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Research Article

Comparative Analysis of Different Methods of Treatment on Pro-Inflammatory Cytokines and the Skin Wound Healing Outcomes

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Abstract

Skin wound healing is a complex and dynamic process essential for maintaining bodily integrity. This study investigates the impact of different therapeutic approaches (silicone, hypochlorous acid, heparin, and glucocorticoid-based preparations: Dermatix Ultra, Epicyn, Contractubex, Flosteron) on pro-inflammatory cytokines (IL-1, IL-6), healing progress and scar appearance in laboratory rats with full-thickness skin wounds. Dermatix Ultra, Contractubex, and Epicyn creams were administered 2–3 times daily, while Flosteron was given via subcutaneous injection weekly. Healing progress and scar appearance were evaluated using the Vancouver Scar Scale (VSS), and cytokine levels were measured by ELISA.

Results showed significant increases in IL-1 by day 7 across all groups. IL-1 levels normalized by day 21 in animals treated with Dermatix Ultra and Epicyn, while Flosteron-treated rats required until day 28. In contrast, Contractubex-treated and control groups exhibited persistent IL-1 elevation beyond day 28. Similarly, IL-6 peaked on day 14 but normalized by day 28 in Dermatix Ultra, Epicyn, and Flosteron groups, whereas it remained elevated in Contractubex and control groups.

Among the treatments, Dermatix Ultra emerged as the most effective, achieving superior scar characteristics, including reduced vascularity, improved pigmentation, pliability, and flattening. Epicyn and Flosteron demonstrated moderate efficacy, while Contractubex showed limited benefits in accelerating wound healing or improving scar quality.

Conclusion: These findings underscore the pivotal role of IL-1 and IL-6 in the inflammatory phase of wound healing and highlight the therapeutic potential of targeted treatments to modulate pro-inflammatory cytokines. Dermatix Ultra demonstrated the most robust outcomes, promoting rapid and effective healing, followed by Epicyn and Flosteron. The limited effectiveness of Contractubex suggests the need for further refinement in its application.

Keywords: Skin Wounds; IL-1; IL-6; Dermatix Ultra; Epicyn; Flosteron; Contractubex

Introduction

The skin, the body's largest organ, serves as a critical barrier against pathogens, ultraviolet radiation, and mechanical injuries while regulating water, electrolytes, and temperature [1-3]. Skin wounds, ranging from minor abrasions to severe injuries, are common and necessitate effective healing to restore tissue integrity and prevent complications. Factors influencing wound healing include age, nutrition, infections, and chronic conditions like diabetes or vascular diseases.

Wound healing progresses through four distinct stages: hemostasis, inflammation, proliferation, and remodeling. Hemostasis involves clot formation to halt bleeding, inflammation recruits immune cells (e.g., neutrophils and macrophages), proliferation drives tissue repair via collagen synthesis and angiogenesis, and remodeling strengthens tissue through collagen maturation [4-9].

Cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), play pivotal roles in these processes. IL-1 promotes inflammation, immune cell recruitment, and keratinocyte proliferation, aiding re-epithelialization. IL-6 supports the inflammatory phase and triggers the production of acute-phase proteins, facilitating tissue repair. Fibroblasts, by synthesizing collagen and extracellular matrix (ECM) components, contribute to wound strength and elasticity. However, dysregulation of these processes can result in chronic wounds, hypertrophic scars, or keloids, affecting functionality and aesthetics [10-12].

Effective wound care strategies include debridement, infection control, and tissue regeneration support through advanced therapies like negative pressure wound therapy and bioengineered skin substitutes [13-22]. However, facial wounds present unique challenges due to hypertrophic scarring risks and psychological impacts, emphasizing the need for optimized interventions.

This study evaluates the effects of four treatments: Dermatix Ultra, Epicyn, Flosteron, and Contractubex on immune parameters (IL-1, IL-6) and wound healing outcomes. The aim is to optimize healing, minimize scarring, and enhance patient quality of life.

Material and Methods

Experimental Animals: Male white laboratory rats (200-250 g) were sourced from the vivarium of Aleksandre Natishvili Institute of Morphology, Tbilisi, Georgia (https://www.tsu.ge/en). Animals acclimated to laboratory conditions (12/12-hour light-dark cycle, 23 ± 2°C, standard laboratory chow, and water) for one week prior to experimentation. The research protocol was approved by the Animal welfare and use Ethics Committee of TSMU.

Wound modeling and treatment

Under nembutal anesthesia (50 mg/kg), full-thickness excisional wounds were aseptically created on the dorsal skin. A 5 cm surgical suture was applied at 1 cm intervals. Rats were divided into six groups (n = 10 per group):

- **Group I:** Intact, healthy rats (control).
- **Group II:** Untreated rats (control).
- **Group III:** Rats treated with Dermatix Ultra**.**
- **Group IV:** Rats treated with Epicyn Hydrogel**.**
- **Group V:** Rats treated with Flosteron**.**
- **Group VI:** Rats treated with Contractubex**.**

Treatments were applied as follows

- Dermatix Ultra (silicones and Vitamin C ester), Epicyn (HOCL, NaOCL), and Contractubex (onion extract, heparin, allantoin) were applied topically 2-3 times daily for 4 weeks.
- Flosteron (Betamethasone Dipropionate, Betamethasone Sodium Phosphate) 0,2 ml was injected subcutaneously into the wound area once weekly for 4 weeks.

Evaluation parameters

- **Scar Assessment:** The Vancouver Scar Scale (VSS), incorporating vascularity, pigmentation, pliability, and height (scores ranging from 0 to 13), was used to evaluate scar progression [23-25].

Data were analyzed using ANOVA or Mann-Whitney U tests. Results with $p < 0.05$ were considered statistically significant.

Results

Results of experiment showed elevation of IL-1 on day 7 across all groups, with significant reductions in Dermatix Ultra and Epicyn-treated groups by day 21. Flosteron showed delayed normalization by day 28, while Contractubex exhibited persistent elevation.

On the 7th day of wound healing, the IL-1 were elevated in the control group by 74%, in Epicyn – by 107%, in Dermatix Ultra – by 101%, in Flosteron – by 88%, and Contractubex group – by 75% ($p < 0.001$). On the 14th day, IL-1 levels remained elevated in all groups, but with slight reductions.

On the 21st day, IL-1 was normalized in Dermatix Ultra and Epicyn groups, with notable reductions of 35% and 32% ($p < 0.001$) compared to control. Meanwhile, Flosteron showed a modest decrease of 11% ($p < 0.05$), and Contractubex-treated animals had no significant change.

By the 28th day, IL-1 returned to baseline in Dermatix Ultra, Epicyn, and Flosteron groups. In the Contractubex group, IL-1 was still elevated but had shown slight non-significant decreases.

In the Control Group**,** Consistent IL-1 elevation throughout the study, reflect sustained inflammation.

Notable reduction in IL-1 levels in Dermatix Ultra group and normalization by day 21 indicate effective in rapidly mitigating inflammation and maintaining cytokine levels near baseline. Epicyn Group animals showed the similar trend to Dermatix Ultra**,** with normalization by Day 21, indicating strong anti-inflammatory properties. In Flosteron Group the moderate IL-1 reduction throughout the study and normalization, achieved by Day 28, suggests a slower anti-inflammatory effect compared to Epicyn and Dermatix Ultra.

In Contractubex group remained elevated levels of IL-1 with only minor decrease by day 28 indicates the limited efficacy in controlling inflammation.

On the day 14 of wound healing**,** IL-6 was elevated and normalized in Dermatix Ultra and Epicyn groups by day 28. Contractubex and control groups showed prolonged elevation, indicating delayed inflammation resolution.

IL-6 levels showed delayed changes compared to IL-1. On the 14th day, IL-6 was slightly increased in control (12%; $p < 0.01$), Epicyn (30%; $p < 0.001$), Flosteron (12%; $p < 0.01$), and Contractubex (11%; $p < 0.05$) groups. In Epicyn and Dermatix Ultra-treated animals, IL-6 was increased by 17% and 25% ($p < 0.02$) on this day. By the 21st day, IL-6 began to normalize, especially in Epicyn, Dermatix Ultra, and Flosteron-treated groups, showing decreases of 12% and 15% ($p < 0.05$) in Epicyn and Dermatix Ultra groups.

By the 28th day, IL-6 levels were fully normalized in Dermatix Ultra and Epicyn-treated animals, while in the control and Contractubex groups, IL-6 levels remained elevated, suggesting delayed resolution of inflammation.

Summary of IL-6 dynamics by treatment

Control group

IL-6 levels increased slightly on day 14, with a modest elevation persisting through the study, reflecting sustained low-grade inflammation.

Epicyn group

- Significant rise in IL-6 on day 14, but levels started to normalize by day 21, showing a trend toward reducing inflammation.
- Full normalization by day 28 suggests effective anti-inflammatory action, albeit with a delayed onset.

Dermatix ultra group

IL-6 levels rose on Day 14, followed by a reduction and eventual normalization by day 28, indicating strong anti-inflammatory properties.

Flosteron group

A slight increase in IL-6 on Day 14, but levels began to decrease by Day 21 and fully normalized by Day 28, suggesting effective, albeit delayed, anti-inflammatory action.

Contractubex group

IL-6 remained elevated throughout the study, similar to the control group, indicating minimal impact on resolving inflammation.

Could be said that Dermatix Ultra and Epicyn**,** both treatments showed a delayed but significant reduction in IL-6 levels, suggesting effective anti-inflammatory properties, with normalization by day 28. The increase in IL-6 initially may reflect a transient inflammatory response to treatment, with later normalization suggesting resolution of the inflammation.

Flosteron also effective in normalizing IL-6, but the effect was slower compared to Epicyn and Dermatix Ultra, which may suggest a less immediate impact on inflammation resolution. IL-6 levels remained elevated, similar to the control, indicating that Contractubex did not significantly contribute to resolving inflammation during the study period.

The scar appearances

The scar appearances for the different treatment groups were characterized using the Vancouver Scar Scale (VSS) data, which includes four criteria: vascularity, pigmentation, pliability, and height [24]. Here's an analysis of the scar characteristics and wound healing process at different time points (7^{th}, 14^{th}, 21^{st}, and 28^{th} days) for each treatment group.

The control group

Vascularity

Day 7 to 21: Vascularity remained elevated (2-3), indicating persistent inflammation in the scar area. This suggests that the healing process was incomplete and inflammatory processes were still active. Day 28**:** A slight decrease in vascularity to a level of 2 suggests some resolution of inflammation, though not complete, as the scar continues to show signs of heightened blood vessel formation.

Pigmentation

Days 7-28**:** Pigmentation remained relatively stable at mild hypopigmentation (1) to mild hyperpigmentation (2), indicating irregular pigmentation. This suggests that the scar was in the process of maturing, but the pigmentation might not have completely normalized by Day 28.

The persistence of irregular pigmentation points to an incomplete healing process, with some areas possibly showing hyperpigmentation due to ongoing inflammatory processes.

Pliability

Day 7 to 28: Pliability worsened over time, with the scar becoming progressively firmer, from "firm" (3) to "contracture" (5). This increase in scar stiffness and contracture indicates the formation of a more rigid, possibly hypertrophic scar. The worsening pliability reflects inadequate remodeling and indicates that the control group's scar healing process did not result in improved flexibility or softness.

Height

Day 7 to 28**:** The scar height remained moderate (2-3), indicating that the scar did not flatten adequately over the 28-day period. This suggests that the scar was raised and showed persistent elevation, which could be a sign of hypertrophic scarring. The lack of significant flattening over time suggests that the control group's wound healing was not optimal.

According to the results could be said that the control group exhibited a persistent inflammatory response (elevated vascularity) that led to irregular pigmentation and poor pliability. The wound healing was incomplete, resulting in a firm, raised, and possibly hypertrophic scar**.** These findings indicate that without any intervention, scarring tends to worsen in terms of pliability and height, with some degree of pigmentation irregularity. The lack of scar resolution and the persistence of inflammatory characteristics suggest that treatment interventions could improve these outcomes by promoting inflammation resolution and better tissue remodeling.

Dermatix ultra group

Vascularity

(Day 7 to 28)**:** Vascularity showed the best improvement among all groups, decreasing from a score of 2 to 0 by day 28, indicating complete resolution of inflammation. This suggests that Dermatix Ultra was the most effective in minimizing the blood vessel proliferation typically associated with inflammation and scarring.

Pigmentation

Throughout the study pigmentation remained consistently within the normal range (0-1), indicating uniform skin color restoration. This early normalization suggests that Dermatix Ultra effectively prevented pigmentation irregularities, such as hyperpigmentation or hypopigmentation, promoting even skin tone recovery.

Pliability

(Day 14 to 28): The scar remained supple throughout the study, with a pliability score of 1, indicating healthy, flexible tissue without excessive stiffness or contracture. This suggests that Dermatix Ultra facilitated optimal tissue remodeling, preventing the development of rigid or hypertrophic scarring.

Height

(Day 14): Scar height normalized by day 14 with a score of 0, indicating no significant elevation. This suggests that Dermatix Ultra was highly effective in flattening the scar early in the healing process, promoting a flat and aesthetically improved scar.

Epicyn group

Vascularity

Day 7 to 28: Vascularity showed moderate improvement, decreasing from a score of 2 on day 7 to 1 on day 28. While there was some reduction in inflammation, the resolution of vascularity was not as efficient as Dermatix Ultra, indicating that Epicyn's effects on inflammation were somewhat less pronounced.

Pigmentation

Day 7 to 28: Pigmentation was generally normal (0-1) but showed a brief period of hyperpigmentation (2) on day 14. This suggests that Epicyn initially promoted some pigmentation irregularity, which normalized by day 28, indicating that it may take a bit longer for pigmentation to fully settle compared to Dermatix Ultra.

Pliability

Day 7 to 28: Pliability was moderate, with an initial score of 3 (firm) on day 7, improving slightly to 2 (less firm) by day 21, and reaching 1 (supple) by day 28. Although pliability improved over time, the scar remained firmer and more rigid compared to Dermatix Ultra, suggesting that Epicyn's treatment resulted in some stiffness, though still less severe than the control group.

Height

Day 7 to 28: The scar height decreased from 3 to 1, indicating a reduction in scar elevation, but it did not achieve the flatness observed in the Dermatix Ultra group. This suggests that while Epicyn helped flatten the scar, the effect was not as pronounced as with Dermatix Ultra.

Flosteron group

Vascularity

(Day 7 to 28): Vascularity remained moderately high during the early phase (scores of 2-3 from day 7 to day 21) but dropped to 2 by day 28, indicating a moderate resolution of inflammation. This suggests that Flosteron was somewhat effective in reducing inflammation, but its impact was not as rapid or efficient as Dermatix Ultra.

Pigmentation

Day 7 to 28: Pigmentation remained within the normal range (1) for most of the time points, with a brief increase in pigmentation on day 14 before normalizing by day 28. This indicates that Flosteron generally supported normal skin color restoration, but there were minor fluctuations in pigmentation early in the healing process.

Pliability

Day 7 to 28: Pliability improved over time, starting at firm (3) on day 7, then progressing to yielding (2) by day 14, and finally achieving supple (1) from day 21 to day 28. This suggests that Flosteron contributed to gradual scar softening and improved flexibility, but it was not as effective in this regard as Dermatix Ultra, which achieved pliability earlier.

Height

Day 7 to 28: Scar height improved from 2 to 1, indicating some flattening of the scar, but it remained elevated compared to the Dermatix Ultra group, which achieved full normalization of height by day 14. Flosteron provided partial flattening, but did not flatten the scar as effectively as Dermatix Ultra.

Contractubex group

Vascularity

(Day 7 to 28): Vascularity remained high (2-3) throughout the healing period, indicating prolonged inflammation and a slow normalization of vascularization. This suggests that Contractubex was less effective at resolving inflammation compared to other treatments like Dermatix Ultra and Epicyn.

Pigmentation

(Day 7 to 28): Pigmentation remained generally within the normal to mild hypopigmentation range (1), suggesting some pigment restoration, but with potential irregularities. This indicates that Contractubex was somewhat effective in pigment restoration but did not provide the same consistent results as Dermatix Ultra.

Pliability

(Day 7 to 28): Pliability started as firm (3) on day 7, improving to yielding (2) by day 14, and reaching supple (1) by day 28. Similar to Flosteron, Contractubex showed gradual improvement in scar flexibility but did not achieve the same level of pliability as Dermatix Ultra, which was supple earlier in the process.

Height

Day 7 to 28: The scar height decreased from 3 to 1, indicating some flattening, but it remained raised compared to the more effective treatments like Dermatix Ultra. Contractubex showed partial scar flattening, but it did not fully normalize the scar height as quickly or effectively as Dermatix Ultra.

Summary of skin scar characteristics

- **Vascularity:** Dermatix Ultra exhibited the best reduction in vascularity, indicating the fastest resolution of inflammation. Epicyn and Flosteron followed with moderate improvement, suggesting they also reduced inflammation, but not as quickly as Dermatix Ultra. The control and Contractubex groups showed slower resolution of inflammation, with persistent vascularity indicating a prolonged inflammatory phase.
- **Pigmentation:** Dermatix Ultra and Epicyn provided the best and most stable pigmentation restoration, ensuring more uniform skin color. The control and Contractubex groups showed more irregular pigmentation, with potential hyperpigmentation or hypopigmentation indicating less consistent color restoration.
- **Pliability:** Dermatix Ultra resulted in the most supple and flexible scar, showing the highest level of scar tissue pliability. Epicyn and Flosteron displayed moderate firmness, indicating a scar that was less flexible but gradually improved. The control and Contractubex groups showed more stiffness, indicating the formation of more rigid and less flexible scar tissue.
- **Height:** Dermatix Ultra achieved a flat scar by day 14, showing the most effective scar height reduction. Epicyn and Flosteron showed moderate improvement in scar height, leading to some flattening but not complete resolution. The control and Contractubex groups exhibited slower reductions in scar height, indicating a less effective flattening of the scar.

Discussion

Wound healing is a complex biological process that involves several overlapping stages: hemostasis, inflammation, proliferation, and remodeling. Each stage is regulated by a variety of biochemical signals, including cytokines IL-1 and IL-6. Both IL-1 and IL-6 are integral to the inflammatory phase of wound healing, with IL-1 typically increasing in the early stages of injury and serving as a primary mediator of inflammation. IL-6, although a pro-inflammatory cytokine, has a dual role in wound healing; it helps promote fibroblast activation and extracellular matrix remodeling during the proliferative phase while also contributing to the regulation of the acute inflammatory response.

The findings from this study demonstrate the differential impact of various treatments on cytokine dynamics and scar characteristics, highlighting their distinct mechanisms of action and efficacy in wound healing [26-29].

Elevated IL-1 levels on day 7, as observed across all treatment groups, reflect the acute inflammatory response to injury. The Dermatix Ultra and Epicyn groups exhibited the fastest normalization of IL-1 levels, with significant reductions by day 21, aligning with more efficient resolution of inflammation. Flosteron also facilitated normalization by day 28, but this was slightly slower compared to Dermatix Ultra and Epicyn. In contrast, the Contractubex group showed a more prolonged elevation of IL-1 levels, indicating slower resolution of inflammation. This prolonged inflammatory response may contribute to the delayed wound healing seen in the Contractubex group.

IL-6 levels showed a gradual increase on day 14 across all groups, which is typical of the transition from inflammation to tissue repair and remodeling. However, Dermatix Ultra, Epicyn, and Flosteron all exhibited a gradual normalization of IL-6 by day 28, suggesting effective regulation of the proliferative phase of

wound healing. In contrast, the control and Contractubex groups continued to show elevated IL-6 levels, which suggests ongoing inflammation and delayed resolution of the inflammatory phase, potentially slowing down the overall healing process. The delayed IL-6 normalization in the Contractubex group further supports the notion that this treatment may not be as effective in promoting timely tissue remodeling.

The cytokine data correlates with the observed differences in scar characteristics across the treatment groups. Dermatix Ultra and Epicyn were more effective in accelerating the resolution of inflammation (evidenced by the cytokine data) and, as a result, promoted better skin appearance and scar formation.

Dermatix Ultra showed the greatest improvement in reducing vascularity, suggesting the most efficient resolution of inflammation, which is typically associated with reduced scarring.

Both Dermatix Ultra and Epicyn showed excellent pigmentation restoration, likely due to their efficient resolution of inflammation, which prevents irregular pigmentation formation.

The most supple scars were observed in the Dermatix Ultra and Epicyn groups, which also had the most rapid reduction in inflammatory cytokines, contributing to improved tissue flexibility.

Dermatix Ultra produced the flattest scar by day 14, aligning with its faster reduction in both IL-1 and IL-6 levels, thus enhancing tissue remodeling.

Conversely, Contractubex exhibited prolonged inflammation, as indicated by slower cytokine normalization, and this was reflected in less favorable scar characteristics (higher vascularity, irregular pigmentation, stiffer scars, and higher scar height). These findings point to a delayed resolution of the inflammatory response in the Contractubex-treated group, which ultimately impedes optimal wound healing and scar formation.

Conclusion

The timely and efficient resolution of inflammation for optimal wound healing and scar formation is very important.

Dermatix Ultra showed the most favorable results across all scar parameters, including vascularity, pigmentation, pliability, and scar height. The rapid reduction in IL-1 and IL-6 levels correlates with efficient inflammation resolution and faster tissue remodeling. Dermatix Ultra-treated scars were flatter, more pliable, and exhibited better pigmentation restoration compared to other groups. Its silicone-based composition likely contributes to these outcomes by modulating cytokine activity and enhancing hydration at the wound site, facilitating optimal healing.

Epicyn demonstrated good anti-inflammatory and scar-improvement effects, though slightly less rapid than Dermatix Ultra. The antimicrobial properties of Epicyn may provide additional benefits in infection-prone wounds. It effectively reduced vascularity and scar height while promoting pigmentation restoration and pliability, albeit at a slower pace compared to Dermatix Ultra.

Flosteron, a corticosteroid, effectively reduced excessive inflammation but showed delayed transitions to tissue remodeling phases, as evidenced by slower IL-1 and IL-6 normalization. While Flosteron improved scar pliability and reduced vascularity over time, its immunosuppressive effects may hinder early wound healing, making it more suitable for cases with excessive inflammation or chronic wounds.

Contractubex exhibited limited efficacy in early wound healing. Prolonged elevation of IL-1 and IL-6 suggests an extended inflammatory phase, which may impede early tissue repair and scar formation. Although Contractubex demonstrated some efficacy in flattening scars during the later stages, its overall performance was suboptimal compared to Dermatix Ultra and Epicyn.

These results highlight the critical role of cytokine modulation in wound healing therapies and underscore the potential benefits of treatments that accelerate inflammation resolution for improving scar outcomes.

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