective and objective problems and treatment results are unsatisfactory. Hypertrophic scars are associated with some local wound factors such as prolongation of wound healing, local wound infection, and mechanical wound tension [1–5]. Hypertrophic scars are frequently associated with surgical injury like sternal incision scars following cardiac surgery and third degree burns [1,6,7]. Development of proliferative scars (hypertrophic scars and keloids) has been shown to be

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associated with abnormalities affecting wound healing steps like cellular proliferation and migration, inflammation, cytokine synthesis and expression, extracellular matrix synthesis and deposition, and maturation [2,3,8]. A variety of methods have been tried for the treatment of proliferative scars with variable results [2–5]. For this reason, probably the best approach would be the prevention of development of these scars [2]. Various therapeutic methods have been tried to achieve the goal of prevention of hypertrophic scar development but they have produced variable results [2,4]. Some methods like silicone gel sheeting, scar massage, pressure and casting, imiquimod cream and onion extract have been used for the prevention of hypertrophic scar development in burn patients, but these methods were found ineffective most of the time and noncompliance of patients was a significant problem [2–5].

In a study designed to examine wound healing in leprosy it was observed that fewer keloids developed following zinc tape application to wounds in comparison with classical wound dressing application [9]. Söderberg et al. [10] showed that adhesive zinc oxide tape was effective in the treatment of proliferative scars. It is logical to assume that a method effective in the treatment of a disease could also be effective in the prevention of the same disease [7]. It is appropriate to test a medication therapeutically in animals before its use in humans [11].

This animal experiment was designed to test the hypothesis that topical zinc oxide application could prevent hypertrophic scar development.

2. Materials and methods

Hypertrophic scar animal (rabbit) model described by Morris et al. [12] was used in this study. This animal experiment was conducted in accordance with a protocol approved by the ethics committee of the institution. Researchers complied with all of the requirements defined by the Animal Welfare Act. Ten albino ''New Zealand'' female rabbits aged 6 months to 1 year were used in this study and they were separated into 2 groups (each group containing 5 rabbits).

2.1. Study design

All surgical operations were performed under aseptic conditions and ketamine/xylasine (35/5 mg/kg intramuscular) anesthesia. Round full-thickness skin excisions were performed from the ventral surface of the ears. For each ear, four wounds were planned in group 1 and each wound was 1 cm in diameter. For each ear, 3 wounds were planned in group 2 and each wound was 1.5 cm in diameter. Prior to skin excision, isotonic saline was injected into subdermis for hydrodissection. Full-thickness skin excisions were performed by using microsurgical techniques that had been described previously [12]. Nothing was applied to the wounds and they were covered by sterile gauze for one day. On the second postoperative day and afterwards, 40% zinc oxide ointment (Çinkos® ointment, Tek-Med Medical Drug Company, Turkey) was applied once daily to the wounds in one ear and base ointment (containing pure vaseline and lanolin) as placebo was applied once daily to the wounds in the other ear. In group 1, once daily application of topical zinc oxide and placebo was continued for 3 weeks (until the time of wound closure) to examine the effects of zinc oxide on the early stages of wound healing process. In group 2, once daily application of topical zinc oxide and placebo was continued for 6 weeks in order to examine the late effects (beyond clinical wound closure) of zinc oxide on wound healing process.

Blood samples were taken only from rabbits in group 2. Blood samples were obtained at the end of 6th week (just before scar removal) for serum zinc level measurements. For comparison, blood samples were also taken from 5 additional rabbits which were not operated.

Rabbits were sacrificed by using overdose of anesthetic medication at the end of the study. Scars were excised completely with a thin rim of normal surrounding tissue at the end of 3rd week in group 1 and at the end of 6th week in group 2. Scars were divided into two halves with reference to the most elevated part. One half of each excised scar was fixed in 10% formalin for histopathological and histomorphometric examinations. The other half of each excised scar (not including underlying cartilage) was kept in liquid nitrogen for biochemical studies.

2.2. Clinical studies

Wounds were examined clinically for local infection, wound closure and scar hypertrophy everyday. Wounds were evaluated clinically every week for scar elevation and scar thickness was measured by using a compass. Findings were recorded and photographs were taken. Scars were graded clinically according to their elevation from the surface from 0 to 3 (0: no elevation, 1: elevation noted on palpation or elevation not completely circular, 2: circular elevation noted on inspection, 3: prominent elevation).

2.3. Morphological studies

Hematoxylin–eosin (H&E) stained sections were examined under light microscopy (Zeiss Axioskop, Germany) for epidermal hyperplasia, presence of epidermal appendages, focal absence or posterior deformation of cartilage, dermal collagen organization, and presence of nodular structures. Scar elevation was determined histopathologically for all samples. Scar elevation was graded semi-quantitatively from −1 for scar depression to 3 for prominent scar elevation. All of the histopathologically examined scar samples were rated semi-quantitatively for epidermal hyperplasia, cartilage hyperplasia, vascularity, inflammation, lymphocytic infiltration, and fibroblast density and they were ranked from 0 to 3. Scar hypertrophy index (HI) was calculated with the help of histomorphometric examination for all scars and a method previously described was employed [1,12].

2.4. Biochemical studies

Tissue hydroxy-proline levels were measured according to the method described by Bergman and Loxley [13]. Serum zinc levels (from group 2 and normal rabbits) were measured as μg/dl.