ORIGINAL ARTICLE

Effect of Stromal Vascular Fraction and Platelet-Rich Plasma on Epithelialization in Anal Trauma Healing in Wistar Rats

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ABSTRACT

INTRODUCTION: Anal trauma should be treated immediately; early debridement should be performed to prevent infection and sepsis. The use of stromal vascular fraction (SVFs) and platelet-rich plasma (PRP) have now become an alternative surgical alternative. The aim of this study was to determine the effect of stromal vascular fraction (SVFs) and platelet-rich plasma (PRP) on morphological scores for epithelialization during induced anal trauma healing in Wistar rats. **MATERIAL and METHODS:** This experimental study assessed 32 male Wistar rats over a 2-month period. The rats were randomly allocated into four groups: Group A (negative control), Group B (anal trauma treated with PRP + SVF), Group C (anal trauma without PRP + SVF), and Group D (donor rats for PRP and SVF preparation; excluded from outcome analysis). **RESULT:** Although Group B (PRP+SVF) demonstrated higher epithelialization scores compared with Group C (control), the differences were not statistically significant on Day 1 (p=0.083), Day 7 (p=0.157), or Day 14 (p=0.317). However, a significant improvement in morphological scores was observed in the within-group comparison of the PRP+SVF treatment group between Day 1 and Day 14 (p=0.049). **CONCLUSION**: The combination of PRP and SVFs led to a significant improvement in morphological scores for epithelialization within the treatment group (PRP+SVF group) over 14 days. However, this combination therapy did not demonstrate a statistically significant acceleration of wound healing when compared to the untreated control group at the observed time points.

Keywords:
Wistar rat, stromal vascular fraction, anal trauma, platelet-rich plasma, histopathology.

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INTRODUCTION

Anal trauma is a medical term for tissue damage in the form of excoriation and/or laceration in anal layers. Even though it is not a life-threatening disease, anal trauma causes discomfort due to pain.[1,2] The causes of anal trauma are blunt trauma (e.g., due to traffic accident), trauma during birth delivery, trauma due to ingested sharp objects, sharp trauma, anal sexual activity, or pneumatic trauma.[2]

Currently, transanal ultrasonography, both 2D and 3D, are the primary methods for diagnosing anal trauma. Endoanal Magnetic Resonance Imaging (MRI) can detect anal trauma as well as visualize muscle fibre and fibrotic tissue better.[3] Traumatic injuries may be isolated and/or low-energy, involving only the anal sphincter or part of a high-energy polytrauma injury. Perineal injury alone is identified in 5.4% of patients and the injury occurs mostly in the urogenital tract.[4]

Anal trauma should be treated after a physician has evaluated the perineum and assessed the sphincter function by asking the patient to contract the muscle. Early debridement should be performed to prevent infection and sepsis. Repair or approximation of the

internal and external anal sphincters with absorbable sutures should be performed immediately.[5] For large perineal trauma, surgical debridement and exsanguination prevention must be done immediately.[6] Other than the surgical approach, certain non-invasive treatments are being researched. One such approach involves the combined use of Platelet-Rich Plasma (PRP) and Stromal Vascular Fraction (SVFs), both derived from autologous sources.[7] PRP is an autologous plasma concentrate characterized by a platelet concentration significantly above baseline. The therapeutic principle of PRP lies in its role as a reservoir of growth factors essential for tissue repair. Following application to a wound, platelet activation and degranulation occur, which releases a high concentration of bioactive proteins directly into the local microenvironment. These signalling molecules are critical for orchestrating the healing cascade and include key mediators such as platelet-derived growth factor (PDGF)-AB, transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF)-2.[8] Concurrently, SVFs enhance tissue regeneration by promoting angiogenesis. This mechanism is driven by the secretion of key growth factors, such as Vascular Endothelial Growth Factor (VEGF), and by its heterogeneous population of regenerative cells, which includes endothelial progenitor cells (EPCs) and adipose-derived stem cells (ASCs).[9]

Recent systematic reviews have highlighted the synergistic potential of this combination therapy in diverse clinical applications, particularly in accelerating the healing of complex wounds. These reviews conclude that the interaction between the mitogenic signals from PRP and the cellular regenerative capacity of SVFs creates a robust pro-healing microenvironment.[10,11] This evidence reinforces the hypothesis that their combined application could offer superior outcomes compared to the use of either agent alone, thus providing a strong impetus for further investigation in specific wound models, such as anal trauma. This study aimed to evaluate the effects of PRP and SVFs on epithelial histopathological parameters in induced anal trauma in Wistar rats. The histopathological features of anal epithelial tissue were assessed over a two-week period. Findings from this research may provide clinically relevant insights into the potential role of PRP and SVF in enhancing wound healing.

MATERIAL AND METHODS

Study Design

This experimental study used 32 healthy adult male Wistar rats (Rattus novergicus), aged 16-24 weeks and weighing 170-260 grams. The animals were randomly allocated into four groups. Group A (Negative Control, n=4) comprised healthy rats without any intervention to serve as a baseline for normal tissue histology. Group B (Treatment Group, n=12) consisted of rats subjected to induced anal trauma followed by treatment with PRP+SVF. Group C (Trauma Control, n=12) also underwent induced anal trauma but did not receive the PRP+SVF treatment, thus serving as the control for the natural healing process. Lastly, Group D (Donor Group, n=4) was designated for the sole purpose of harvesting blood and adipose tissue to prepare the PRP and SVFs administered to Group B.

Sample Size

The minimum sample size was determined using the Federer formula $(t-1)(n-1)\geq 15$, a standard guideline to ensure sufficient statistical power in animal experimental studies.[12,13] In this formula, t represents the number of experimental groups, and n denotes the number of subjects per group. In the present study, six experimental subgroups were included: Group B (treatment) and Group C (control), each evaluated at three distinct time points (Day 1, Day 7, and Day 14). With six groups (t= 6), the calculation yields $(6-1)(n-1)\geq 15(6-1)(n-1)\geq 15(6-1)(n-1)\geq 15$. Therefore, the minimum sample size required for each group was four rats. Exclusion criteria were the following: (i) biopsy tissue could not be analysed, (ii) infection occurred, and (iii) death before being sacrificed.

Study Protocol

All rats underwent a 2-week adaptation period with a 12-hour-long light-dark cycle in a 40 x 20 x 20 cm^2 cage, with each cage consisting of 4-5 rats. Environment temperature was controlled at 28 ± 2ºC with 5–60%

humidity. A standard diet using AD2 diet (20 grams for each rat) was given and the rats had free access to water.

Wistar rats were shaved on the back and anesthetized using ether. Thoracotomy was performed in 4 donor rats and blood was taken from the apex cordis using a 25G needle. Fat tissue was taken from both thighs. After blood and fat tissue were taken, the 4 donor rats (Group D) were sacrificed.

Group A (n=4, negative control group) were sacrificed after the adaptation period (Day-0). Groups B and C both underwent induced anal trauma, each had 12 rats (n=12) were sacrificed on Day-1 (n=4), Day-7 (n=4), and Day-14 (n=4). A biopsy was carried out on each rat at the induced anal trauma site.

On Day-0, anal injury was induced on to rats in Groups B and C Rats were anesthetized with ether, placed in supine position, the perineal and anal areas were sterilized. The anal canal was emptied and 6Fr catheter was inserted as a marker. Anterior perianal incision was made at 10-15 mm and adipose tissue was identified and dissected. A 5 mm incision was made in the muscular layers until the submucous was visualized. Mucous layers should not be injured (a catheter was used as a marker). If perforation occurred, an interrupted suture was made in the mucosal layer. The submucosal and muscularis layers were sutured using a 6.0 absorbable surgical suture. PRP+SVF were injected after induced anal trauma in Group B rats in their surgical wounds. Moreover, on the cutaneous layer, an interrupted suture was made using an absorbable surgical suture.

The surgical wound was then washed using sterile normal saline and covered with gauze. Postoperatively, rats received ceftriaxone 50 mg/kg intravenous once daily for 3 days as antibiotic prophylaxis and ketorolac 2 mg/kg intravenous once daily for 3 days for analgesia.

On Day-1, Day-7, and Day-14, rats were sacrificed using ether as an anaesthetic agent. The wound area was documented using a Nikon D5600 digital camera (Nikon Corporation, Tokyo, Japan) under standardized lighting conditions prior to biopsy collection. Epithelialization during wound healing was subsequently analysed by histopathological examination.

Preparation of Platelet-Rich Plasma and Stromal Vascular Fraction

To prepare the Platelet-Rich Plasma (PRP), blood collected from donor rats was placed in EDTA tubes and subjected to a first centrifugation at 2400 rpm (450 G) for 10 minutes. Supernatant plasma with buffy coat was then put into the second centrifugation with 3600 rpm (850 G) for 15 minutes. Infranatant buffy coat was stored for preparing the final product of PRP.[14] For the SVF, fat tissue from the thigh fold of donor rats was washed with phosphate buffer, minced, and digested with 0.15% collagenase in a 37 ℃ incubator for 30 minutes. The collagenase activity was neutralized by adding Dulbecco Modified Eagle Media (DMEM) with 10% FBS and 1% antibiotic-antimycotic. The sample was centrifuged at 1500 rpm for 5 minutes. The resulting cell pellet was resuspended, and the SVF cell count was measured using Trypan blue with a Neubauer counting chamber. The final PRP+SVF product was prepared by adding a 50,000 SVF cell preparation to 0.5 ml of PRP.[1,14,15]

Histopathological Assessment

Quantitative assessments of epithelialization score were performed on H&E-stained histopathological sections from the excised wound tissue. The degree of epithelialization was graded on an ordinal scale with four steps: (i) whole skin, if no new epithelialization was present; (ii) discrete, if new epithelium covered at least 1/3 of the wound area; (iii) moderate, if new epithelium covered more than 1/3 of the wound area; and (iv) complete epithelialization, if the new epithelium covered the entire wound area.

Statistical Analysis

All data were analysed using SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as median (interquartile range [IQR]) for ordinal data. The Mann-Whitney U test was used to compare differences between Group B (PRP+SVF) and Group C (control) at each observation day and for the

pooled analysis. The Wilcoxon signed-rank test was applied for within-group comparisons across time points (e.g., Day 1 vs. Day 14 in Group B). A *p*-value <0.05 was considered statistically significant.

RESULT

Epithelialization scores were analysed across observation days for all groups (Table I). On Day 0, Group A (negative control) demonstrated early epithelial coverage with a mean ± SD score of 0.57±0.31, representing baseline histological characteristics before any treatment.

On Day 1, epithelialization remained limited in both experimental groups. In Group B (treatment group), discrete epithelialization was observed in three samples (75%) and whole-skin coverage in one sample (25%), with a median score of 1.0 (1.0-1.0). In contrast, Group C (control) exhibited whole-skin epithelialization in all samples (100%), with a median score of 0.0 (IQR 0.0-0.0). The between-group comparison showed no statistically significant difference (p=0.083, Mann-Whitney U test).

By Day 7, Group B (PRP+SVF) showed a higher proportion of complete epithelialization (50%) compared to Group C (0%). The median epithelialization score was 2.5 (2-3) in Group B and 2.5 (2-3) in Group C, indicating a statistically significant difference (p=0.157) between groups.

On Day 14, all rats in Group B (100%) achieved complete epithelialization, while in Group C, complete epithelialization was found in 75.0% of samples. The median score in Group B was 3 (3-3) compared to 3 (2-3) in Group C. This between-group difference was statistically significant (p=0.317).

Overall, the results indicate that epithelialization progressed over time in all groups, with a more consistent and complete healing pattern observed in the PRP+SVF group, although not all between-group comparisons reached statistical significance.

When cumulative epithelialization morphology across all observation days (Day 1, 7, and 14) was analysed using the Wilcoxon rank-sum test, a significant difference was found between groups (p=0.026) (Table II). The group B demonstrated a higher proportion of complete epithelialization (50 %) and a lower incidence of unhealed whole-skin areas (8.3 %) compared with the group C (25 % and 50 %, respectively).

Table I. Epithelialization Stages by Observation Day and Treatment Group

Day	Group	Whole Skin n (%)	Discrete n (%)	Moderate n (%)	Complete Healing	Epithelialization Score, Median	p value
0	Group A (Negative Control)	1 (25.0)	3 (75.0)	0 (0.0)	0 (0.0)	1 (1–1)#	—
1	Group B (Treatment	1 (25.0)	3 (75.0)	0 (0.0)	0 (0.0)	1 (1–1)	—
	Group C (Trauma Control)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0–0)	0.083*
7	Group B (Treatment	0 (0.0)	1 (25.0)	1 (25.0)	2 (50.0)	2.5 (2–3)	—
	Group C (Trauma Control)	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (0–2)	0.157*
14	Group B (Treatment	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	3 (3–3)	—
	Group C (Trauma Control)	0 (0.0)	0 (0.0)	1 (25.0)	3 (75.0)	3 (2–3)	0.317*

Notes: Data are presented as frequency (percentage) and median (interquartile range [IQR]) for ordinal epithelialization scores, except for Group A, where mean ± SD is shown due to single baseline measurement. *Mann-Whitney U test (between groups at the same day). #Mean ± SD=0.57 ± 0.31 for Group A (Day 0 baseline). PRP: Platelet-Rich Plasma; SVF: Stromal Vascular Fraction.

Table II: Comparison of cumulative epithelialization morphology across all observation days between Group B and Group C

Epithelialization Category	B (Treatment) (n = 12)	C (Trauma Control) (n = 12)	p-value
Whole Skin (no epithelializa-tion)	1 (8.3 %)	6 (50.0 %)	0.026
Discrete Epithelialization	4 (33.3 %)	1 (8.3 %)	
Moderate Epithelialization	1 (8.3 %)	2 (16.7 %)	
Complete Healing	6 (50.0 %)	3 (25.0 %)	

Note: Data represent the cumulative distribution of epithelialization morphology assessed at Day 1, Day 7, and Day 14 following experimentally induced anal trauma in rats. Statistical comparison between group B and group C was performed using the **Wilcoxon rank-sum test**. PRP = Platelet-Rich Plasma; SVF = Stromal Vascular Fraction.

A within-group comparison in the group B showed a significant improvement over time. On Day 1, most animals exhibited discrete epithelialization, whereas by Day 14, all demonstrated complete epithelial healing. Statistical analysis using the Wilcoxon signed-rank test confirmed a significant temporal difference between Day 1 and Day 14 (p = 0.049) (Table III).

Table III: Comparison of Epithelialization Morphology between Day 1 and Day 14 in the PRP + SVF Group

Epithelialization Category	Day 1 (n = 4)	Day 14 (n = 4)	p-value
Whole Skin	1 (25%)	0 (0%)	0.049
Discrete Epithelialization	3 (75%)	0 (0%)	
Moderate Epithelialization	0 (0%)	0 (0%)	
Complete Healing	0 (0%)	4 (100%)	

Note: Data represent morphological changes in epithelialization from Day 1 to Day 14 following PRP + SVF treatment. Statistical analysis was performed using the **Wilcoxon signed-rank test**. PRP = Platelet-Rich Plasma; SVF = Stromal Vascular Fraction.

DISCUSSION

In this study, the application of PRP+SVF to induced anal trauma in Wistar rats was associated with a positive trend in epithelialization. While a direct comparison between the treatment and control groups did not yield statistically significant differences on Day 1, Day 7, or Day 14, a significant improvement in morphological scores was observed within the treatment group between Day 1 and Day 14 ($p=0.049$). This suggests that the combination therapy contributes to the progression of healing over time. The lack of statistical significance in between-group comparisons may be attributable to the small sample size or the relatively short observation period, which might have been insufficient to capture the full extent of the therapeutic effect.

The observed acceleration of epithelialization in the group B is biologically plausible. PRP provides a concentrated source of autologous growth factors such as PDGF, TGF-β, IGF, EGF, and FGF which act as potent chemotactic and mitogenic signals for keratinocytes, fibroblasts, and endothelial cells. Meanwhile, SVF contains a heterogeneous population of regenerative cells, including MSCs, pericytes, EPCs, and immune-modulatory macrophages. Together, these components contribute to angiogenesis, extracellular matrix remodelling, and re-epithelialization, thereby establishing a pro-healing microenvironment at the wound site.

Several biological factors may explain the lack of a statistically significant difference between the treatment and control groups at the specified time points, despite the positive trend observed with PRP+SVF administration. First, healthy Wistar rats possess a robust and efficient intrinsic wound healing capacity. The perianal region is highly vascularized,[16] which naturally promotes rapid cell migration and proliferation. This potent endogenous healing in the control group could have narrowed the observable therapeutic window, making a statistically significant advantage for the treatment group difficult to detect within a 14-day period.

Second, the mechanisms of PRP and SVFs operate on different timelines. PRP provides an immediate, potent bolus of growth factors (such as PDGF and TGF-β) that primarily accelerates the initial inflammatory and proliferative phases of healing.[17,18] In contrast, the regenerative contribution of SVFs which contain a population of mesenchymal stem cells, endothelial progenitors, and fibroblasts[19] is often more gradual, involving longer-term processes such as cell differentiation, sustained paracrine signalling, and tissue remodelling. Our 14-day endpoint may have been sufficient to capture the initial surge driven by PRP but too short to fully appreciate the more profound, structural contributions of the SVF cellular components that manifest in later stages of wound maturation. This could explain why a significant improvement was seen *within* the treatment group over time, but a significant advantage *over* the control group was not yet established

In our study, we also examined the effects of PRP+SVF on anal wound healing and compared it to healing without these treatments, specifically focusing on epithelialization. Our findings align with previous research that demonstrated faster wound healing with SVF+PRP compared to controls, SVF alone, or PRP alone.[20] A study found that SVF+PRP is beneficial in lower extremities with diabetic ulcer.[21]

Comparison of epithelialization between Group B (anal trauma treated with PRP+SVF) and Group C (anal trauma without PRP+SVF), on Day-1, Day-7, and Day-14 did not show a significant difference (Table I). Nevertheless, we found a significant difference in epithelialization on Day-1 and Day-14 only in the Group B (Table III). A study showed that average duration for wound healing in diabetic ulcer in lower extremities was 71.75 ± 29.57 days.[21] Hence, wound healing still required several days to be completed even after intervention. A study also showed effective wound healing in PRP+SVF in rats with a radiation wound one month, two months, and three months after intervention.[22] Another study found that EGF was significantly higher on Day-14 of anal trauma rats compared to Day-1.[15]

Our findings, which demonstrate a positive trend and a significant within-group improvement, are broadly

consistent with the conclusions of recent systematic reviews. For example, a study on regenerative therapies for skin quality found that combination therapies including PRP and a cellular component like SVFs offer a statistically significant advantage in improving skin quality over conventional treatments.[23] While our study did not demonstrate a significant between-group difference likely due to limitations such as sample size and the potent intrinsic healing of the animal model the observed pro-healing trend aligns with the direction of effect reported in this higher-level evidence. This suggests that our results are biologically plausible and contribute to the growing body of literature supporting this therapeutic strategy.

Our study has several important limitations that must be acknowledged. First, the study was conducted with a small sample size (n=4 per subgroup), which significantly limited its statistical power. This increases the likelihood of a Type II error, meaning a true therapeutic effect of the PRP+SVF intervention may exist but was not detected as statistically significant in our analysis. Second, the 14-day observation period was relatively short. This timeframe may have been insufficient to fully capture the later stages of wound maturation and tissue remodelling, where the regenerative contributions of SVFs might become more apparent.

For future studies, we recommend an experimental design that includes not only the combination therapy but also separate arms for PRP administration alone and SVF administration alone. Such a design is essential for several reasons. First, it would make it possible to distinguish the individual therapeutic contributions of each component. This would help determine whether the healing benefits are driven primarily by the immediate bolus of growth factors from PRP, the longer-term cellular regenerative capacity of SVFs, or a true synergistic interaction between the two. Second, understanding the efficacy of each component individually has significant clinical implications, potentially leading to more targeted, cost-effective treatment strategies for anal trauma and other complex wounds.

CONCLUSION

The combination therapy of PRP and SVFs was associated with a significant improvement in morphological scores for epithelialization within the treatment group over a 14-day period in this rat model. However, the therapy did not demonstrate a statistically significant acceleration of wound healing when compared directly to the control group at the observed time points. These findings suggest a potential benefit, but further studies with larger sample sizes and longer observation periods are warranted to fully elucidate the therapeutic efficacy of this combination for anal trauma healing.

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CONFLICTS OF INTEREST

None

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study obtained ethical approval from the Ethical Committee of Faculty of Medicine, Hasanuddin University (Number: 328/UN4.6.5.31/PP36/2021).

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