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Comparative Evaluation of Steroid, Antimicrobial, Silicone, and Heparin-Based Preparations in Skin Wound Healing: An Experimental Study in a Rat Model

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Abstract

Skin wound healing outcomes vary, ranging from successful healing to the formation of scars or keloids. Treatment for keloids and scar management may involve silicone gel sheets, pressure therapy, and topical treatments to improve appearance and texture. This study investigates the effects of four different treatments—Dermatix Ultra, Epicyn, Flosteron, and Contractubex—on the wound healing process in a rat model. Full-thickness excisional skin wounds were created and monitored over four weeks, with treatments applied according to specific protocols. The focus was on analyzing pro-inflammatory cytokines (IL-1, IL-6) using ELISA, and conducting histological assessments to observe changes in fibroblasts, collagen, and elastic fibers. **Results.** The results demonstrated that IL-1 levels returned to baseline by the 21st day in the groups treated with Dermatix Ultra and Epicyn, while IL-6 levels followed suit by the 28th day. In contrast, both cytokines remained elevated in the control and Contractubex-treated animals. Histological evaluation revealed that vascularization and fibroblast activity normalized more rapidly in the Dermatix Ultra-treated group, achieving this by the 14th and 21st days, respectively. Collagen and elastic fiber restoration occurred earlier in the Dermatix Ultra-treated group compared to the others. Although Epicyn also had a positive impact, its effectiveness was somewhat lower than that of Dermatix Ultra. On the other hand, treatments with Flosteron and Contractubex were associated with extended inflammation and slower collagen deposition. **Conclusion.** Dermatix Ultra appeared as the most effective treatment for promoting wound healing and reducing inflammation, making it a promising therapeutic option in clinical settings.

Keywords: Wound Healing, Fibroblasts, Collagen, Elastic Fibers, Cytokines, Steroids, Antimicrobial agents, Silicon, Heparin-Based Preparation.

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Introduction

Wound healing is a multifaceted biological process involving hemostasis, inflammation, proliferation, and remodeling. Successful healing depends on the orchestrated actions of several cell types, including fibroblasts, inflammatory cells, and extracellular matrix (ECM) components such as collagen and elastic fibers. Impairment in any of these processes can lead to chronic wounds or excessive scarring [4]. Inflammatory cytokines like interleukin-1 (IL-1) and interleukin-6 (IL-6) play a crucial role in mediating the early phases of wound healing, promoting immune cell recruitment and ECM remodeling [2]. Fibroblasts, collagen, and elastic fibers play critical roles in the skin wound healing process.

Fibroblasts are essential for wound healing as they migrate to the wound site in response to signals from growth factors like transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF) [9]. Once at the wound site, they produce collagen, extracellular matrix (ECM) proteins, and elastin, which are essential for tissue repair. Fibroblasts also regulate the wound contraction process by differentiating into myofibroblasts, which pull the edges of the wound together [3]. They contribute to tissue remodeling by synthesizing matrix metalloproteinases (MMPs) that degrade and restructure the ECM. Their activity is crucial during the proliferative phase of wound healing, promoting tissue strength and flexibility [8].

Collagen, the most abundant protein in the ECM, is critical for providing structural support and tensile strength to the healing tissue. Collagen synthesis is initiated by fibroblasts in response to signals during the inflammatory and proliferative phases of wound healing [12]. Initially, collagen forms a temporary scaffold at the wound site. As the healing process advances, collagen fibers mature and become more organized, providing long-term stability to the wound [1]. Proper collagen deposition minimizes scar formation, while imbalances in its synthesis or degradation can lead to excessive scarring or fibrosis [6].

Elastic fibers, composed of elastin and fibrillin, are less prominent than collagen but play an important role in restoring tissue elasticity and flexibility. During wound healing, these fibers allow the skin to regain its ability to stretch and recoil. Elastic fibers are synthesized by fibroblasts and smooth muscle cells and are gradually incorporated into the ECM as the wound transitions from the proliferative phase to the remodeling phase [7]. Their restoration ensures that the healed tissue not only has tensile strength but also the flexibility necessary for normal skin function. Delayed or impaired elastic fiber formation can result in stiff, less pliable scar tissue [11].

Together, fibroblasts, collagen, and elastic fibers coordinate to ensure successful skin repair, with disruptions in any of these components potentially leading to delayed healing, chronic wounds, or pathological scarring [10].

Various treatments, including corticosteroids, silicone gels, antimicrobial hydrogels, and heparin-based preparations, are employed to manage wounds, reduce inflammation, and enhance tissue regeneration [3]. This study **aims** to assess the comparative efficacy of Dermatix Ultra, Epicyn, Flosteron, and Contractubex in modulating fibroblast activity, cytokine levels, collagen, and elastic fiber restoration during wound healing.

Materials and Methods

Experiments were conducted on male white laboratory rats (200-250 g), obtained from the vivarium of the Aleksandre Natishvili Institute of Morphology, Tbilisi, Georgia. After a one-week acclimatization period under controlled environmental conditions, full-thickness excisional skin wounds were aseptically created on the dorsal side of the anesthetized rats using nembutal (50 ml/kg). Surgical sutures of 5 cm were placed on the skin at 1 cm intervals.

The rats were divided into groups: intact healthy, control (untreated), and treated with Dermatix Ultra, Epicyn, Flosteron, and Contractubex.

Dermatix Ultra is a silicone-based gel. Its key components include: **Cyclopentasiloxane**. A type of silicone that provides a smooth texture and helps in the even application of the gel. **Dimethicone/Vinyl Dimethicone Crosspolymer.** Another form of silicone that forms a protective barrier over the skin, aiding in scar management by hydrating and protecting the scar tissue.

Epicyn is an antimicrobial hydrogel. Its primary components are: **Hypochlorous Acid (HOCl).** A naturally occurring molecule in the body that has antimicrobial properties, helping to reduce the risk of infection. **Electrolyzed Water:** Acts as a carrier for hypochlorous acid, providing a stable and effective medium for wound irrigation and antimicrobial action.

Flosteron is a corticosteroid injection. Its main active ingredient is: **Betamethasone Dipropionate:** A potent corticosteroid that reduces inflammation by suppressing the immune response and decreasing the production of inflammatory substances.

Contractubex active ingredients include: **Extractum Cepae (Onion Extract):** Known for its anti-inflammatory and antibacterial properties. **Heparin:** An anticoagulant that promotes blood flow to the affected area, reduces swelling, and has anti-inflammatory effects. **Allantoin:** Promotes wound healing, encourages cell regeneration, and softens the skin.

Each of these treatments has unique properties tailored to address different aspects of wound healing and scar management.

Treatments were applied for four weeks, Contractubex, dermatix ultra and epicyn creams were applied to the wound surface as a thin layer 2-3 times a day in the corresponding group animals. Flosteron (0.2 ml) was injected subcutaneously in the wound area once a week during 4 weeks.

Pro-inflammatory cytokines (IL-1, IL-6) were studied by ELISA. Histological assessments included H&E staining, immunohistochemistry for fibroblasts, Masson's trichrome for collagen, Van Gieson's for collagen differentiation, and Weigert's staining for elastic fibers. Blood and skin samples were collected on the 7th, 14th, 21st, and 28th days of the experiment.

Results were analyzed statistically using ANOVA or Mann-Whitney’s U test. A p-value of <0.05 was considered statistically significant.

Results and discussion

The investigations revealed that on the 7th day of wound healing, IL-1 levels were significantly higher in all experimental groups compared to healthy animals. In the following days, IL-1 levels gradually decreased in the groups treated with Epicyn and Dermatix Ultra, returning to normal by the 21st day. In Flosteron-treated animals, IL-1 normalized by the 28th day, whereas it remained elevated in both the control and Contractubex-treated groups.

IL-6 levels increased later, becoming detectable on the 14th day of wound healing. By the 21st day, IL-6 levels had gradually decreased in the Epicyn-, Dermatix Ultra-, and Flosteron-treated groups. IL-6 normalized by the 28th day in the Epicyn- and Dermatix Ultra-treated animals, but remained elevated in both the control and Contractubex-treated animals.

Histological analysis showed that by the 7th day, animals in the experimental groups exhibited varying degrees of increased vascularization at the injury site. Control animals continued to show increased vascularization up to the 28th day. In contrast, vascularization normalized by the 14th day in the Dermatix Ultra-treated group and by the 21st day in the Epicyn-treated group. However, animals treated with Flosteron and Contractubex showed persistent elevated vascularization through the 28th day.

A high number of myofibroblasts and inflammatory cells were present in the wound bed on the 7th day in both the control and Dermatix Ultra-treated groups. Moderate levels of these cells persisted throughout

the healing process in the control and Epicyn-treated groups. By the 21st day, myofibroblasts and inflammatory cells had returned to normal only in the Dermatix Ultra-treated group.

Initially, collagen fibers were scarce across all groups. By the 14th day, moderate levels of collagen were observed only in the Dermatix Ultra-treated animals, and these levels remained stable throughout the healing process. Collagen levels returned to normal in the Epicyn- and Flosteron-treated groups by the 21st day, while Contractubex-treated animals showed abundant collagen by the 28th day.

The presence of elastic fibers was moderate across all groups. In Dermatix Ultra-treated animals, elastic fibers normalized by the 21st day, while in Epicyn-treated animals, normalization occurred by the 28th day.

This study demonstrates that different treatments have varying impacts on the wound healing process. Dermatix Ultra showed the most rapid normalization of cytokine levels, reduced inflammatory cell infiltration, and enhanced collagen and elastic fiber restoration. Its silicone-based formulation likely contributes to reduced inflammation and improved tissue regeneration, consistent with existing literature on silicone's efficacy in scar management antimicrobial properties, also proved effective, though it was less potent than Dermatix Ultra in promoting collagen and elastic fiber restoration. Flosteron, while useful for reducing inflammation due to its corticosteroid nature, appeared to delay collagen deposition, possibly due to its immunosuppressive effects. Contractubex, aneficial in promoting collagen synthesis, showed prolonged inflammation, suggesting it may be more effective in later stages of wound healing but less ideal for acute management. Future studies are needed to understand the molecular mechanisms underlying these effects and explore potential combination therapies to optimize wound healing outcomes.

Conclusion

Among the treatments studied, Dermatix Ultra emerged as the most effective in modulating the inflammatory response and promoting tissue repair, followed by Epicyn. Flosteron and Contractubex showed limited efficacy, particularly in the early stages of healing. The findings highlight the therapeutic potential of Dermatix Ultra in clinical applications for wound healing and scar management. Further research is warranted to explore the molecular pathways involved and to investigate the potential benefits of combination therapies.

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