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Platelet-rich fibrin as an alternative adjunct to tendon-exposed wound healing: A randomized controlled clinical trial

*Shuang Zhang, DongSheng Cao *, Juan Xie, HongHong Li, ZengHong Chen, Qiong Bao*

Department of Plastic and Reconstructive Surgery, The Second Affiliated Hospital of AnHui Medical University, China

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ABSTRACT

Background: The use of platelet-rich fibrin (PRF) has attracted great interest in the treatment of oral and maxillofacial procedures, gingival recessions, and bone healing. However, PRF has been reported hardly to prepare wound bed before skin grafting. This randomized clinical study sought to identify the effect of PRF as an alternative adjunct to tendon-exposed wound healing.

Methods: Thirty-six patients with tendon-exposed wounds were treated by applying Integra or PRF (n = 18 per group). The take rate of Integra or PRF and pain levels assessed with the four-point verbal rating scale (VRS-4) for the first 5 days after application were measured for each condition. Data of texture change analysis were assessed and recorded for a duration of 3 months postoperatively.

Results: The take rate was less in the Integra group than in the PRF group (92.39 vs 97.83 $P < 0.001$). After surgery, compared to the Integra group, the patients in the PRF group reported significantly lower pain scores ($P < 0.001$). Texture changes from the Integra group were rated higher than those from the PRF ($P < 0.001$).

Conclusion: The use of PRF could be an option for tendon exposed areas where the wound is unfit for standard skin grafting or flap transfer.

1. Introduction

Full-thickness skin defects, including tendon exposure, frequently occur after trauma, vascular problems, or tumor excision. The treatment options for tendon-exposed wounds are skin grafts, local pedicled flaps, or free flaps [1]. Exposed areas of tendon in the wounds, unless very small and in nonfunctional areas, require coverage with vascularized tissue, excluding skin grafting directly, in order to avoiding dysfunction after wound healing. Performing local or free flap transfer procedures acutely in patients with tendon-exposed wounds is neither technically nor clinically appropriate because of the relative severe avulsion around the wound and poor blood supply [2]. To this end, skin grafting is often regarded as the workhorse of wound closure as it is simple to perform, reliable, minimally invasive, and cost-effective. Furthermore, skin grafts can be repeated as necessary which can be acceptable to the patients [3]. To ensure skin grafts are supported in an areas with exposed tendons, it is important to prepare the area to ensure a clean, granular wound bed [4]. Since introduced in 1981, Integra has rapidly gained popularity and been widely applied for skin defects with bone or tendon exposure before skin grafting [5,6].

* *Corresponding author at*: Department of Plastic and Reconstructive Surgery, The Second Affiliated Hospital of AnHui Medical University, 678, FuRong Road, Hefei, AnHui Province, 230601 China.
E-mail address: cds1966@sina.com (D. Cao).

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Integra is a three-dimensional structure which consists of an inner layer of collagen and chondritin-6-sulfate covered by a temporary silicone epidermal substitute that is usually removed after 21 days [7]. Integra allows the migration of various cells and capillary ingrowth to the covered area which prepares the wound bed for skin grafting. Integra has been reported as being an effective and safe method for preparing the wound bed before skin grafting; however, it is a costly method that has a risk of infection [8].

Platelet-rich fibrin (PRF) is reported to consist of bioactive and biological components, including growth factors, which stimulate cell proliferation and promote angiogenesis [9]. Like Integra, PRF has a three-dimensional fibrin network that mimics the extracellular matrix to create an environment that allows cells to function optimally in terms of its structure [10]. Furthermore, PRF is autologous material which is readily available and relatively easy to produce within the daily clinical routine [11]. Therefore, PRF could be an alternative for the preparation of wound beds for skin grafting in areas including exposed tendons. PRF has been reported as option in the treatment of various oral and maxillofacial procedures, gingival recessions, and bone healing [12–14]. However, studies on its use in tendon-exposed wound treatment are limited. Therefore, paper aimed to evaluate the effect of using PRF to prepare the wound bed in tendon-exposed areas on clinical healing parameters before skin grafting, compared to Integra. An assessment of parameter scores was also conduced. The study is a prospective randomized clinical study conducted to determine the potential of using PRF to better promote tendon-exposed wound healing.

2. Materials and methods

This clinical study followed a prospective, randomized design with an observation period of 3 months. Thirty-six patients (aged between 18 and 60 years old) were recruited and divided into 2 groups: the Integra treatment group (n=18) and the PRF treatment group (n=18). All the patients would not receive the treatment methods that the tendon-exposed wounds were repaired by local flap or free flap. Patients in the PRF treatment group received PRF to treat a wound with exposed tendons before skin grafting while patients in the Integra group received Integra to treat a wound with exposed tendons before skin grafting. Participants were recruited from patients seeking tendon-exposed wound treatment in the Department of Plastic and Reconstructive Surgery, the Second Affiliate Hospital of Anhui Medical University, between January 2016 and January 2018. All procedures were approved by the Ethics Committee of the Second Affiliate Hospital of Anhui Medical University. Informed consent was obtained from all participants.

Exclusion criteria included: smoking and/or any uncontrolled systemic disease that might contraindicate wound repair, unwillingness to give informed consent, and any long term medication that might affect the inflammatory cycle, pain perception, or wound healing.

3. Surgical procedures

In the Integra group, Integra was grafted on an area of tendon exposure after the wound was debrided completely using negative-pressure techniques. After full Integra neovascularization and granulation tissue covering of the tendon-exposed area, the patients returned to the operating room for full-thickness skin transplantation.

In the PRF treatment group, after the wounds were debrided completely, no more than 55 ml of venous blood, which was drawn from the patient's antecubital vein, was collected in plastic tubes without anticoagulant agents. The volume of blood drawn was determined by the size of the tendon-exposed area. The blood-containing tubes were centrifuged at 1500 rpm for 15 min, as reported by Choukroun [15]. The G-force of 1500 rpm (approximately 370 g) was used at the RCF-clot. And the PRF was squeezed gently between two pieces of gauze to form a membrane (about 0.5 mm). The PRF membrane was shaped into the form of a consistent membrane to apply over the tendon-exposed area, and negative-pressure techniques were used to secure the grafted PRF in place. After granulation tissue covering of the tendon-exposed area, patients returned to the operating room for full-thickness skin transplantation.

All surgeries were performed under general anesthesia. After surgery, a strict surveillance protocol was followed for infection and pain.

4. Analysis of clinical results

Patients were instructed to complete a pain dairy during the first 8 h after surgery, and then once a day until the fifth day after surgery. The four-point verbal rating scale (VRS-4) which was used to measure clinical postoperative pain intensity had 4 options in this study: no pain, some pain, considerable discomfort, or discomfort that could not be more severe [16]. One postgraduate student and one professional doctor who were blinded to experimental groups judged the clinical parameters taken from the postsurgical observations. The take rate of PRF or Integra was determined by the examiners, who traced and determined the area of vascular granulation tissue in relation to the total grafted PRF or Integra area. And the wound healing criteria after the skin graft was based on the degree of tissue texture of the surgical tendon-exposed area compared to the adjacent tissue which was related to scar contracture. The scores from analysis of texture changes were calculated as a weighted average of the following scales: (1) exactly similar to the adjacent tissue, (2) slightly different to the adjacent tissue, and (3) totally different to the adjacent tissue.

A one-way ANOVA was performed to evaluate the changes in pain scores over time for VRS-4 and texture change, and a two-way ANOVA was used to compare the pain scores at the different time-points between the 2 groups. Other statistical analysis was performed using a t-test. A P-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 19.

5. Results

Thirty-six patients were included in this study. Their mean age was 40 years (range, 21–56 years) in the PRF group and 42 years (range, 23–58 years) in the Integra group (P=0.54). Both sex and

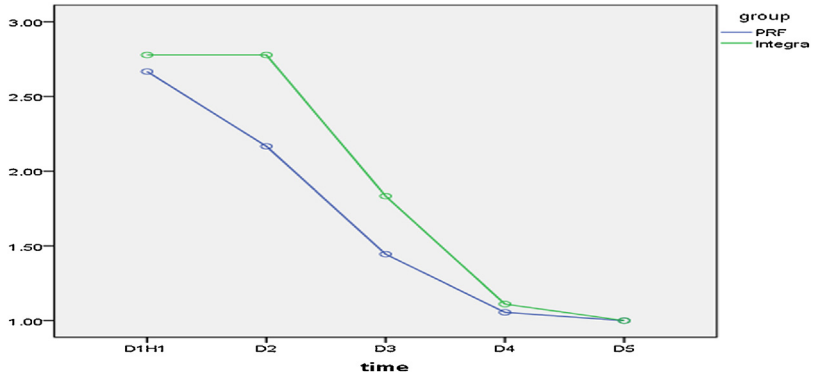

Fig. 1 – Estimated marginal means of VRS-4 with time in the two groups.

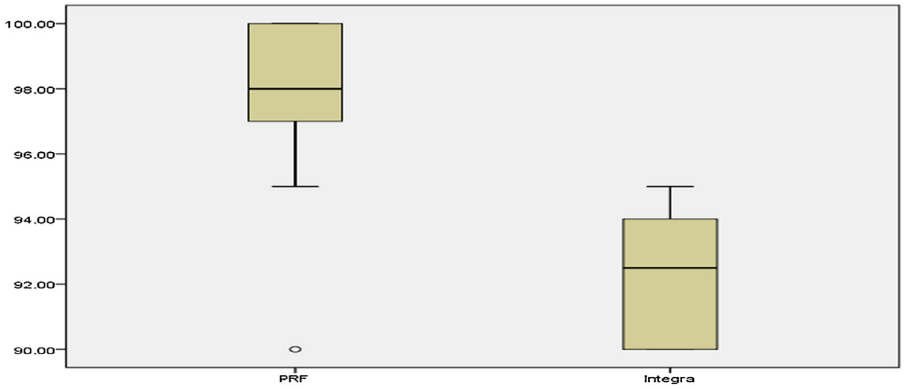

Fig. 2 – Mean take rate for the PFR and Integra. Compared with the Integra group, the PRF group demonstrated a significantly higher take rate ($P<0.001$).

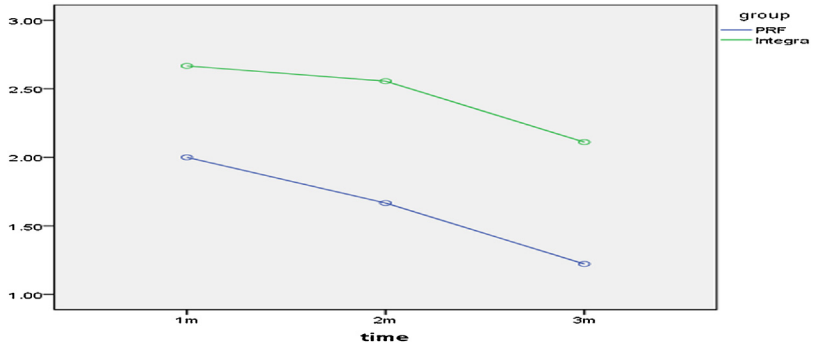

Fig. 3 – Change of texture index with time in two groups.

wound location were similarly distributed between the 2 groups, and neither age nor gender had an obvious effect on the pain scores assessed in this study. The size of the tendon-exposed areas were: mean 9.28 cm^2 (range, 12–8 cm^2) in the PRF group and 8.78 cm^2 (range, 12–6 cm^2) in the Integra group. There were no significant differences between the 2 groups with respect to the size of wounds ($P=0.32$).

After all patients has high scores of VRS-4 reflecting the pain after surgery, while there was a significant change in the VRS-4 scores within each group and a significant difference between the 2 groups ($P<0.001$). Furthermore, the scores reached 1 on day 5 in both groups as shown in Fig. 1. Before skin grafting, the grafted PRF or Integra areas were covered by vascular granulation tissue. The take rate was an average of 92.3% in the Integra group, compared with 97.83% in the PRF group ($P<0.001$), as shown in Fig. 2. Analysis of texture changes after wound healing revealed that changes in the Integra group were rated higher than those from the PRF group at every time-point during the 3 month postoperative period, as shown in Fig. 3. Higher scores resulted from a poorer texture match compared to the adjacent tissue. Two typical cases from the PRF group were shown in Fig. 4 and Fig. 5.

6. Discussion

Skin grafting might be the simplest option for complex defects due to its minimal morbidity and cost-effectiveness [17],

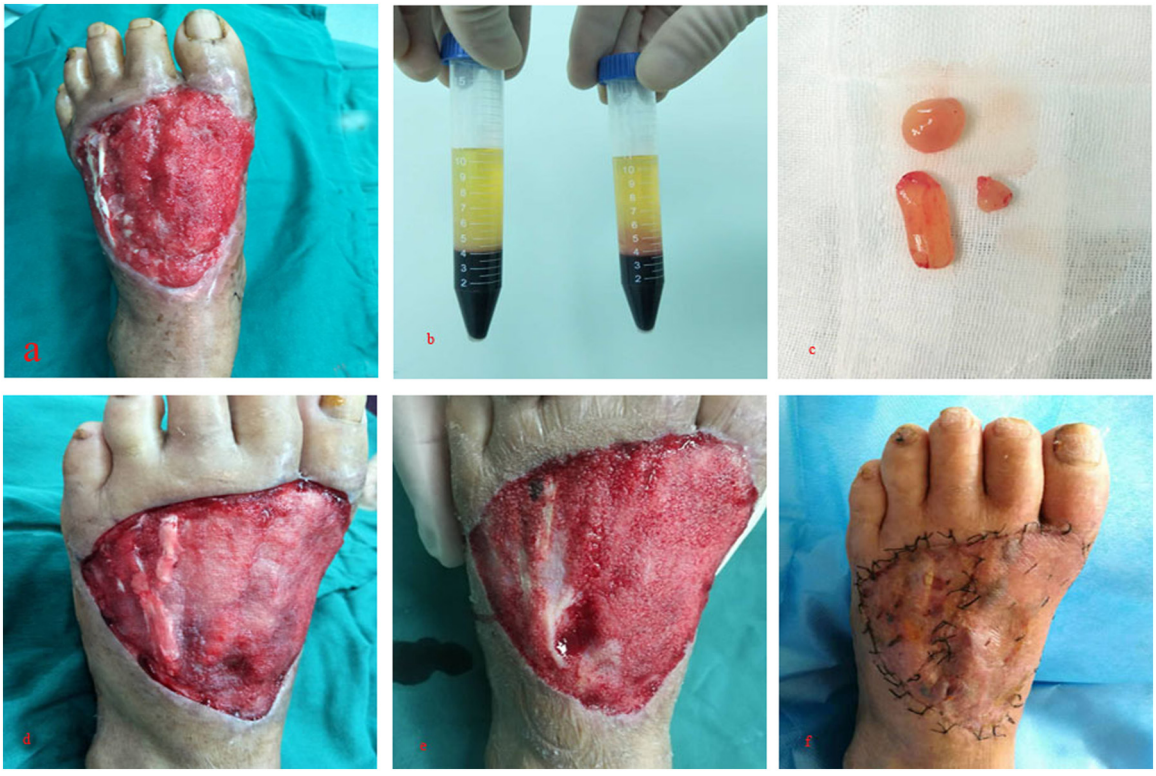

Fig. 4 – A 50-year-old man with a tendon-exposed wound on the left foot dorsal was treated for 1 month with PRF. (a) Wound status before PRF graft. (b and c) To gain the PRF. (d) Shaping the PRF and covering the tendon-exposed area. (e) A number of fresh granulation tissues on the tendon-exposed wound bed after 11 days postoperatively. (f) The skin grafts surviving after full-thickness skin transfering for 10 days.

however, skin grafting was prone to contraction and should be avoided when tendons, bones or nerves were exposed [18]. In this study, all patients with tendon-exposed wounds had PRF or Integra applied to prepare the wound bed before skin grafting. It was more effect to utilize PRF than Integra to prepare the wound bed before skin grafting and to improve patient discomfort following surgery.

Since being introduced in 1981 [19], Integra has rapidly gained popularity as a new means of covering non-vascularized wound beds, such as exposed tendons, receiving its vasculature from the edges. However, the major disadvantages of Integra include the risk of infection and its high cost. In this study, the take rate of Integra grafts averaged 92.39%, which resulted in removing some of the Integra before skin grafting. However, in the PRF group, the take rate of PRF grafts was higher (average 97.83%). It was reported that the PRF was a type of platelet concentrate containing leukocytes and platelets in a fibrin network [20]. Therefore, the PRF including leukocytes had antibacterial and immunological properties which resulted in the higher take-rate of PRF grafts.

Both PRF and Integra had a three-dimensional structure; however, the PRF was also platelet-rich and fibrin-dense [21]. The massive fibrin in the PRF was reported to protect growth factors and cytokines from proteolytic degradation which allowed them to maintain their activity for a longer time [22]. Some studies have reported that the PRF contained platelets in a concentration many times that of blood and released high quantities of pro-inflammatory cytokines, including IL-6. during the early days of wound healing [23]. In this study, the PRF group patients reported less pain than in the Integra group during the first 5 days after surgery.

Like Integra, the bioresorbable scaffold of PRF had the ability to guide the migration of epithelial cells and factors to the wound and promote vascular tissue formation in the tendon-exposed area [24]. Furthermore, the PRF could release an arsenal of potent growth factors, including platelet-derived growth factor, transforming growth factor beta-1, fibroblast-derived growth factors, and vascular endothelial growth factor, which could promote neoangiogenesis in the tendon-exposed area, thus increasing the granulation tissue thickness and remodeling the wound bed [25]. It was reported that through modifying centrifugation speed and time with low-speed concept, PRF had an increase in growth factor concentrations and released essential growth factors slowly for about 10 days, which resulted in stimulating the wound bed remodeling process [26,27]. In this study, PRF was produced by the low speed centrifugation concept. This could explain why there were less texture changes in the PRF group than in the Integra group in this study. It has been suggested that PRF could increase granulation tissue formation for skin grafting with

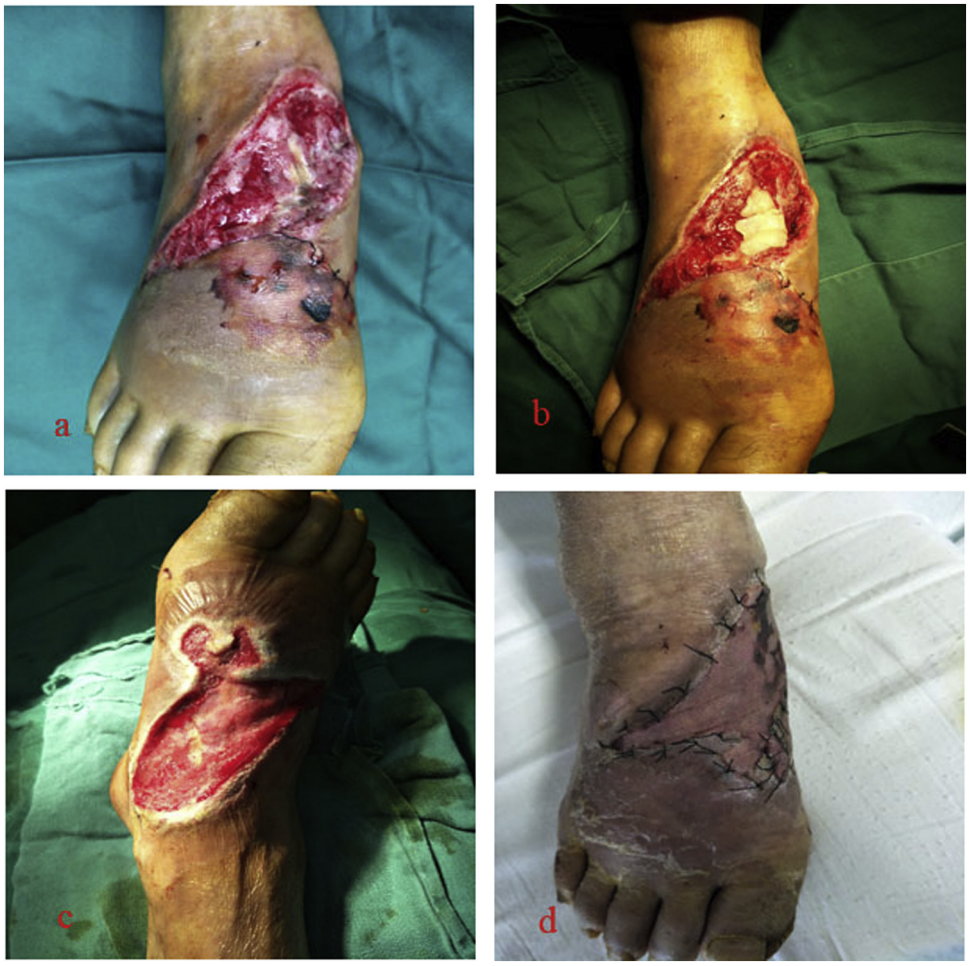

Fig. 5 – A 60-year-old man with a tendon-exposed wound on the right foot dorsal received PRF treatment for about 1 month. (a) Wound status before PRF graft. (b) Shaping the PRF and covering the tendon-exposed area. (c) Many fresh granulation tissues on the tendon-exposed wound bed after 10 days postoperatively. (d) The skin grafts surviving after full-thickness skin transfering for 10 days.

functional and aesthetic results. It was necessary for further studies to be conducted to validate and explain these findings.

7. Conclusions

PRF might be an option for the reconstruction of tendon-exposed wounds that were unfit for a standard skin graft or flap transfer due to the lack of adequate flap donor sites or poor general clinical conditions. PRF was simple and cheap for clinical use and could increase granulation tissue formation in the tendon-exposed area for skin grafting with a functional and aesthetic result.

Conflict of interest

The authors declared that there are no financial or other relationships that might lead to a conflict of interest of the present article. All authors have reviewed the final version of the manuscript and approved it for publication

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