Acta Veterinaria-Beograd 2025, 75 (2), 151-165
UDK: 616-001
DOI: 10.2478/acve-2025-0013

Research article

COMPARISON OF THE EFFECTS OF AUTOLOGOUS CYTOKINE-RICH SERUM (ACRS) AND PLATELET-RICH PLASMA (PRP) ON SKIN WOUND HEALING

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(Received 08 January, Accepted 27 February 2025)

Wound healing is one of the most complex biological events, involving physiological processes such as tissue restoration and intricate cellular and molecular activities. The aim of this study was to investigate the effects of Autologous Cytokine Rich Serum (ACRS) and Platelet-rich plasma (PRP) on wound healing and to compare their impact on tissue repair using histopathological and immunohistochemical methods. A total of 42 healthy Wistar-Albino rats were used as material. The histopathological and immunohistochemical evaluations showed that ACRS is more effective than PRP on wound healing. The superior efficacy of ACRS is attributed to its stimulation of anti-inflammatory cytokines and provision of essential nutrients such as amino acids, vitamins, and lipids. Further detailed studies are recommended to explore these findings.

Keywords: rat, wound, PRP, ACRS

INTRODUCTION

The skin is the largest organ of the body, serving as a protective barrier against the external environment. It performs various functions, including immunological and endocrinological activities, preventing toxic, thermal, and mechanical effects, and maintaining body heat balance [1]. Wound is defined as the distruption of tissue integrity caused by trauma, surgery, or various diseases. Wound healing is one of the most complex biological events, involving physiological processes such as tissue restoration and intricate cellular and molecular activities [2]. These biological processes include hemostasis, inflammation, growth, reepithelialization, and remodeling. Multiple cell

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types and signaling pathways are crucial for the spatial and temporal coordination of these processes [3,4]. During the inflammatory phase, which peaks within 2–3 days, platelets play a key role by releasing various growth factors and cytokines that promote the recruitment and activation of inflammatory cells. In the proliferative phase, newly formed extracellular matrix (ECM), particularly collagen type I fibers, is deposited, while epithelialization and angiogenesis are stimulated, thus they reach peak between 2 and 3 weeks after injury. The remodeling phase begins 2–3 weeks after injury and continues longer than the other phases. The reorganization of the collagen matrix and the replacement of granulation tissue with an acellular scar are created in this phase [5,6]. Factors such as the etiology and size of the lesion, blood supply, tension and mobility of wound margins, infection, and the type and condition of the underlying tissue significantly influence the completeness of wound healing [6].

Platelet-rich plasma (PRP), derived from whole blood through centrifugation, is defined as autologous conditioned plasma with a high platelet concentration. It has been used for the treatment of various wounds, including chronic skin and soft tissue ulcerations, for the past 25 years [7]. Activated platelets in PRP release multiple growth factors and cytokines, such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), and others involved in promoting tissue repair and regeneration [8].

Several researchers [9,10] have emphasized that PRP can enhance the proliferation and migration of adipose-derived stem cells (ADSCs), indicating its potential synergistic regenerative effects on chronic wounds.

Autologous Cytokine Rich Serum (ACRS) is prepared by exposing a whole blood sample to glass beads. This process stimulates the secretion of anti-inflammatory cytokines, including IL-4, IL-10, and IL-1 receptor antagonist (IL-1Ra) in humans [11]. ACRS also contains high concentrations of IGF-1, hepatocyte growth factor (HGF), and fibroblast growth factor (FGF) [12]. In recent years, ACRS has been reported as a treatment for various diseases [13-15]. The growth factors in ACRS are known to accelerate skin regeneration and repair. Additionally, it has been reported that ACRS provides essential nutrients, such as amino acids, vitamins, inorganic substances, lipids, and other compounds, to promote ulcer healing [13,16]. Gholian et al. (2022) [17] suggested that ACRS could be used for wound dressing to improve and accelerate healing, though they emphasized that its mechanism of action remains unclear.

The essential role of PRP in tissue regeneration and wound healing has been confirmed by many studies. Some findings suggest that PRP has a strong effect on vascularization and it can release a higher content of VEGF to promote the vascularization which is beneficial to the prognosis of wounds. At the same time PRP can promote the formation of new capillaries in a transplanted skin flap, accelerate the local revascularization of the wound and protect from infection. Although studies have been conducted on PRP,

it is still not comprehensive and there is a lack of systematic exposition to evaluate the effects of PRP at different stages of wound healing [8].

ACRS stimulates a set of anti-inflammatory cytokines, containing IL-1Ra, and several growth factors, in the liquid phase of blood. It is currently evident that other anti-inflammatory cytokines and soluble receptors, which demonstrate difference dissociation rates for IL-1α, IL-1β, and IL-1Ra, can influence IL-1 receptor signaling and inflammatory circumstances [13].

The aim of this study was to investigate the effects of ACRS and PRP on wound healing and to compare their impact on tissue repair using histopathological and immunohistochemical methods.

MATERIAL AND METHODS

The present study was conducted at the Erciyes University Experimental Research Application and Research Center (DEKAM) with the approval of the Erciyes University Animal Experiments Local Ethics Committee (HADYEK, Decision no: 24/027). The animal material consisted of 42 healthy, 4 months old, non-pregnant female Wistar-Albino rats with 150-200 g body weight. While 18 of these 42 animals included in the study were used as donors of PRP and ACRS, 24 animals were divided into four groups with 6 rats in each group

- Group I: No operation (control group)
- Group II: Operation control
- Group III: Operation + PRP
- Group IV: Operation + ACRS

To groups II, III, and IV, general anesthesia was administered using a combination of 10 mg/kg xylazine HCl and 60 mg/kg ketamine HCl, mixed in the same syringe and injected intraperitoneally. The dorsal hair of the animals was shaved, and the skin sterilized with 70% alcohol and 10% povidone-iodine. A standard rectangular full-thickness wound measuring 2 × 1 cm (including the panniculus carnosus muscle, subcutaneous tissue, and skin) was created on the backs of the animals (Fig 1a,b). Group II: Wounds were covered with moistened gauze soaked in physiological saline on the 1st, 4th, 7th, and 14th days (Fig 1c). Group III: 0.5 ml of PRP was injected into the operation site using a 32-gauge needle attached to an insulin syringe on the 1st, 4th, 7th, and 14th days. The wounds were then covered with moistened gauze soaked in physiological saline (Fig 2a,b). Group IV: 0.5 ml of ACRS was injected into the operation site using a 32-gauge needle attached to an insulin syringe on the 1st, 4th, 7th, and 14th days (Fig 2c). The wounds were then covered with moistened gauze soaked in physiological saline. Postoperative analgesia was provided to all operated animals using a single subcutaneous dose of ketoprofen (0.04 cc). No specific nutritional program or dietary regimen was applied, and the animals were observed for 21 days

postoperatively. At the end of the observation period, all animals were euthanized via decapitation method under general anesthesia. Skin samples were collected for histopathological examination.

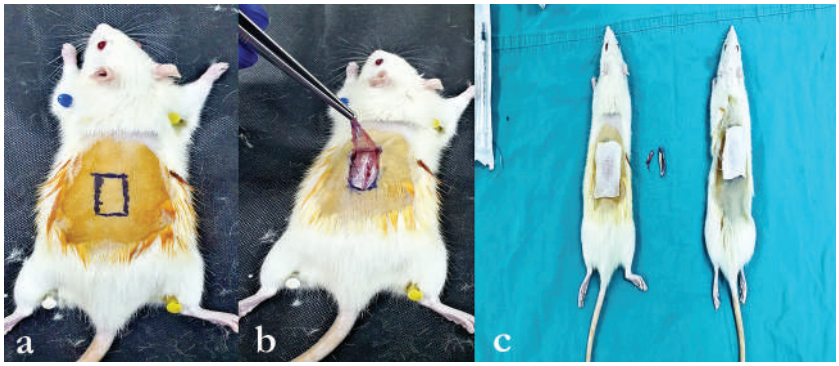

Figure 1. a,b: A standard rectangular full-thickness wound on the back (2 × 1 cm, including the panniculus carnosus muscle, subcutaneous tissue, and skin). **c**: Wounds were covered with moistened gauze soaked in physiological saline.

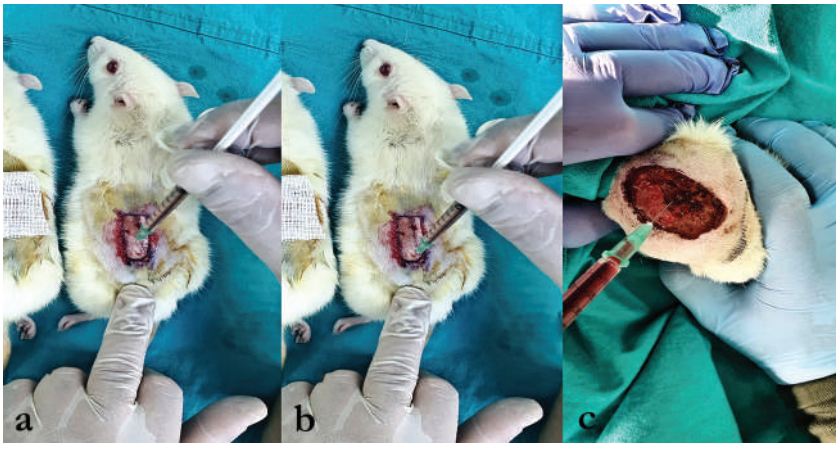

Figure 2. a,b: Wound covered with moistened gauze with physiological saline and PRP injection into the operation site. **c**: ACRS injection into the operation site.

PRP and ACRS protocols

Donor group animals were anesthetized with a combination of 10 mg/kg xylazine HCl and 60 mg/kg ketamine HCl. 10 mL blood sample was collected from the heart of each animal into tubes containing 0.3% heparin sodium as the anticoagulant. For PRP preparation, the plasma was first separated by centrifugation at 300 × g for 10 min. The platelets in the plasma were then isolated through a second centrifugation at 300 × g for 10 min. From each 10 mL blood sample, approximately 6 mL of PRP was obtained. For ACRS preparation, the blood samples were collected into special kit tubes and incubated for 3 h. Following incubation, the samples were centrifuged at

4000 × g for 5 min, and the serum was transferred to standard tubes. From each 10 mL blood sample, approximately 6 mL of ACRS was obtained.

Histopathological staining

Skin samples collected from the animals were fixed in 10% neutral formaldehyde solution for 24–48 h. Subsequently, routine tissue processing (alcohol and xylene series respectively) was performed to prepare paraffin blocks. The sections were cut 4–5 μm thick from the paraffin blocks and stained with Hematoxylin-Eosin (HE) and Masson's Trichrome (MT).

Histopathological scoring was conducted based on the criteria described by Eruygur *et al.* (2023) [18]. Inflammatory cell infiltration, angiogenesis, and edema were evaluated as: none (-), mild (+), moderate (++), severe (+++). Reepithelialization was scored as: newly formed around the wound edge (+), small opening adjacent to epithelialization (++), completed epithelialization with a thin structure (+++), completed epithelialization with a mature structure (++++). The granulation tissue was evaluated as: very dense fibroblasts, few fibrocytes, no collagen (+), equal proportions of fibrocytes and fibroblasts with new collagen formation (++), dense fibrocytes and collagen formation, few fibroblasts (+++), no fibroblasts, few fibrocytes, and dense collagen (++++). All evaluations were performed semi-quantitatively at ×20 magnification by a blinded evaluator.

Immunohistochemical staining

The 4–5 μm thick sections were placed on adhesive slides prepared from paraffin blocks. The sections underwent paraffin extraction and rehydration. Immunohistochemical staining was performed using a commercial kit, following the protocol described by Akçakavak *et al.* (2024) [19] and the manufacturer's recommendations. The following primary antibodies used were: VEGFA (Vascular Endothelial Growth Factor A; Affinity Biosciences, AF5131, USA, 1:200 dilution), MMP-9 (Matrix Metalloproteinase-9; Affinity Biosciences, AF5228, USA, 1:300 dilution), α-SMA (Alpha-Smooth Muscle Actin; Affinity Biosciences, AF1032, USA, 1:200 dilution), and IL-6 (Interleukin-6; Affinity Biosciences, DF6087, 1:400 dilution). 3, 3'-diaminobenzidine (DAB) was used as a chromogen, and counterstaining was performed with Mayer's hematoxylin. Immunohistochemical evaluation was carried out semi-quantitatively at ×20 magnification by a blinded pathologist and scored as none (0), mild (1), moderate (2), severe (3), very severe (4) [20,21].

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 21.0 for Windows (USA). Descriptive statistics were presented as numbers and percentages for categorical variables and as mean, standard error, minimum, and maximum for numerical variables.

The Kruskal-Wallis test was used to analyze non-normally distributed variables, and the Mann-Whitney U test was used for group comparisons. $P<0.05$ was accepted as the significance level.

RESULTS

Macroscopic evaluation and infection control were done on days 1, 4, 7, and 14 for all groups. No infections were detected during the observation period. Necrotic areas and wound scabs were more pronounced on days 4, 7, and 14 in group II compared to the other groups (Fig 3a,b,c). The wound edges were smoother and more defined in groups III and IV compared to group II (Fig 4a,b,c). By day 21, wound edges in group IV had completely closed and healed (Fig 5a,b,c).

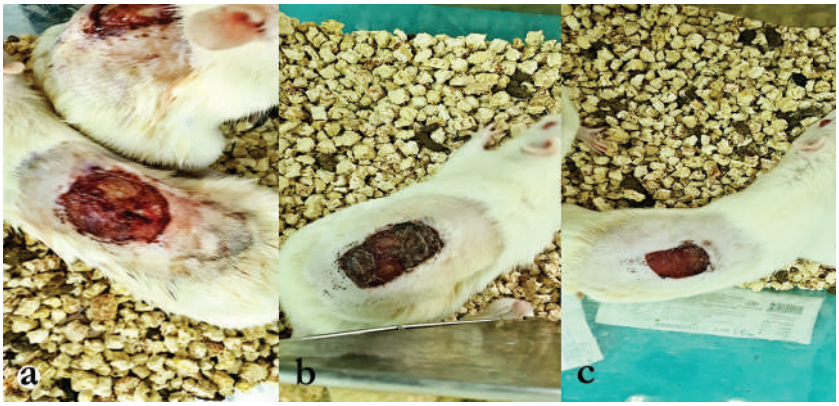

Figure 3. Macroscopic wound control on 4th day: **a**: group II; **b**: group III; **c**: group IV.

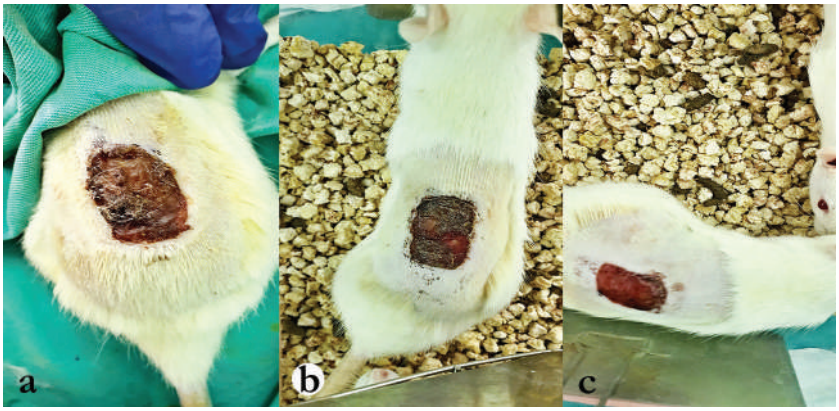

Figure 4. Macroscopic wound control on 7th day: **a**: group II; **b**: group III; **c**: group IV.

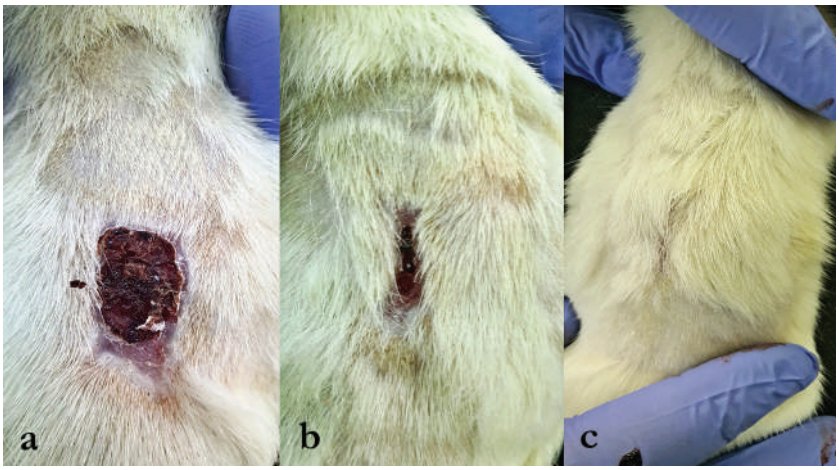

Figure 5. Macroscopic wound control on 14th day, **a**: group II, **b**: group III, **c**: group IV.

Histopathological results

Histopathological evaluations between groups are shown in Table 1. Animals in group I showed normal epidermis and dermis histology. The lowest statistical score of granulation tissue formation and epitheliazation were found in group II. The group III and IV had significant high scores than group II. The lowest angiogenesis score was found in group I and the highest scores were detected in group IV. The inflammatory cell infiltration and edema were found high in group II. The significant decreases in edema finding in group IV and the decreases inflammatory cell infiltrates both group III and IV were statistically significant compared to group II. In addition, necrotic areas were widespread observed in group II than group III and IV. In MT staining intense collagen accumulation was seen in group IV than group II (Fig 6).

Table 1. Histopathological statistical scores between groups.

Pathological Lesion	Group I	Group II	Group III	Group IV
Edema	$0.33+0.21^{c}$	$2.67+0.21^{a}$	$2.33+0.21^{a}$	$1.67+0.21^{b}$
Inflammatory cell inf.	$0.17+0.17^{d}$	$2.83+0.17^{a}$	$2.17+0.17^{b}$	$1.50+0.22^{c}$
Angiogenesis	$0.17+0.17^{c}$	$1.50+0.22^{b}$	$2.00+0.25^{b}$	$2.67+0.21^{a}$
Re-epithelialization	$3.83+0.17^{a}$	$1.33+0.21^{d}$	$2.50+0.22^{c}$	$3.17+0.17^{b}$
Granulation tissue	$3.50+0.22^{a}$	$1.50+0.22^{c}$	$2.33+0.21^{b}$	$2.83+0.17^{b}$

[a-d]Letters in the same row indicate statistical significance between groups ($P<0.001$). Group means are given as Mean+SE (n;6). (Group I: Healthy control; Group II: Operation control; Group III: PRP; Group IV: ACRS)

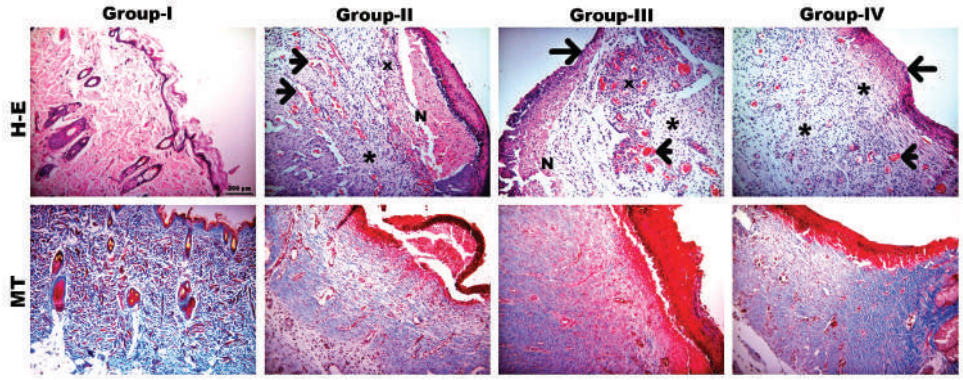

Figure 6. Microscopic appearance of samples between groups with Hematoxylin-Eosin (HE) and Masson's trichrome (MT), reepithelialization (arrows), angiogenesis (arrowheads), granulation tissue (asteriks), inflammatory cell infiltration (x), N; necrosis (Group I; Healthy control, Group II; Operation Control, Group III; PRP, Group IV; ACRS).

Immunohistochemical evaluation

Immunohistochemical evaluations between groups are shown in Table 2. There was no significant immunoreactivity seen in group I to all used primers. Group IV had significant high VEGFA and α-SMA immunoreactivity compared to group II. VEGFA immunoreactivity was found in the vascular endothelium, connective tissue cells, keratinocytes and inflammatory cell infiltrates, while α-SMA immunoreactivity was found in the vascular endothelium and connective tissue cells (especially myofibroblasts). The highest statistical values of MMP-9 and IL-6 were found in group II compare to group III and IV. The immunoreactivity of MMP-9 and IL-6 were detected in connective tissue cells, inflammatory cell infiltrates and keratinocytes (Fig 7).

Table 2. Immunohistochemical scores between groups.

Primers	Group I	Group II	Group III	Group IV
VEGFA	$0.50+0.22^{c}$	$1.5+0.22^{b}$	$1.83+0.22^{b}$	$2.67+0.21^{a}$
α-SMA	$0.33+0.21^{d}$	$1.17+0.17^{c}$	$1.83+0.17^{b}$	$2.50+0.22^{a}$
IL-6	$0.33+0.21^{c}$	$2.67+0.21^{a}$	$2.00+0.26^{b}$	$1.67+0.21^{b}$
MMP-9	$0.50+0.22^{d}$	$2.83+0.17^{a}$	$2.00+0.36^{b}$	$1.33+0.21^{c}$

a-d Letters in the same row indicate statistical significance between groups ($P<0.001$). Group means are given as Mean+SE (n;6). (**Group I**: Healthy control; **Group II**: Positive control,; **Group III**: PRP; **Group IV**: ACRS; **VEGFA**: Vascular Endothelial Growth Factor A; **α-SMA**: alpha-smooth muscle actin; **IL-6**: Interleukin-6; **MMP-9**: Matrix metalloproteinase-9)

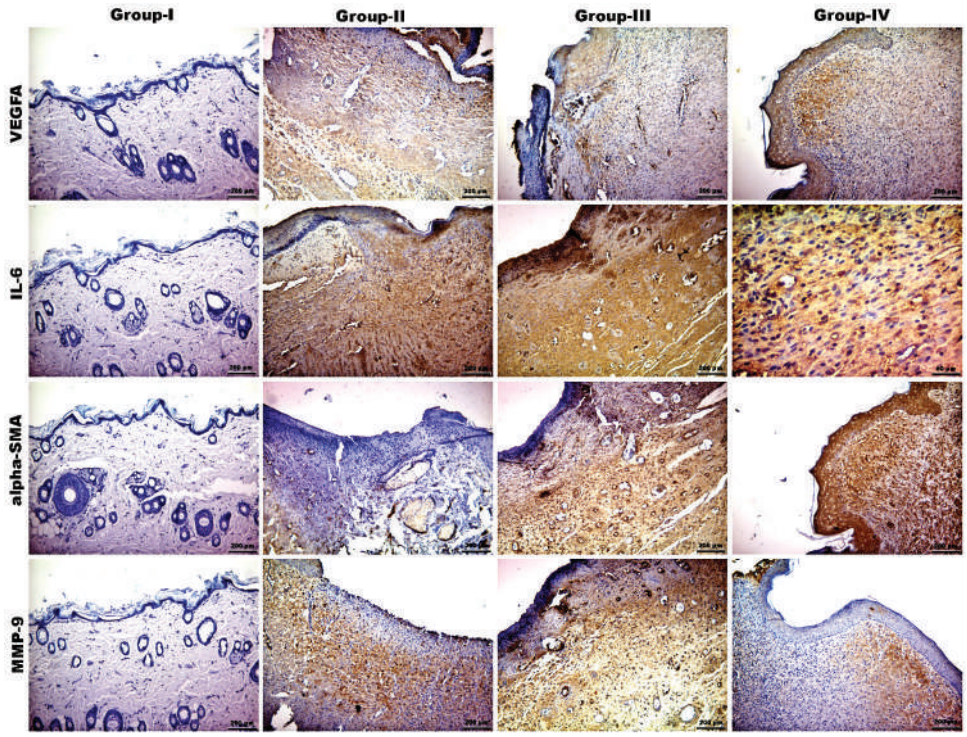

Figure 7. Immunohistochemical demonstration of VEGFA, IL-6, α-SMA and MMP-9 expressions among groups (DAB), (Group I; Healthy control, Group II; Operation Control, Group III; PRP, Group IV; ACRS, VEGFA; Vascular Endothelial Growth Factor A, MMP-9; Matrix metalloproteinase-9, IL-6; Interleukin-6, α-SMA; alpha-smooth muscle actin)

DISCUSSION

The blood vessels surrounding the wound edge are essential for delivering nutrients and oxygen required for wound healing. Wound contraction and collagen deposition represent other critical stages in the healing process. Wound contraction shortens the healing time, while the deposition of collagen fibers around the wound promotes orderly scar repair, which is vital for improving the quality of tissue remodeling [22,23].

The quality and quantity of neovascularization significantly determine the success of wound healing. VEGF, a heparin-binding growth factor specific to vascular endothelial cells, promotes endothelial cell proliferation and angiogenesis by binding to receptors on the vascular endothelium. VEGF reflects the capacity for wound angiogenesis [8]. Angiogenesis is critical for the formation of granulation tissue and the overall wound healing process [24,25]. It is induced by angiogenic factors such as VEGF

and bFGF [26]. VEGF, the most prominent proangiogenic factor, facilitates multiple stages of angiogenesis, including vasodilatation, basement membrane degradation, endothelial cell migration, and proliferation [4]. In this study, group IV had higher VEGFA levels compared to other groups. Histopathological angiogenesis scores supported these findings, showing increased blood vessel formation in parallel with VEGFA upregulation. This indicates that ACRS positively contributes to angiogenesis in wound healing.

Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are endopeptidases that play critical roles in degrading the extracellular matrix (ECM) components, enabling angiogenesis and cell migration. MMPs are calcium-dependent and zinc-containing enzymes whose activity is regulated by tissue inhibitors. The balance between MMPs and their inhibitors reflects the progression of wound healing. In the early stages, MMPs facilitate wound debridement. However, in later stages, excessive MMP activity can lead to the degradation of the newly formed matrix and delay wound healing [27-29]. Different phases of wound healing involve distinct MMPs; however, MMP-2 and MMP-9 are constitutively expressed [27,30]. MMP-9 is particularly important for keratinocyte migration, reepithelialization, and angiogenesis. Angelou *et al.* (2022) [31] observed peak level in MMP-9 on day 14 in cats treated with PRP, attributing this to the activation of angiogenic cytokines such as TNF-α and VEGF.

In the present study, MMP-9 levels were higher in group II compared to other groups, indicating that local PRP and ACRS injections reduced MMP-9 levels. Notably, group IV had lower MMP-9 levels than group III, while VEGFA and angiogenesis levels were higher. This suggests that ACRS has a more effective role in controlling MMP-9 expression than PRP, preventing excessive degradation of granulation tissue. The increased granulation scores in group IV supported this control mechanism.

The inflammatory response is a critical defense mechanism and necessary for wound healing. A balanced inflammatory response is maintained through the interaction of anti-inflammatory and pro-inflammatory signals. IL-6, a multifunctional cytokine with roles in inflammation and hematopoiesis, plays a central role in acute inflammation and wound healing. Early IL-6 release promotes the secretion of pro-inflammatory cytokines by keratinocytes, endothelial cells, macrophages, and stromal cells. In normal wound healing, IL-6 levels decrease significantly during the remodeling phase. Excessive pro-inflammatory cytokine expression must be inhibited, while anti-inflammatory cytokine expression should increase to promote healing [32,33]. In present study, IL-6 levels decreased in groups III and IV by the 21st day, indicating that PRP and ACRS have an effective anti-inflammatory activity. ACRS was found more effective than PRP in reducing IL-6, through has higher levels of anti-inflammatory cytokines [34]. However, there was no statistical significance between group III and IV in our study. This condition thought that PRP has potential synergistic regenerative effects on wound healing, and supports the wound healing as ACRS.

PRP reduces inflammation by lowering IL-17 and IL-1β levels [35,36]. In contrast, ACRS contains IL-1Ra and anti-inflammatory cytokines (IL-4, IL-10, IL-13), while PRP is enriched with VEGF, IGF-1, IGF-2, FGF, and HGF [37,38]. Studies by Jee *et al.* (2016) [39] and Farghali *et al.* (2017) [40] demonstrated that PRP accelerates reepithelialization and epidermal differentiation in dogs, while Xu *et al.* (2020) [8] reported similar findings in mice. These researchers attributed the effects to VEGF, EGF, FGF, TGF-β, PDGF, and IGF-1, which act through autocrine and paracrine mechanisms. In this study, reepithelialization scores were higher, and edema scores were lower in group IV compared to group III. Contrary to previous studies about PRP, ACRS demonstrated superior effects on reepithelialization compared to PRP in our study. This suggests that ACRS's rich composition of amino acids, vitamins, lipids, and other essential nutrients plays a significant role in enhancing wound healing.

Alpha-smooth muscle actin, an actin isoform primarily expressed in vascular smooth muscle cells, is crucial for fibroblast activation and is a marker of differentiated myofibroblasts. Myofibroblasts are essential for wound healing and tissue contraction [41,42]. Xiang *et al.* (2020) [43] used PRP to treat wounds and identified α-SMA as an indicator of myofibroblast activity. Li (2024) [16] found that ACRS treatment significantly improved wound healing in diabetic mice by enhancing fibroblast growth and inhibiting the STING pathway.

In this study, ACRS increased α-SMA expression more effectively than PRP, indicating its superior role in activating myofibroblasts during wound healing.

CONCLUSION

This study demonstrated that both PRP and ACRS positively impact skin wound healing by accelerating reepithelialization, angiogenesis, and granulation tissue formation while reducing inflammatory cell infiltration. Immunohistochemical scores indicate that ACRS is more effective than PRP in promoting skin wound healing. The superior efficacy of ACRS is attributed to its stimulation of anti-inflammatory cytokines and provision of essential nutrients such as amino acids, vitamins, and lipids. Further detailed studies are recommended to explore these findings.

Authors' contributions

HE conducted the experimental animal studies and drafted the manuscript. HE, EK and NEA performed the experimental design. NEA and EK participated in the review and editing of the manuscript. HE, EK, and ME conceived the study, participated in its design and coordination, and assisted in the preparation of the manuscript. GA performed histopathology and statistical analyses. GA and OK performed immunohistochemical staining and analysis. All authors read and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

No funding was received for this study. The authors funded the study themselves.

Data avalibility

All the data are included in the manuscript.

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POREĐENJE EFEKATA AUTOLOGNOG SERUMA BOGATOG CITOKINIMA (ACRS) I PLAZME BOGATE TROMBOCITIMA (PRP) NA ZARASTANJE RANA NA KOŽI

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Zarastanje rana je jedan od najsloženijih bioloških događaja, koji uključuje fiziološke procese kao što su obnavljanje tkiva i složene ćelijske i molekularne procese. Cilj ove studije bio je da se ispitaju efekti autolognog seruma bogatog citokinima (ACRS) i plazme bogate trombocitima (PRP) na zarastanje rana i da se uporedi njihov uticaj na sanaciju tkiva korišćenjem histopatoloških i imunohistohemijskih metoda. Ukupno 42 zdrava pacova rase Vistar-Albino korišćena su kao ogledni materijal. Histopatološke i imunohistohemijska ispitivanja pokazala su da je ACRS efikasniji od PRP u zarastanju rana. Superiorna efikasnost ACRS-a pripisuje se njegovoj stimulaciji antiinflamatornih citokina i obezbeđivanju esencijalnih hranljivih materija kao što su aminokiseline, vitamini i lipidi. Preporučuju se dalja istraživanja kako bi se detaljno ispitali ovi nalazi.