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# The clinical and histopathological study, the effects of platelet-rich fibrin on skin pedicle graft healing

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***Abstract***---Background: Tissue engineering aims to repair or replace damaged tissue in response to various injury circumstances. One of these sectors is platelet-rich fibrin (PRF), extensively employed for soft tissue regeneration in recent years. Objective: The research aimed to examine the clinical and histological effects of allogenic PRF on skin pedicle grafts used to treat experimental avulsion wounds. Materials and method: Fifteen adult female goats were used for this study. Under heavy sedation and complete aseptic conditions, 2 skin marks (2×2 cm) were created on both sides of the trunk region of the animal. Two total thicknesses of the blotchy skin are cut carefully. Advancement (sliding) flaps (2×6 cm) are harvested parallel to the lines of most minor tension and slid over the adjacent wound. These wounds are allocated into two groups, the first one as the control group and the second group treated with autogenic platelet-rich fibrin. Each goat has two groups represented. The edges of the wounds were closed by 2-0 nylon monofilament sutures with a simple interrupted pattern. Results: Clinical examination showed the amount of wound exudation in the treated group significantly increased compared to the control group. The swelling of the grafts in the treated group disappeared within the next three postoperative days. However, in the control group, it was more incredible and remained for a more extended period, as it continued until the seventh day. After 7, 14 and 21 days post grafting, the histopathological results showed there was an improvement in the stages of healing in the skin pedicle wounds of the PRF-treated group. These improvements include accelerating the end of the inflammatory phase, the quality of the granulation tissue, epithelialization, reaching the maturation stage, and complete regeneration of epidermal and


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dermal layers as compared with the control group. Conclusions: The PRF induces excessive healthy acute exudates that promote and accelerate healing. PRF could effectively promote wound healing of the skin pedicle flap, essentially in collagen deposition, tissue formation, angiogenesis, and re-epithelialization.

***Keywords*---**Goats, pedicle graft, PRF, Skin, Histopathology.

## Introduction

The skin is the body's biggest organ when measured in terms of its surface area. This essential structure protects internal tissues against harm caused by mechanical forces, an infection caused by microorganisms, UV light, and severe temperatures. Because of this, it is very prone to damage, which may have a substantial effect on individual patients and the economics of the healthcare sector. (Rodrigues et al. 2019).

The breakdown of dead tissue intercalates with the development of new extracellular matrix structures and the covering lining of the epithelium at wounds, which may be likened to a "huge biological building site." The injury must have a highly active metabolic state so that the regeneration process may be completed properly. (Tottoli, *et al.* 2020 and Schneider, *et al.* 2007 and Alfars, 2009).

Healing wounds continues to be a complex clinical issue, and treating injuries accurately and effectively is vital. There has been a significant amount of work put into wound care, with an emphasis placed on developing innovative treatment techniques and technology for managing both acute and chronic wounds. Multiple cell populations, an extracellular matrix, and the activity of soluble mediators like growth factors and cytokines are all involved in the healing process once a wound has been sustained. Although the process of recovery is ongoing, (Velnar *et al.* 2009), It can be split into four stages at will: I coagulation and haemostasias; II inflammation; III proliferation; and IV wound remodeling with the creation of scar tissue. The appropriate method of wound treatment has the potential to impact the therapeutic outcome significantly. (Velnar *et al.* 2009; Hashim, *et al.* 2021; Khashjoori, *et al.* 2019 and Abdulrazaq, 2012, Naeem, et al. 2021).

Skin grafting is the most effective treatment for injuries that result in only skin loss. If the bed is adequately vascularized, difficulties are often limited to mechanical ones, such as forming a barrier, such as a hematoma, between the bed and the graft or shearing forces pulling the graft from the bed. Skin flaps generally have their blood supply, so they are not susceptible to these issues. Nonetheless, they rely on the continuance of appropriate circulation until vascularization occurs. This is a lengthy procedure since flaps are much thicker than grafts and are susceptible to base tension issues. Coverage of skin Wound complications may be split into two groups: those connected with difficulties in the wound bed and those associated with failure of skin graft or flap covering. Inadequate preparation, infection, or excessive scarring due to a lengthy delay between damage and dressing application are the most common causes of wound complications. (Browne, 1986).

Despite recent advancements in wound closure techniques and devices, there is an urgent need for novel approaches to optimize the healing process. Wound healing is a complicated series of intracellular and extracellular activities controlled by signaling proteins. Currently, this process is not well understood. The topical use of growth factors to improve routine wound healing is one of the promising but complex areas of current therapeutic research. (Desai, et al. 2013). One of the most significant difficulties confronting clinical research is the development of bioactive surgical additives capable of controlling inflammation and promoting healing. Indeed, following each intervention, surgeons must deal with complicated tissue remodeling events and their effects on tissue survival and recovery. Platelet-rich fibrin (PRF) is a member of a new class of platelet concentrates designed for preparations requiring no biochemical blood processing. It is nothing more than blood that has been centrifuged without additives. (Dohan *et al.* 2006).

PRF is characterized as a biodegradable scaffold containing enhanced levels of platelets and leukocytes that may release high concentrations of bioactive structural proteins and functions as a time-release healing hemoderivative. (Soares, *et al.* 2021).

**The study aimed** to evaluate the effect of autogenic genic PRF on skin pedicle grafts to treat experimental avulsion wounds. The evaluations that were performed included clinical signs of injuries and histopathology.

## 2 Materials and Methods

The experiment was done on 15 mature female goats weighing 18 and 20 kg and aged between 7 and 8 months. Ten millilitres of blood were collected from the jugular vein before surgery. Blood was transferred immediately to a 10-mL sterile plastic tube (PRF Tube; anticoagulant-free, evacuated tube) and centrifuged at 1500 rpm for 14 minutes (figure 1). The final product has three layers. The top layer of the test tube contains acellular PPP (platelet-poor plasma), followed by a PRF clot in the center and RBCs at the bottom (Figure 2). After centrifugation, the fibrin clot and associated red blood cells are extracted from the tube and discarded, respectively (figure 3).

Under intense sedation and complete asepsis, two 2×2 centimeter skin markings were made on opposite sides of the trunk area of the animal. Two total thicknesses of the blotchy skin are cut carefully (figure 4, a). Advancement, or sliding flap (26 cm), is harvested parallel to the lines of least stress and is afterwards moved over the surrounding incision (figure 4, b). These wounds are divided into two groups, the first as the control group (without local therapy) and the second as the PRF-treated group (treated with autogenic platelet-rich fibrin) (figure 4, c). Each goat is a representative of both groups. The margins of the incisions were sutured using 2-0 nylon monofilament suture in a simple interrupted pattern. Grafts were protected from dehydration and infection by occlusive dressing.

Following surgery, clinical wound evaluation was conducted with the following factors: The animal's overall health status, Inflammation and exudation.

The exudates scores were estimated as non (1), light (2), moderate (3), and heavy (4), while swelling scores classified into non 0, mild 1, and obvious 3 (Bosanquet, *et al.* 2013).

At the end of the 1, 2, and 3-week follow-up surgeries, the flap tissues were removed for histology under severe sedation. The area of excision includes a portion of the flap, the suture line, and a 1 cm wide band of intact skin. The removed tissue samples were preserved with 10% formaldehyde and transferred to the Department of Pathology, where they were paraffin-embedded and sectioned. H & E (hematoxylin and eosin) staining was used. (Ahmed et al. 2017)

## 3 Results and Discussions

### Clinical evaluations

After surgery, there was no change in the animal's appetite. On the day after the operation, the temperatures of all animals rose by one degree and then reverted to normal .

On the first postoperative day, fluid exudation was noted at the wound site in the treated group but only in minor amounts in the control group. On the second, third, and fourth postoperative days, it was noticed that the exudates in the treated wounds were minimal and eventually eliminated. However, on the third day, fluid exudates disappeared from the control wounds (figure 5, table 1).

The treated group of wounds exhibited swelling in the patched skin region on the first and second day, but oedema subsided within three days. In contrast, the swelling was higher and lasted longer in the control group since it persisted until the seventh day (figure 6, table 2)

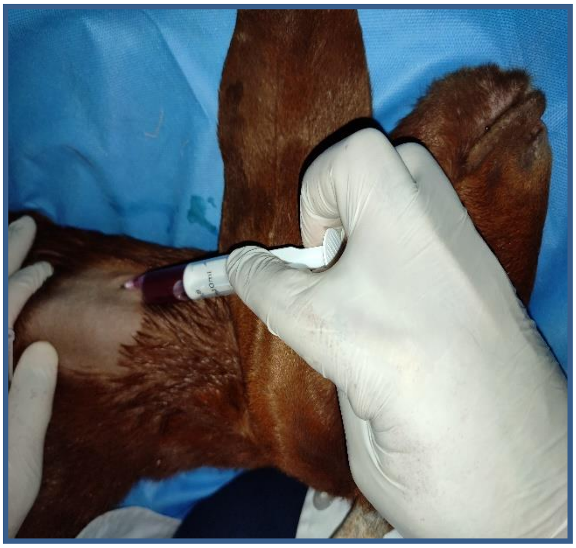

Figure 1: collection the venous blood from the jugular vein

Figure 2a: centrifugation the blood sample with 1500 round per 14 mints

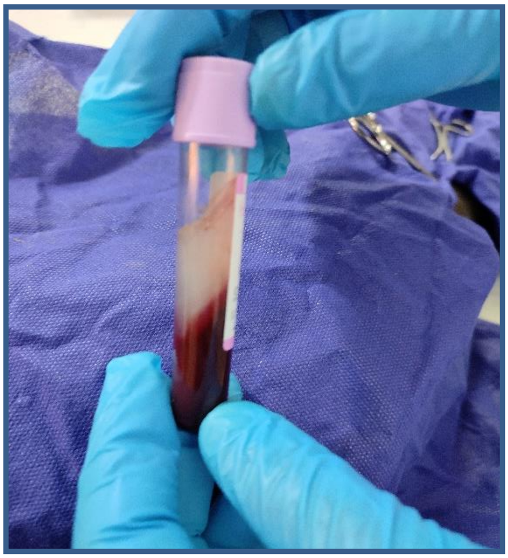

Figure 2b: the accumulation of PRF inside tube after centrifugation

Figure 3: the PRF glue was isolated from the blood

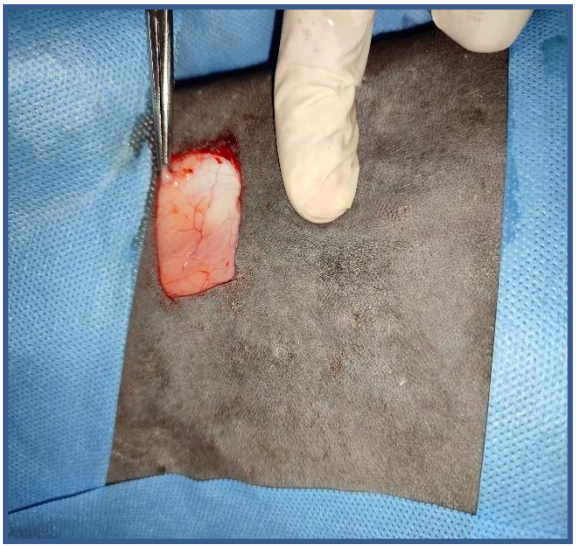

Figure 4a: skin pedicle flap was done by 2 parallel incisions

Figure 4b: Suturing the pedicle flap was complete with simple interrupted suture pattern


Figure 4c: the site of surgery was covered by wound dressing

Figure 5: measuring the level of acidity by using PH test paper

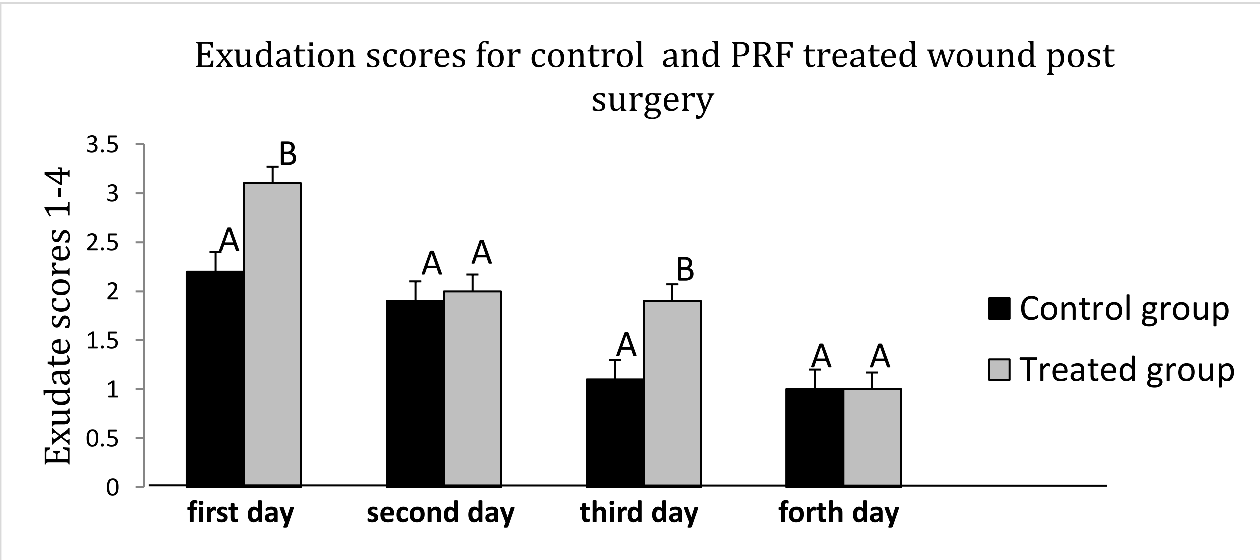


Figure 6: clinical study showed the exudates scores for skin grafts of Control and PRF treated groups wounds during (1, 2, 3 and 4 days post surgery). [ABC] Different letters among groups indicates significant differences (P< 0.05).

Table 1: clinical study showed the exudates scores for skin grafts of Control and PRF treated groups wounds (1, 2, 3 and 4 days post surgery) (means and standard errors).

| Groups | 1st day | 2nd day | 3rd day | 4th |
| --- | --- | --- | --- | --- |
| Control | 2.2±0.2A | 1.9±0.17A | 1.1±0.1A | 1.0±0.0A |
| PRF | 3.1±0.17B | 2.0±0.14B | 1.9±0.1B | 1.0±0.0 A |

ABC Different letters within each column indicates significant differences ($P<0.05$).

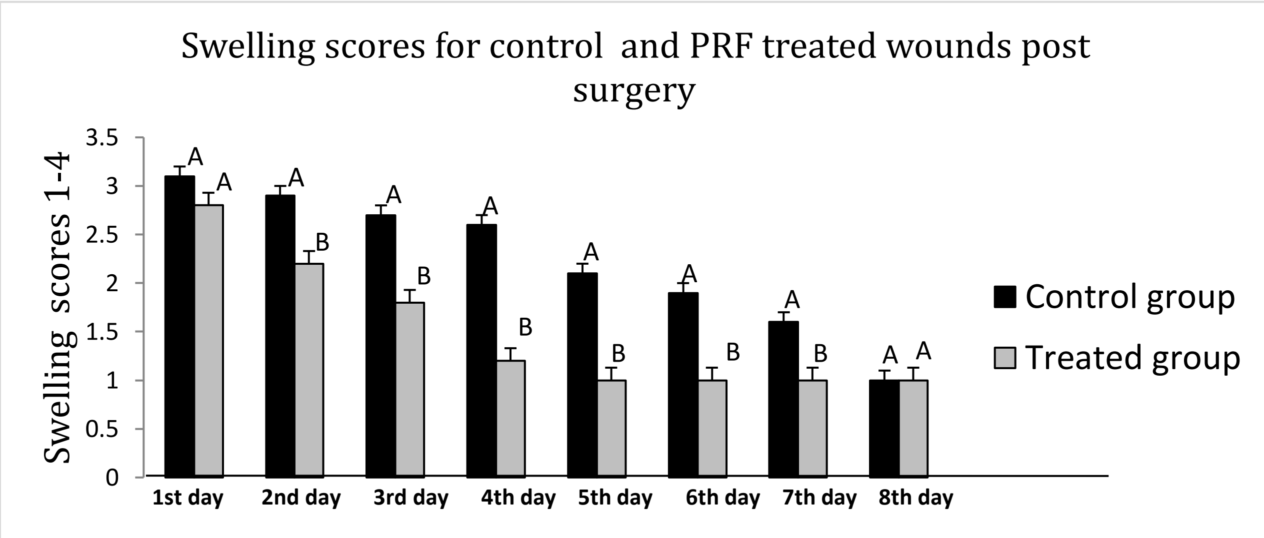


Figure 7: clinical study showed the Swelling scores for skin grafts of Control and PRF treated groups (1-8 days post-surgery). ABC Different letters among groups indicates significant differences ($P< 0.05$).

Table 2: clinical study showed the swelling scores for skin grafts of Control and PRF treated groups (1-8 days post-surgery) (means and standard errors).

| Group | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day | 8th day |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Control | 3.1±0.1A | 2.9±0.1A | 2.7±0.15A | 2.6±0.16A | 2.1±0.1A | 1.9±0.17A | 1.6±0.16A | 1.0±0.0A |
| PRF | 2.8±0.13A | 2.2±0.13B | 1.8±0.13B | 1.2±0.13B | 1.0±0.0B | 1.0±0.0B | 1.0±0.0B | 1.0±0.0A |

ABC Different letters within each column indicates significant differences ($P<0.05$).

**Histopathological Findings**

During the first week after wound induction, epithelial cells migrated to the incision line (Figure 8). In addition, a thick scab and epithelialization were seen on the top section of the inner wound wall margins (Figures 9 and 910). During this stage, the stratum corneum and stratum lucidum layers are re-epithelialized (Figure 11). In contrast, the wound inflicted in the control group during the same period exhibited a gap at the incision line between wound edges and a tiny region of re-epithelization on one edge (Figures 12, 13, and 14).

The PRF group demonstrated regeneration of epidermis layers, creation of an epithelial tongue in the dermis, and oedema in the afflicted area 14 days after damage (Figure 15). Additionally, during this era, newly created blood vessels and sweat glands were detected (Figure 16).

In contrast, after 14 days, the control group had a gap between the regenerated epidermal layer and the dermis layer, demonstrating oedema's existence (Figure 17). Voids were found between the regenerated stratum corneum and the stratum spinosum layers (Figures 18 and 19). In addition, the Figure demonstrates perivascular lymphocytic infiltration in the subcutaneous layer (Figures 20 and 21).

After 21 days after wound induction, the PRF group demonstrated complete epidermal and dermal regeneration (Figures 22). During this phase, the formation of new blood vessels and the infiltration of inflammatory cells were also noticeable (Figures 23 and 24). In contrast, the control group during the same period showed a fully-regenerated epidermal layer, freshly created blood vessels, and newly produced hair follicles, but gaps and separation between the epidermis and dermis layers, as well as few inflammatory cells (Figures 25 and 26).

Figure 8: PRF group, 1st week post surgery. Section of skin wound showed incision line (yellow line and black arrow), migration of epithelial cells (yellow arrow), and epithelialization was seen on the upper portion of the inner wall of the wound edges in PRF-treated group. H&E, 40X.

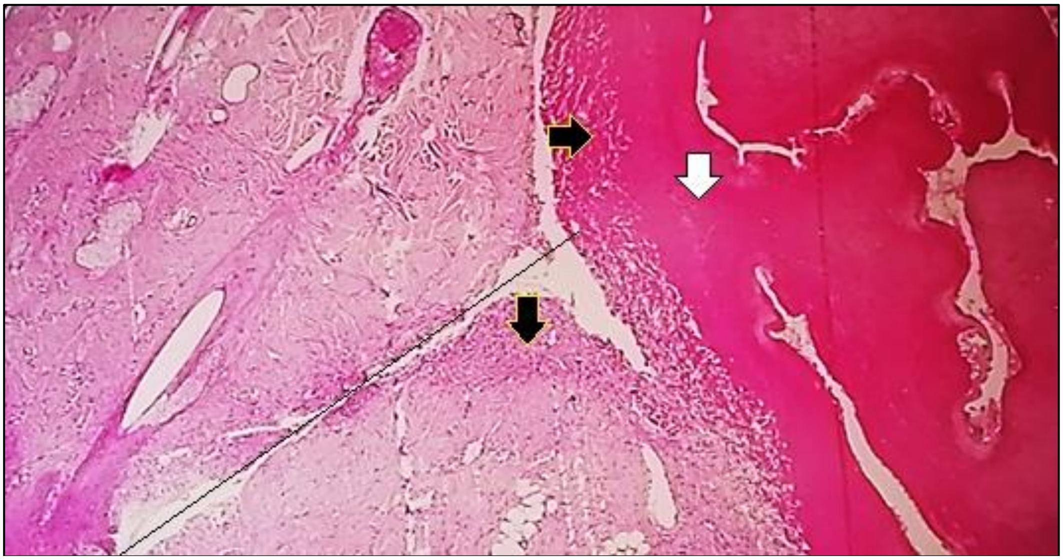

Figure 9: PRF group, 1st week post surgery. Section of skin wound showed incision line (black line), formation of a thick scab (white arrow) epithelialization was seen on the upper portion of the inner wall of the wound edges (black arrows) in PRF-treated group. H&E, 40X.

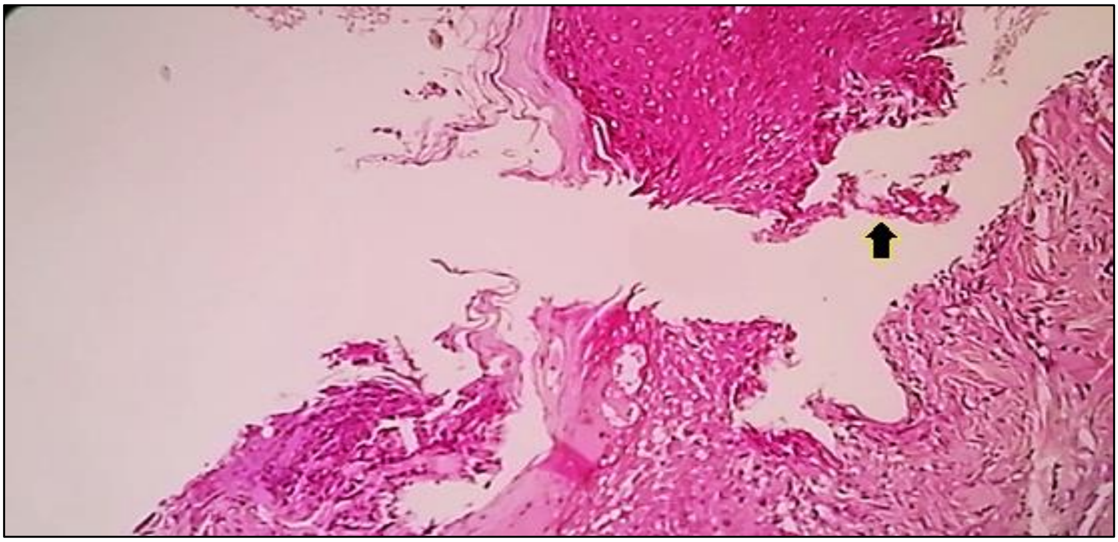

Figure 10: PRF group, 1st week post surgery. Section of skin wound showed migration of epithelial cells (black arrow) at incision line. H&E, 100X.

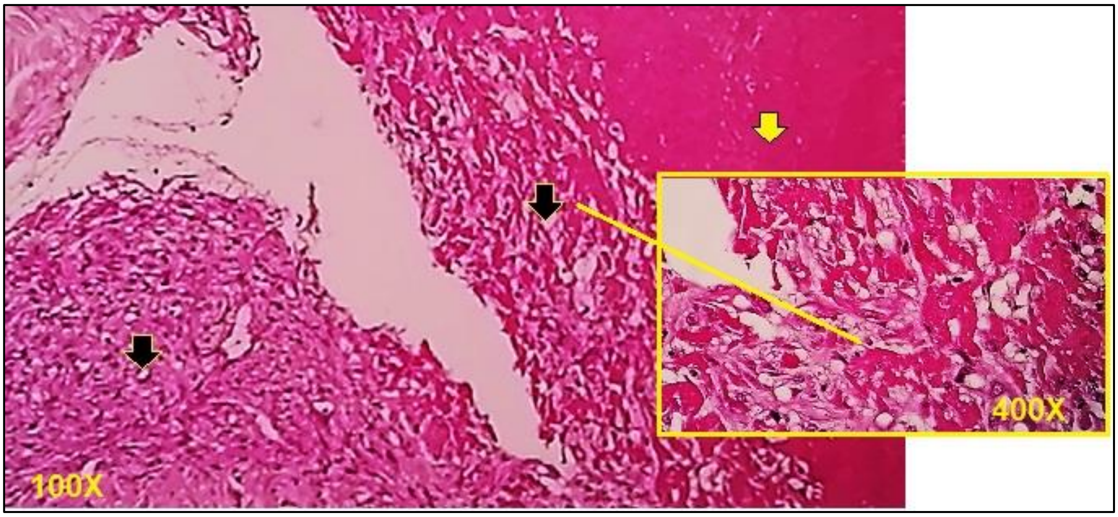


Figure 11: PRF group,1st week post surgery. Section of skin wound showed incision site, formation of a thick scab (yellow arrow), epithelialization was seen on the upper portion of the inner wall of the wound edges (black arrows) in PRF-treated group. H&E, 100X. The focused area represents the re-epithelized area of stratum corneum and stratum lucidum layers. H&E, 400x.

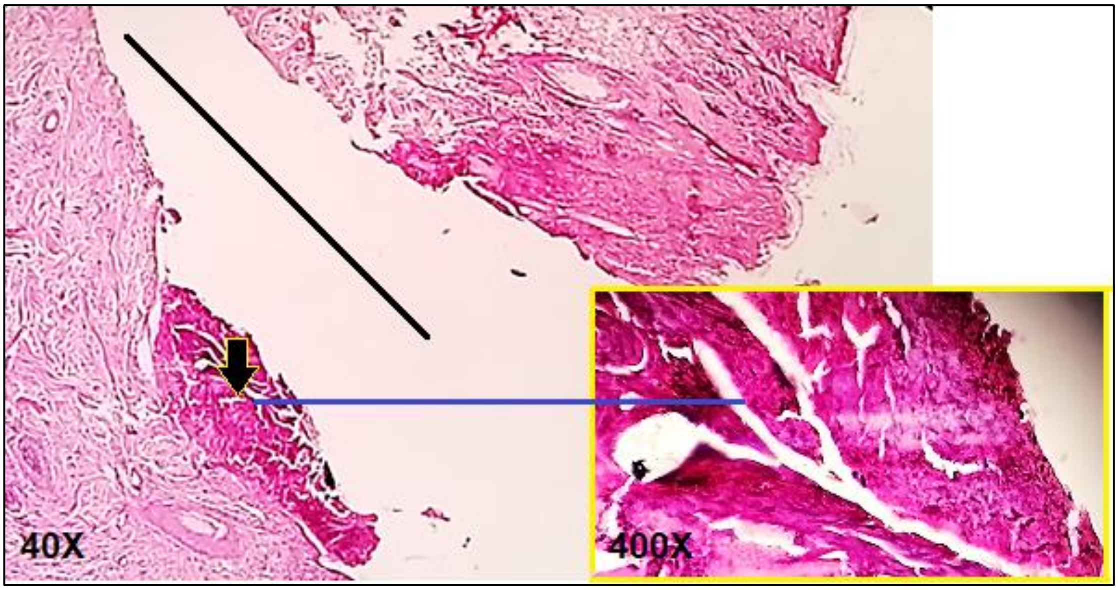


Figure 12: Control group, 1st week post surgery. Section of skin wound showed presence of a gap at incision line (yellow arrow) between wound edges, and a small area of re-epithelization in one edges of the wound was evident (black arrow). H&E, 40X. The focused area represents formation of small area of re-epithelization (blue line). H&E, 400X.

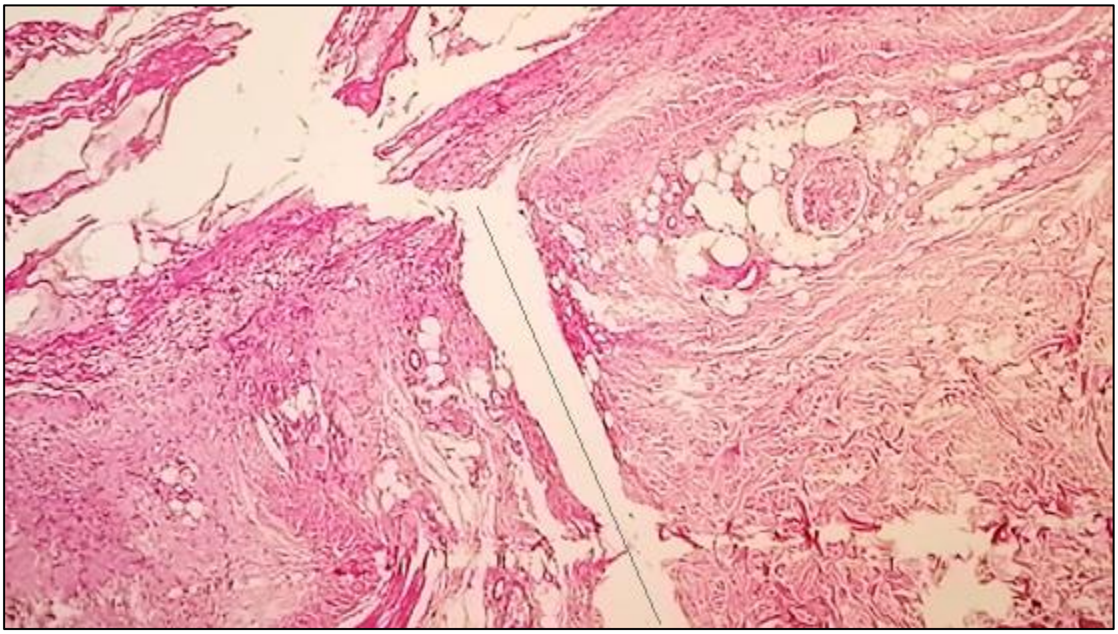

Figure 13: Control group, 1st week post surgery. Section of skin wound showed presence of a gap at incision line (black line) between wound edges. H&E, 40X.

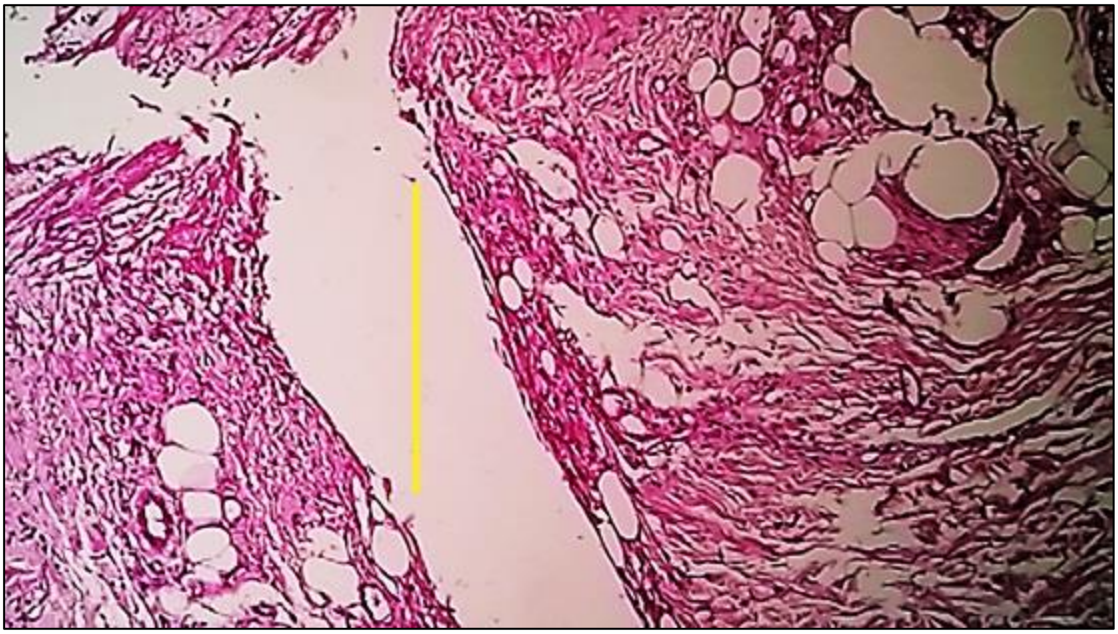

Figure 14: Control group, 1st week post surgery. Section of skin wound showed presence of a gap at incision line (yellow line) between wound edges. H&E, 100X.

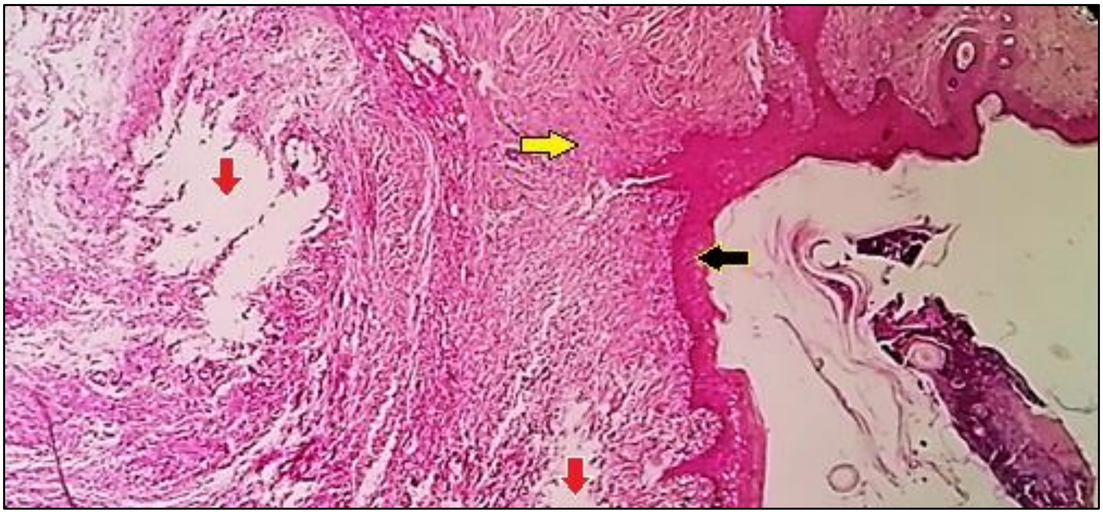

Figure 15: PRF group, 2nd week post surgery. Section of skin wound showed regenerated epidermis layers (black arrow), formation of an epithelial tongue (yellow arrow), edema (red arrows) also evident in the effected part. H&E, 40X.

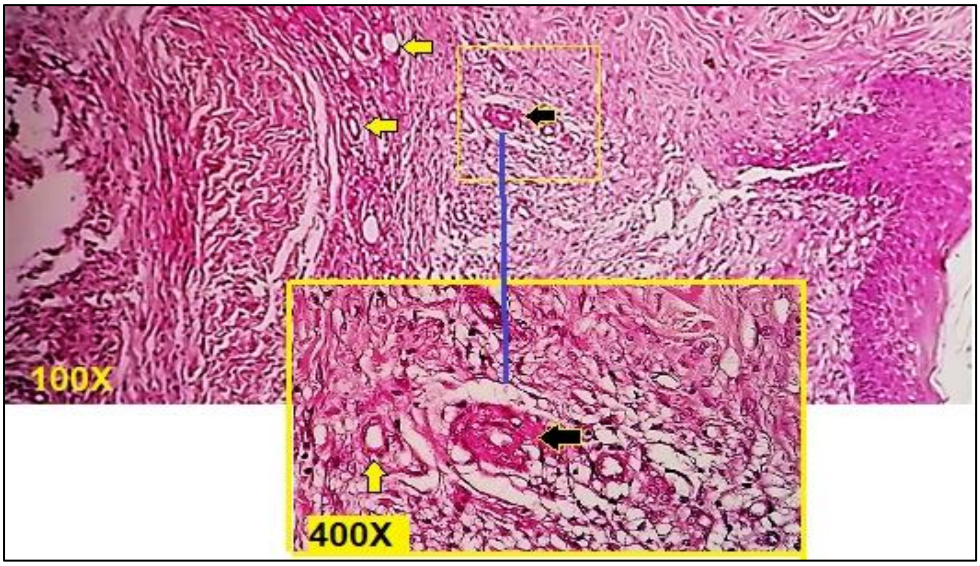


Figure 16: PRF group, 2nd week post surgery. Section of skin wound showed regenerated epidermis layers, newly formed blood vessels (yellow arrows), and sweat glands (black arrows (black arrow) are also evident. H&E, 100X. The focused area represents the newly formed blood vessels and sweat glands. H&E, 400X.

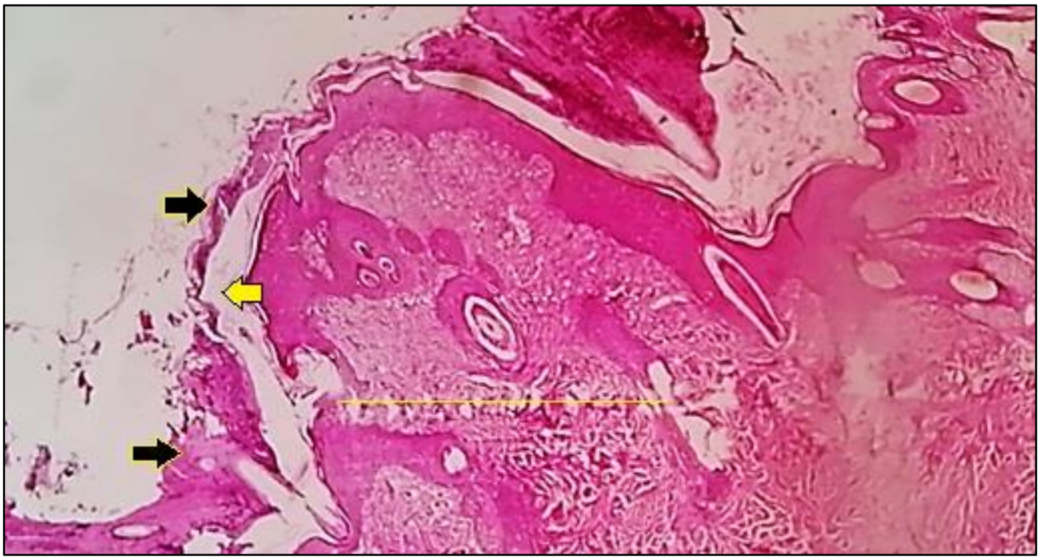

Figure 17: Control group, 2nd week post surgery. Section of skin wound showed presence a gap (yellow arrow) between regenerated epidermal layer (black arrows), and the dermis layer revealed presence of edema (yellow line). H&E, 40X.

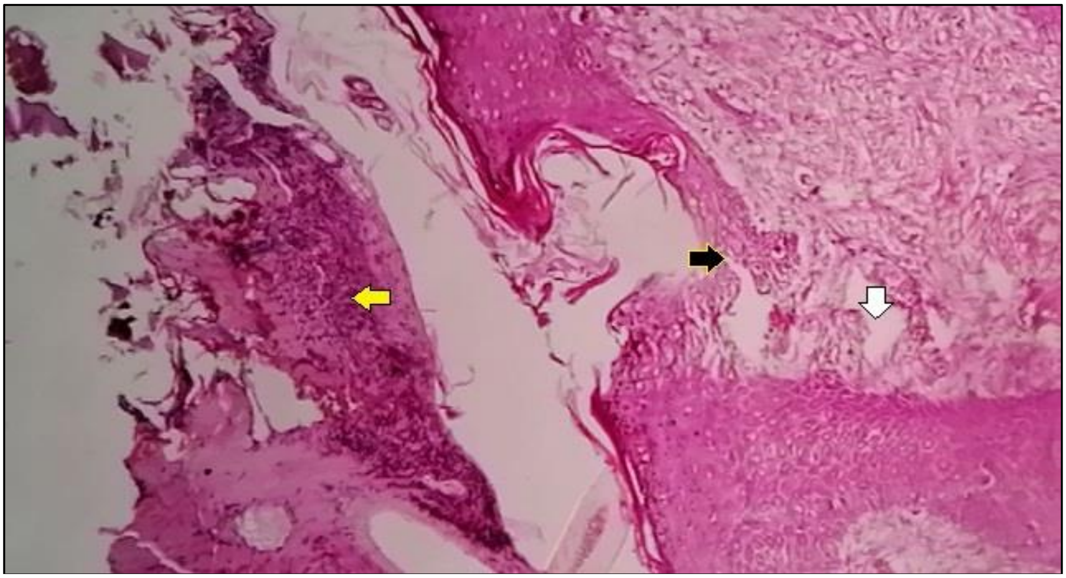

Figure 18: Control group, 2nd week post surgery.. Section of skin wound presence of gaps between regenerated stratum corneum layer (yellow arrow) and stratum spinosum layer (black arrow), and edema in the dermis was evident. H&E, 100X.

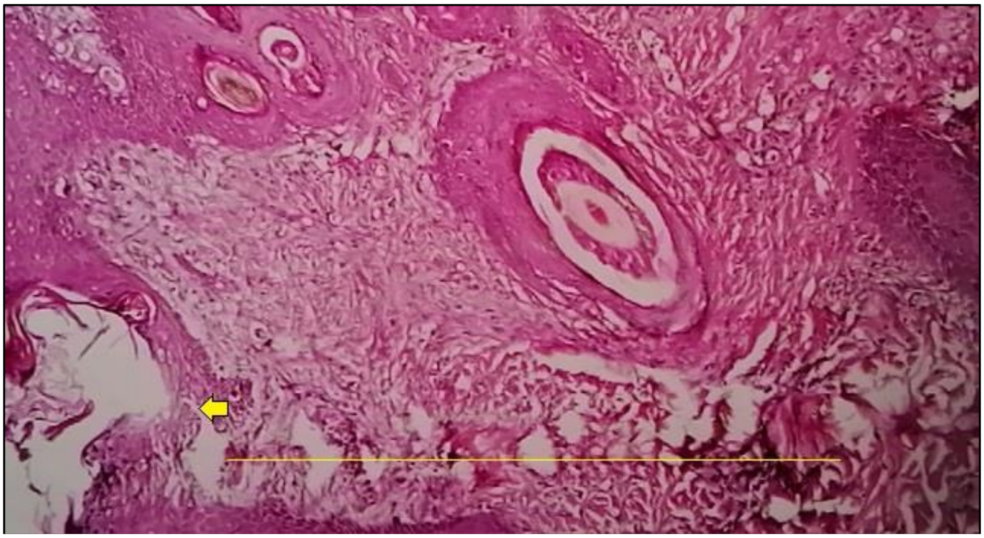

Figure 19 : Control group, 2nd week post surgery. Section of skin wound regenerated stratum spinosum layer (yellow arrow), and edema (yellow line) in the dermis was evident. H&E, 400X.

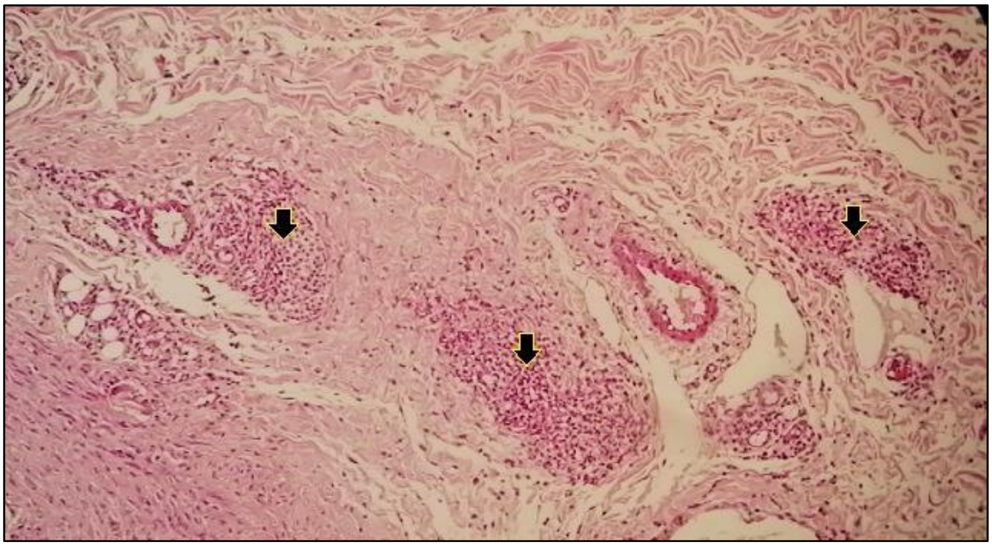

Figure 20: Control group, 2nd week post surgery. Section of skin wound presence tight perivascular lymphocytic infiltration (black arrows) in the subdermal layer. H&E, 100X.

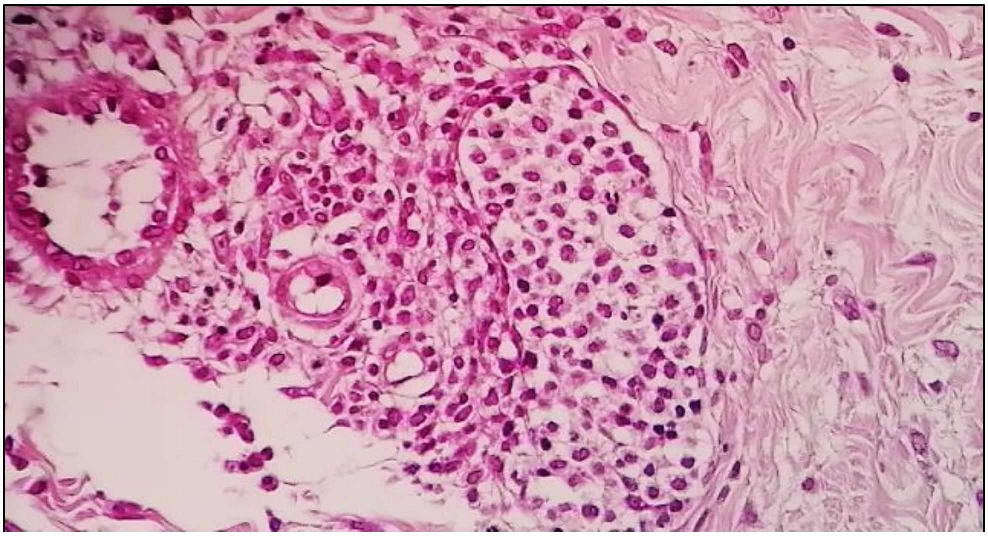

Figure 21: Control group, 2nd week post surgery. Section of skin wound presence tight peri/intravascular lymphocytic accumulation (black arrows) in the subdermal layer. H&E, 400X.

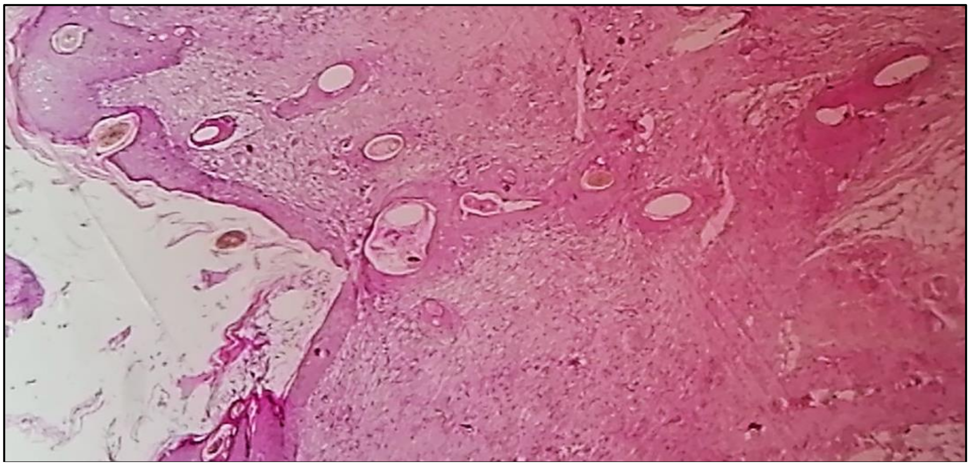

Figure 22: PRF group, 3rd week post surgery. Section of skin wound showed complete regenerated epidermal and dermal layers. H&E, 40X.

Figure 23: PRF group, 3rd week post surgery Section of skin wound showed complete regenerated epidermal and dermal layers. H&E, 100X.

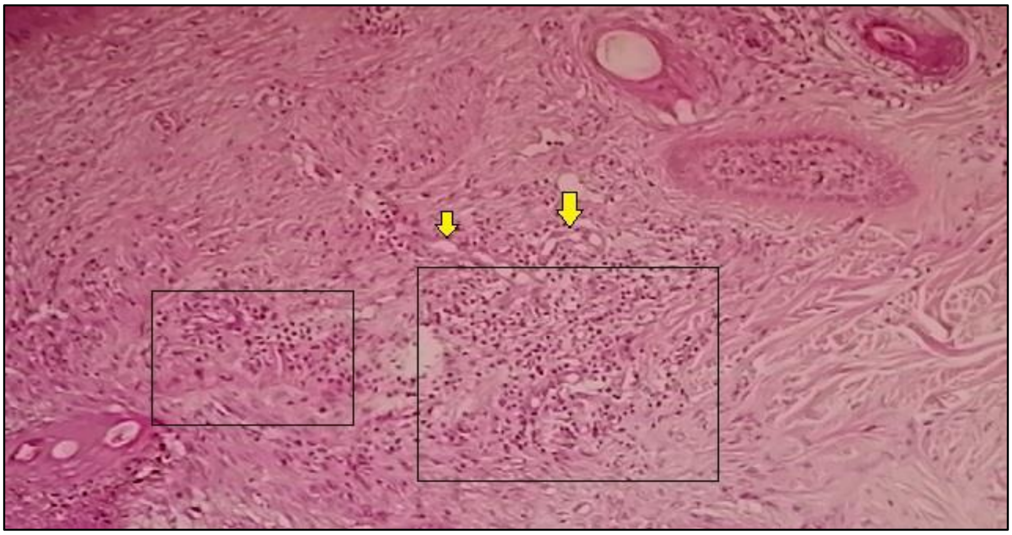

Figure 24: PRF group, 3rd week post surgery. Section of skin wound showed presence of newly formed blood vessels (yellow arrows) and infiltration of inflammatory cells (black boxes). H&E, 100X.

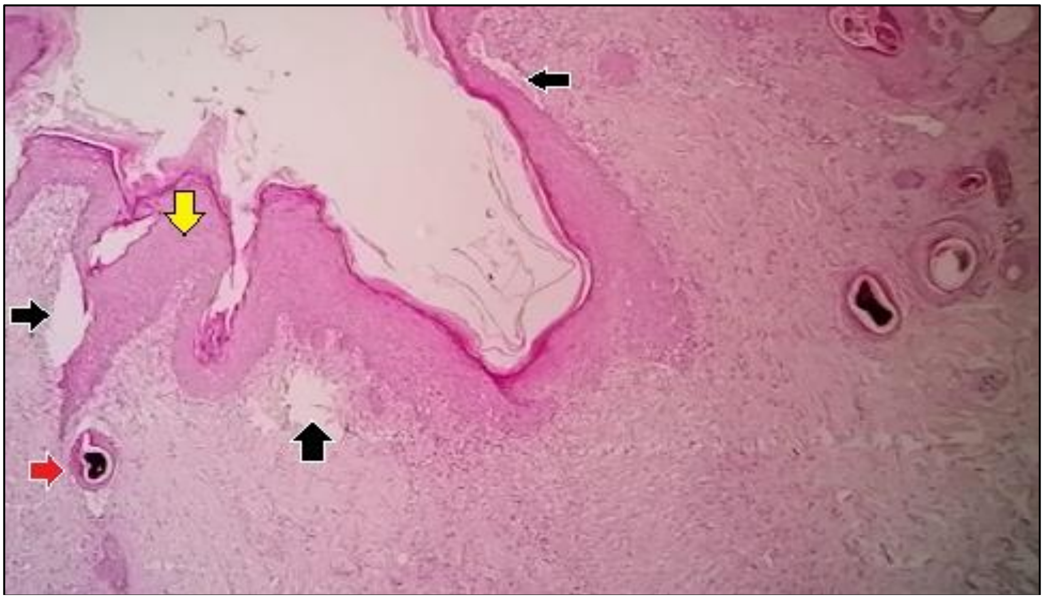

Figure 25: Control group, 3rd week. Section of skin wound showed well regenerated epidermal layer (yellow arrow), but there was a gap a detachment between the epidermis and dermis layers (black arrows), and newly formed hair follicles (red arrow) were also evident. H&E, 100X.

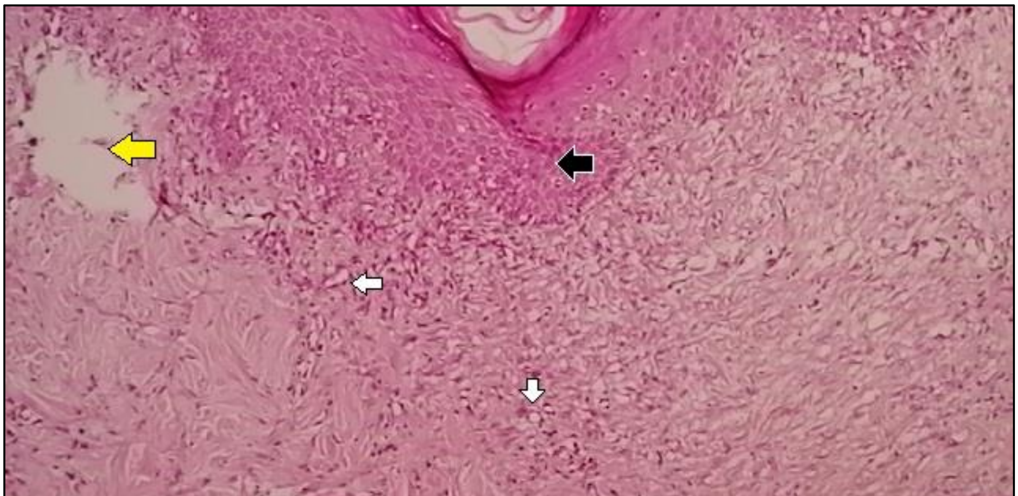

Figure 26: Control group, 3rd week. Section of skin wound showed well regenerated epidermal layer (black arrow), but there were a gaps and detachment between the epidermis and dermis layers (yellow arrows), newly formed blood vessels (white arrows) and few inflammatory cells were also evident. H&E, 400X.

**Discussion**

The healing process after any surgical procedure has always been challenging for doctors. Despite the advancements in wound closure techniques and technologies, there is an urgent need for novel approaches to optimize the healing process (Desai et al., 2013).

Optimal postoperative wound healing involves limiting local, systemic, and environmental variables contributing to poor wound healing to decrease scarring. Local wound tenets include keeping the wound clean and moist and reducing stress and infection. Systemic tenets include reducing drugs that hinder wound-healing processes, ensuring proper nutrition, administering pain relief, and using UV protection (Gantwerker & Hom, 2011).

Vital to a successful reconstructive procedure is the feasibility of diverse composite flaps. Mechanical injury during flap preparation and placement, bending and torquing of the pedicle's arteries, thrombosis, oedema, and inflammation may all result in flap necrosis (Molnar et al., 2019).

This research aimed to examine the clinical and histological effects of allogenic PRF on skin pedicle grafts used to treat experimental avulsion wounds.

As determined by clinical examination, the quantity of wound exudate in the treated group was significantly more than in the control group. However, these exudates are visible in acute wounds within the usual range of the inflammatory phase. Therefore, these abundant healthy acute exudates created by PRF aid in the healing of the treated group.

Exudates are sometimes called "wound fluid" or "wound drainage." When there is a rupture in the skin, an inflammatory reaction is triggered, and the capillaries become more permeable, causing exudates to be released. Serous fluid seeps into the wound bed and serves as the foundation for exudates, water, electrolytes, minerals, proteins, inflammatory mediators, proteases, growth factors, white blood cells, and microbes. It is a natural element of the healing process and provides a moist environment that permits epithelial cells to move over the wound. The growth hormones and nutrients included in exudates are essential for healing, and the wet environment promotes autolysis (the separation of necrotic from healthy tissue) (Nichols, 2016).

Three days after surgery, oedema disappeared in the treated group. In contrast, the swelling in the control group was higher and lasted longer since it persisted until the seventh day.

Due to the release of vasoactive amines and histamine-rich granules from mast cells, this stage is characterized clinically by redness, heat, swelling, and discomfort. These mast cell mediators induce surrounding arteries to become leaky, facilitating the effective transport of neutrophils to the site of damage through the vasculature. Because the veins become permeable, fluid also flows into the affected region, producing swelling and pressure-related discomfort (Goldberg & Diegelmann, 2010; Broughton et al., 2006; Cutting et al., 2015).

As expected, we added PRF, rich in inflammatory cells, growth factors, and fibrin, to the treated group. This resulted in an acceleration of the debridement or inflammatory stage and a quickening of the proliferation stage (Ding et al., 2017). The histology of the PRF group, seven days after surgery, revealed migration of epithelial cells to the incision line, the development of a thick scab, and epithelialization on the top section of the inner wound wall margins. The re-epithelization of the stratum corneum and stratum lucidum layers was evident at this time. In contrast, the control group demonstrated a gap at the incision line between wound edges as well as a tiny region of re-epithelialization at one wound edge.

The PRFs include the above-physiologic numbers of platelets and leucocytes, which are considered critical factors for wound healing and induce local angiogenesis, cell migration, proliferation, and differentiation (Soares et al., 2022). In addition, fibrin is a biological adhesive composed mainly of fibrinogen and thrombin. It may efficiently increase blood vessel development and creation and halt bleeding (Zhang et al., 2022).

These wound healing enhancements in the PRF group demonstrate that platelet-rich fibrin accelerates the inflammatory phase, enhances the creation of granulation tissue, and reduces the stress factors that affect skin pedicle flaps.

At 14 days after the damage, the PRF group demonstrated epidermis regeneration, developing an epithelial tongue in the dermis, and oedema in the afflicted area. Also noticed are freshly created blood vessels and sweat glands. On the other hand, the control group had a gap between the regenerated epidermal layer and the dermis layer, demonstrating oedema's existence. The gaps between the regenerated stratum corneum layer and the stratum spinosum layer were noticed. In addition, a subdermal perivascular lymphocytic infiltrate was detected. PRF grafting treatments were well tolerated in all treated wounds, inducing significant granulation tissue formation because PRF clots acted as a natural tissue-filler, promoting epithelization and wound closure without the need for topical antimicrobial or antiseptic application or additional debridement (Soares et al., 2022).

Zhang et al. studied in 2022 the effects and probable processes of porcine fibrin sealant (PFS) on the healing of skin wounds in rats. At 14 days post-surgery, they discovered that the PFS improved skin wound healing, particularly tissue creation, re-epithelialization, angiogenesis, and collagen deposition.

After 21 days, the PRF group demonstrated complete epidermal and dermal regeneration. During this phase, the formation of new blood vessels and the infiltration of inflammatory cells were also noticeable. During the same period, the control group displayed a well-regenerated epidermal layer, freshly formed blood vessels, and newly formed hair follicles, but gaps and detachment between the epidermis and dermis layers and a small number of inflammatory cells.

A PRF is a platelet and immune cell concentration that gathers on a single fibrin membrane; all blood components promote healing and immunity. Although platelet and leukocyte cytokines play a significant role in the biology of this biomaterial, the fibrin matrix that supports them is the defining factor in PRF's therapeutic potential. The PRF membranes concurrently promote the development of angiogenesis, immunity, and epithelial cover, the three determinants of healing and soft tissue maturation. This membrane shields open wounds and speeds healing, promotes micro vascularization, and directs the migration of epithelial cells to its surface. Additionally, this matrix contains and facilitates the movement of leukocytes (Desai et al., 2013).

## Conclusion

The PRF causes excessive, beneficial acute exudates that stimulate and speed up the healing process. PRF might enhance successful wound healing of the skin pedicle flap, primarily by collagen deposition, tissue creation, angiogenesis, and re-epithelialization.

## Acknowledgments

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