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Platelet-rich fibrin enhances wound epithelialization in the skin graft donor site

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Abstract. Platelet-rich fibrin (PRF) is among the newest autologous growth factors used to accelerate the wound healing process. The application of PRF on the donor site after skin grafting can accelerate wound epithelialization. This multiple-measure study used a general linear model to evaluate the effect of PRF on the post-harvest donor site defect. The patients were divided into two groups: those with and without PRF application. To evaluate the wound epithelialization at the donor site, wound care was provided at both femoral sides, and the patients were assessed on days 3, 7, 14, and 30 using the ImageJ software. The application of PRF accelerated wound epithelialization in the donor site ($p < 0.05$). In the PRF group, the inflammation reactions (hyperemia, pain, hyperthermia, and edema) in the wound at the donor site were less. PRF administration can improve the condition of the wound by providing growth factors in the wound environment that help accelerate the epithelialization process, and this results in cost-effective wound management.

1. Introduction

In otorhinolaryngology, reconstruction is associated with the closure of a defect. Skin grafting covers open defects that cannot be closed primarily with a local flap, which include post-radiation or post-tumor resection defects, post-trauma defects, or skin deficiencies after the reconstruction of congenital abnormalities. Skin grafting is a simple technique that covers widespread wounds with good vascularization, and it can reduce the strain in skin tissues and contractures. Within the first 24 h, when the skin tape is attached to the recipient bed, a fibrin layer will form under the skin graft and will attach to the bed, and subsequently, vascularization of the skin graft will occur.

This skin patch comprises all epidermal and dermal components with varying thickness. If the entire dermis thickness is included, then it is called a full-thickness skin graft (FTSG). If less than the entire dermis thickness is included, this skin graft is called a split-thickness skin graft (STSG). STSG is categorized into thin STSG (0.0127–0.3048 cm), medium (0.03048–0.04572 cm), or thick (0.04572–0.00762 cm) based on the thickness [1]. According to reconstruction needs, STSG can be applied using dermatomes adjusted to the thickness of the skin that is used in accordance with the above-mentioned criteria. Skin grafts are applied using dermatomes with sizes that can be adjusted accordingly [2]. Skin tanning can cause defects in the donor site, which will undergo epithelialization. The treatment of post-harvest skin donor lesions varies with the condition of the patient [3]. To date, several treatment modalities are available for the post-harvest treatment of genetically modified



harvested wounds. However, several healthcare practitioners continue to administer only primary wound care.

There is an increasing number of patients who seek services for wound care at the donor post-harvest procedure. Natural wound care results in scarring in the wound area of the donor site [4]. With technological advancements, an intervention must be provided for wound care in the donor area using an autologous material. Studies on wound care have only focused on the donor skin graft skin, and the donor area is often ruled out.

The paradigm of soft tissue wound management in the last decade has changed. Keeping the wound clean and dry is part of the passive wound healing process. However, currently, there are many more active actions that accelerate this process. The development of tissue engineering has created several of the latest biological and clinical products that can accelerate the wound healing process. The development of biological products has a significant impact on the operation results, particularly in the field of otorhinolaryngology (head and neck surgery) [5]. The application of these products may help in reducing the number of patients who visit healthcare institutions, accelerating the wound healing process, and lowering the treatment costs. Platelets contain large amounts of major growth factors, such as platelet-derived growth factor (PDGF)-AB, transforming growth factor $\text{TGF}\beta$ 1, and vascular endothelial growth factor (VEGF). These factors can stimulate cell proliferation, matrix, and angiogenesis. Currently, two platelet components are used: platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). Both PRP and PRF are sources of various growth factors, and they promote soft tissue healing. However, to date, no specific research has assessed the role of PRF in promoting wound healing at post-harvest skin donor sites [6,7]. An autologous growth factor (AGF) is a cytokine that improves and accelerates the wound healing process. AGFs are derived from platelets, which are a major component of both PRP and PRF. PRF is a platelet concentrate that comprises PDGF, $\text{TGF}\beta$, including β -1 and β -2 -isomer, VEGF, and epidermal growth factor, all of which are capable of maintaining skin viability [1]. Dohan et al. [6] have reported on fibrin and fibrin biochemical adhesives, concentrated PRP, and PRF. The three types of fibrin are highly dependent on artificial polymerization, such as the use of massive bovine thrombin. The PRF undergoes a slow polymerization of fibrin in PRP, causing the PRF structure to resemble a natural fibrin, which contributes to cell migration, cell proliferation, and cicatrix formation. In this process, all platelets in the PRP will be deposited between the fibrin fibers of the PRF [8]. In laboratory experiments that used a special medium for PRF, the levels of PDGF, VEGF, FGF, and $\text{TGF}\beta$ increased on the first day and then gradually decreased the following day. This characteristic is not observed when using PRP because some growth factors are released on the first day of application in the wound. Unlike PRP, PRF has fibrin characteristics with platelet distribution that is more similar to the body's response to the wound and bending macroscopic structures [9]. The process involves a three-dimensional formation of fibrin matrix, which is useful for platelet clot formation and gathering sites along with growth factors (scaffolding). Scaffolding helps localize growth factors to improve tissue regeneration.

The use of PRP and PRF has several advantages: growth factors derived from platelets have special effects on the recipient tissue, thereby increasing the activation of gene expression and protein production. In addition, differentiation factors also affect platelet activation [10]. These factors regulate and stimulate the healing process and play an important role in regulating cellular processes, such as mitogenesis, chemotaxis, differentiation, and metabolism [11]. Wound epithelialization in the present study was analyzed using the ImageJ. The device is a scoring program that uses planimetry and digital photography. The program can display, edit, process, store, and print images with 8-, 16-, and 32-bit densities. The advantage of using this modality is that it does not require direct contact with the wound. The results of the image can also be used as a permanent documentary to record the size and appearance of the wound. Important considerations in using these modalities include lighting, photo quality, and angle when taking an image. Variations from the angle of shooting can reduce the estimates of wound area up to 10%. Based on the above-mentioned description, the present study aimed to evaluate the effect of PRF in accelerating wound epithelialization in the donor site after skin grafting.

2. Methods

This study was conducted at the Department of Ear, Nose, Throat, Head, and Neck Surgery Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital between November 2017 and February 2018. This was an experimental study on humans that compared two treatment groups. The PRF group comprised 10 patients with post-split thickness skin grafting defects who received PRF. The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital. The control group comprised 10 patients with post-split thickness skin grafting defects who did not receive PRF. To evaluate epithelialization and inflammation reactions (pain, fever, edema, and hyperemia) in the wound at the donor site, the same wound care was provided on both femoral sides. An evaluation was conducted at days 1, 3, 7, 14, and 30, and photo-analysis was performed using the ImageJ software by observing macroscopic changes. Data were analyzed with the Statistical Package for the Social Sciences software version (SPSS; IBM Corporation) 20.0. P values <0.05 were considered significant.

2.1 Skin graft

Skin grafting was performed at both femoral sides of the patient, and 0.018-inch dermatome was used to harvest STSG.

2.2 PRF preparation

Approximately 10 mL of citrate blood was placed in the RegenKit tube (RegenLab, Le Mont, Switzerland) and centrifuged at $1,500 \times g$ for 5 min to obtain three layers, a red blood cell layer sedimented at the base of the tube, a gel that was part of the RegenKit tube, and a plasma layer above the gel. The plasma layer comprised two parts: the one adjacent to the gel was PRP and that above the PRP was platelet-poor plasma (PPP). In this study, both PRP and PPP layers were homogeneously mixed to obtain a sufficient volume of PRF. The mixture of PRP and PPP was defined as PRP in this study. The preparation of PRF was a continuation of PRP preparation, which was performed using the modified Fibrinet method. Then, 25 mM CaCl_2 was added into the PRP, followed by the mixture.

2.3 PRF application

After harvesting, the donor site on the right femur was sutured with silk 2.0 using 3×3 -cm frame after skin grafting, and the donor site on the left femur was sutured with silk using a 3×3 -cm frame after skin grafting. PRF was subsequently injected into the donor site.

3. Results

3.1. Patient characteristics

The characteristics of the patients involved in this study is shown in Table 1 below.

Table 1. Patient characteristics

Participants	
Patients	
Age 6–60 years	10 (mean: 19.2 ± 15.8)
Sex	
Male	5
Female	5
Comorbidities	
Yes	2
No	8
Intraoperative	
Microtia	7
Others	3

3.2. Inflammation reactions at the donor site after skin grafting with or without PRF

3.2.1. Pain

Table 2. Pain reaction

Pain		Without PRF	PRF	p value (95% CI)
Day 1	Mild–Moderate	0	9	0.000
	Severe	10	1	0.000
Day 3	Mild–Moderate	8	10	0.474
	Severe	2	0	0.474
Day 7	Mild–Moderate	10	10	NA
	Severe	0	0	
Day 14	Mild–Moderate	10	10	NA
	Severe	0	0	
Day 30	Mild–Moderate	10	10	NA
	Severe	0	0	

As shown in Table 2, a p value of 0.000 was obtained on day 1.

3.2.2. Fever

Table 3. Presence of fever

Fever	Without PRF	PRF	p value (95% CI)
Day 1	0	0	NA
Day 3	0	0	NA
Day 7	0	0	NA
Day 14	0	0	NA
Day 30	0	0	NA

From day 1–3, whether PRF was administered or not, the result was the same. In accordance with the data shown in Table 3, 10 patients did not present with postoperative fever after PRF or without PRF administration.

3.2.3. Edema

Table 4. Edema

Edema	Without PRF	PRF	p value (95% CI)
Day 1	0	0	NA
Day 3	0	0	NA
Day 7	0	0	NA
Day 14	0	0	NA
Day 30	0	0	NA

As shown in Table 4, 10 patients did not present with edema which sized more than 1 cm in diameter after operation with or without PRF. The statistical results were not calculated because all patients

who received or did not receive PRF did not present with edema more than 1 cm postoperatively.

3.2.4. Hyperemia

Table 5. Hyperemia

High resolution of Hyperemia	Without PRF	PRF	p value (95% CI)	
Day 1	10	10	NA	
Day 3	9	10	1.000	<i>Fisher's exact test</i>
Day 7	2	10	0.001	<i>Fisher's exact test</i>
Day 14	1	1	1.000	<i>Fisher's exact test</i>
Day 30	0	0	NA	

The association between the occurrence of hyperemia and wound healing on days 1, 3, 7, 14, and 30 at the donor site after skin grafting with and without PRF is shown in Table 5. In the table, on day 7, a statistically significant difference was observed in the incidence of hyperemia after PRF administration versus without PRF. On days 1 and 3 after PRF and without PRF administration, the patients were evaluated, and hyperemia was observed in 10 patients. However, no statistically significant difference was observed.

3.3. Wound epithelialization

Table 6. Wound epithelialization in the donor site after skin grafting

	Without PRF mean $\pm$ SD	PRF mean $\pm$ SD	p value (95% CI)
Day 1	0.07 $\pm$ 0.04	0.13 $\pm$ 0.06	0.000
Day 3	0.15 $\pm$ 0.06	0.28 $\pm$ 0.114	0.000
Day 7	0.34 $\pm$ 0.11	0.49 $\pm$ 0.13	0.000
Day 14	0.47 $\pm$ 0.14	0.60 $\pm$ 0.14	0.000
Day 30	0.72 $\pm$ 0.11	0.86 $\pm$ 0.08	0.000

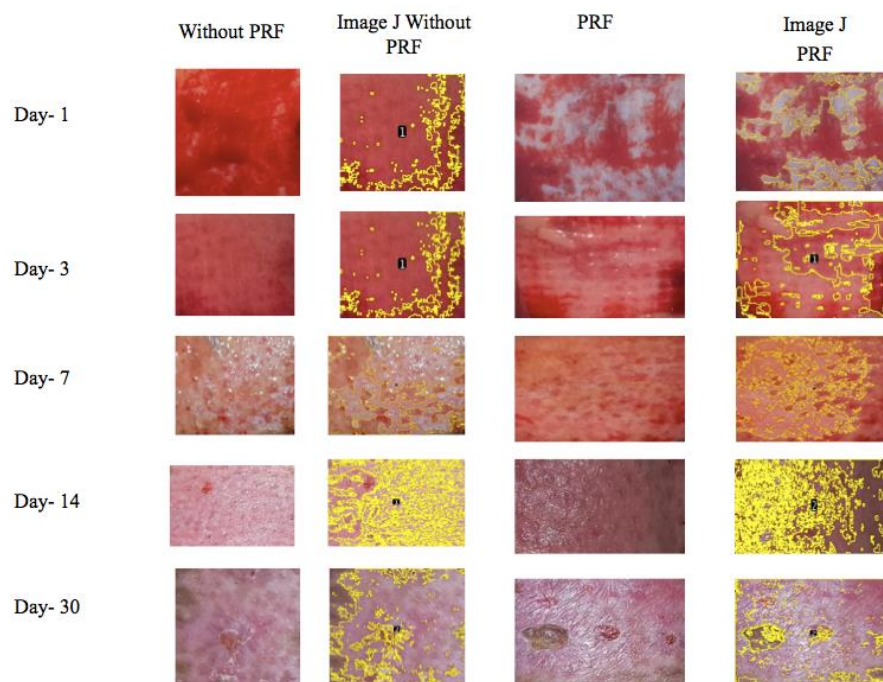


Figure 1. Images of epithelialization with or without PRF obtained using the ImageJ software

As shown in Table 6, wound epithelialization in the donor site after skin grafting was assessed using the ImageJ software, and it differed in terms of clinical and statistical significance.

Figure 1 shows images of the results of wound epithelialization in the donor site after skin grafting with and without PRF administration. Yellowish-colored results are areas that have not reached the stage of complete epithelialization. The assessment uses Image J software by evaluating the area of the wound that has been objectively measured using a measuring frame.

3.4. Platelet analysis

Data on the platelet count of the patients at the preoperative and postoperative stage and during PRP administration are shown in Table 7. The preoperative platelet count was assessed at the Cipto Mangunkusumo Hospital laboratory, whereas the PRP and postoperative calculations were performed at the Eijkman Cipto Mangunkusumo Hospital laboratory.

Table 7. Platelet count (per μL)

Patient	Preoperative platelet count (whole blood)	Platelet count during PRP	Postoperative platelet count (whole blood)
1	313.000	38.000	283.000
2	289.000	540.000	241.000
3	282.000	112.000	269.000
4	410.000	165.000	298.000
5	232.000	124.000	321.000
6	350.000	40.000	369.000
7	394.000	64.000	302.000
8	371.000	25.000	330.000
9	312.000	136.000	318.000
10	301.000	90.000	277.000

PRP was obtained using the laboratory reagent device. Based on these calculations, the platelet counts obtained using the laboratory-made PRP reagents were lower than the actual platelet counts.

4. Discussion

No studies have evaluated the incidence of fever after PRF administration. All patients who received or did not receive PRF did not present with edema more than 1 cm postoperatively. From day 1–30, similar results were observed in both groups. The assessment of hyperemia during the first week (day 7) was significantly associated with PRF administration in all treatment groups ($p < 0.05$), and this result is similar to that reported by previous study which evaluated the inflammation process from day 4–6 [12]. On the second week of evaluation, the same process was conducted, and based on the hyperemic parameters, two patients in the control group still presented with hyperemia. However, no statistically significant difference was observed between all treatment groups ($p = 1.000$). Thus, the lower number of patients with hyperemia during the second week showed that the inflammation process decreases after physiological wound healing, and there is an increase in the number of growth factors and collagen deposition after day 7 from administration. During the fourth week after administration, the hyperemic parameters begin to decrease, either with PRF or without PRF. However, it cannot be statistically calculated. This corresponds to the wound healing process during the proliferative and remodeling phases, and the role of inflammatory cytokines has begun to diminish in the fibrin matrix and granulation tissue.

The results of this study is in accordance with another study which revealed that PRF administration resulted in complete wound healing or a significant reduction in the wound diameters without any adverse effects on diabetic wounds [13]. Previous study stated that PRF administration accelerated the wound healing process on day 5 in comparison to no PRF administered to patients who underwent postoperative reconstruction [14]. In addition, Reksodiputro et al. have revealed that PRF administration to FTSG and STSG enhances the formation of type 1 collagen [15].

5. Conclusion

The addition of PRF as a source of AGF in the donor site of patients undergoing skin grafting can accelerate wound healing and epithelialization, showing clinically and statistically significant outcomes, and can also affect inflammatory reactions (hyperemia, pain, edema, and fever) during wound healing. However, hyperemia and pain had remarkable differences in terms of clinical and statistical significance.

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