Platelet-Rich Plasma Versus Autologous Fat Graft for Chronic Wound Management in Low-Resource Settings: A Single-Center Pilot Randomized Controlled Trial

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Summary

Background: Autologous fat grafts (AFGs) and platelet-rich plasmas (PRPs) are useful adjuncts to healing of chronic wounds. In the resource-limited setting, PRP is the more attractive option owing to its ease of use. There is, however, a paucity of data comparing the two. **Methods**: In this single-center randomized controlled trial, we recruited 56 participants in the AFG (26) and PRP (30) groups. Bed preparation and standard dressings were done, then AFGs or PRPs were injected at the wound base and peri-wound area. On days 3, 7, 14, 21, and 28 data for epithelialization, granulation, wound contraction, pain, and infections were collected and analyzed using SPSS. **Results**: Granulation and epithelialization increased from day 0 to 28 in both groups with statistical differences observed on days 0, 14, and 21 (p values = 0.033, 0.002, and 0.002, respectively, for granulation and no significant difference noted for epithelialization). Contraction was observed in both groups from day 0 to 28 with a significant difference noted on days 3 and 7 (p value = 0.015 and 0.004, respectively). Pain decreased from day 0 to 28, with the PRP group recording lower values. There were no infections among the AFG group, while in the PRP group, infections were reported on day 3. **Conclusions**: PRP provides a viable option over fat graft in the management of chronic wounds.

Keywords: Platelet-rich plasma, Autologous fat grafting, Chronic wound healing, Granulation

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Introduction

Chronic wounds are those that take more than 6 weeks to heal (1), mostly due to an arrest in the inflammatory phase (2). A prolonged inflammatory phase leads to sustained high levels of pro-inflammatory cytokines and tissue proteases, which degrade granulation tissue and tissue growth factors, and delay collagen deposition. In the treatment of chronic wounds, the goal is thus to eliminate barriers that have arrested the wound in the inflammatory phases of wound healing. This involves converting a chronic wound to an acute one in order to facilitate early wound closure. The TIME principle of necrotic tissue debridement, inflammation/infection control, moisture balance, and management of wound edge is key in wound bed preparation (3–5). Once a

wound is in Phase II of healing, modalities such as vacuum dressings/negative wound therapy and a combination of autologous fat grafts (AFGs) have been used to accelerate wound healing.

Conventionally, the standard dressing is petrolatum gauze impregnated with chlorhexidine combined with plain absorbent gauze (6). This has protective, absorbent, and draught control properties with good results; however, delayed healing has been reported (7). Although AFGs and autologous platelet-rich plasmas (PRPs) have been shown to provide regenerating cells and important growth factors that aid in orderly and accelerated wound healing, there is a dearth of data in control trials that have documented their use in the management of chronic wounds (8).

There is a heavy burden of chronic wounds, straining the meager resources in the healthcare system. Second, in their management, these wounds have a huge financial impact and psychological strain on the affected patients and their relatives (9). There is also a lack of affordable and effective tools to tackle chronic wounds promptly. Additionally, as compared with AFG, PRP has been noted to be easier to prepare and at a cheaper price, therefore a comparsion between it and AFG would inform on the use of the better one. This study hence aims to investigate the role of PRP versus AFG in the management of chronic wounds. The findings of this study may, therefore, aid in pushing the acceptance of AFGs and/or PRPs as adjuvants in the management of chronic wounds.

Methods

This study is a single-center pilot randomized controlled trial, with two arms, involving 56 consenting participants with chronic wounds at the Kenyatta National Hospital.

The calculation used was borrowed from a study documenting the best sample size formula for randomized control pilot studies as shown in the below equation (10):

$$\frac{n = (r+1)(z_{1-\beta} + z_{1-\alpha/2})^2\sigma^2}{\mathrm{rd}^2}$$

Where the sample size per treatment arm is n; to ensure adequate power ($1–\beta$), β is the Type II error rate while controlling the Type I error rate, α; for a specified/required treatment difference, d; and standard deviation, σ, r is the allocation ratio of participants between the two treatment arms.

In this study, the allocation ratio was at 1:1; $Z_{1-\beta} = 2.326$, $Z_{1-\alpha/2} = 2.326$, $\sigma = 1.55$, $r = 1$, and $d = 2$ (derived from studies documenting that the average time to healing for chronic wounds with fat grafts is 14 weeks, while for PRP it is 12 weeks). Given the aforementioned, $n = 28$.

Initial screening and recruitment of patients by the principal investigator yielded 65 patients who met the inclusion criteria, which included as follows: all consenting participants >18 years who had chronic wounds (non-healing wounds for a duration of more than 6 weeks), ASA (American Society of Anesthesiologists) I–III, and those who had glycemic control evidenced by HBA1C of <6.5. However, those who had malignancies, anemia, post-traumatic wounds requiring flaps, immunosuppression, allergies to medication, or had stopped smoking less than 6 months to the presentation were excluded.

For simple randomization, sequentially numbered, opaque, sealed envelopes were developed and used to conceal the allocation from the participants, experimenters, and analyzers. Patients were then consecutively enrolled and assigned to the study groups. Intervention assignment was performed after the start of surgery. The participants were assigned into either the AFG or PRP arm of the study (26 and 30 participants for AFG and PRP, respectively). Each group had equal representation of arterial, diabetic, and hematological wounds. Wound bed preparation guided by the TIME principle and standard dressing with tulle and cotton gauzes were applied indiscriminately to all wounds prior to and after the intervention.

Harvesting the AFG, Preparation of PRP, and Injection

The tumescent manual liposuction harvesting technique was used. It involved fat harvesting with a blunt-tipped 3 mm cannula using a standard 10 mL luer lock syringe with 2 mL of negative pressure space in the barrel of the

syringe providing low-level suction. The lipoaspirate was processed via decantation. Aliquots of the processed lipoaspirate were then injected into a chronic wound base and peri-wound area at a dose of 1 mL per 1 cm^2 of the wound area.

The method of PRP preparation used was as illustrated by Dhurat et al. (11). Whole blood (WB) is initially collected in tubes that contain anticoagulants. The first spin step is performed at constant acceleration to separate red blood cells (RBCs) from the remaining WB volume. After the first spin step, the WB separates into three layers: an upper layer that contains mostly platelets and white blood cells (WBC); an intermediate thin layer that is known as the buffy coat and that is rich in WBCs; and a bottom layer that consists mostly of RBCs. For the production of pure PRP (P-PRP), the upper layer and superficial buffy coat are transferred to an empty sterile tube. The second spin step is then performed. "g" for second spin should be just adequate to aid in the formation of soft pellets (erythrocyte-platelet) at the bottom of the tube. The upper portion of the volume that is composed mostly of platelet-poor plasma (PPP) is removed.

Pain Management, Antibiotic Administration, and Dressing

Diclofenac in combination with paracetamol was given for the first 3 days after the intervention. Tramadol 100 mg three times a day for 4 days was added when required. A preoperative intravenous dose of ceftriaxone at 50 mg/kg per dose with a maximum of 2 g/24 h dose was administered within 1 h of the procedures; all procedures were done within 1 h (12).

The wounds that complicated with infection after the intervention were treated with sensitive antibiotics, guided by tissue microscopy and culture studies upon clinical suspicion of local infection. Infectious wounds were those in which bacteria or other microorganisms invaded damaged skin and caused associated impaired healing, pain, swelling, redness, and loss of function (international consensus). All were successfully treated after a 1-week course of antibiotics.

All wounds had tulle combined with plain absorbent gauze and a tertiary dressing to secure it in the form of a crepe bandage. Compression dressing was added in the case of lower limb edema (e.g., in venous ulcers) indiscriminately. Change of dressing was done twice a week for the duration of the study.

Wound Assessment

The primary objective of the study was assessing and comparing the epithelialization and granulation rates. Secondary outcomes were assessing the contraction, pain, and infection rates.

Wound assessment by two trained, research assistants was done on days 3, 7, 14, 21, and 28. The wounds were observed for granulation, epithelialization, and contraction. The percentage of the wound covered by granulation tissue was measured using a transparent grid, whereas epithelialization was measured clinically by wound tracing via a transparent gridiron technique. The wound surface area was estimated and the area covered by new epithelial tissue was also estimated and a percentage calculated as follows:

$$\frac{\text{Percentage of wound surface area under new epithelialization} \times 100}{\text{Epithelialization total wound surface area}}$$

Pain was also assessed using the universal pain assessment score (Wong Baker pain rating scale) and any complication(s) noted. The patients and the research assistants were all blinded to the intervention type.

All data collected in the study were sorted, coded, and entered into SPSS version 21. Data were crossed-checked for any inconsistencies and data entry errors. Independent T-test was then used to measure the statistically significant difference in the (dependent variables) pain, granulation, wound contraction, epithelialization, and complication incidences between the treatment groups at different time intervals of the study. The independent variables were the allocation (either into AFG or PRP groups). A p value of ≤ 0.05 was considered statistically significant at 95% CI. The study findings were presented using figures and tables.

Ethical Approval

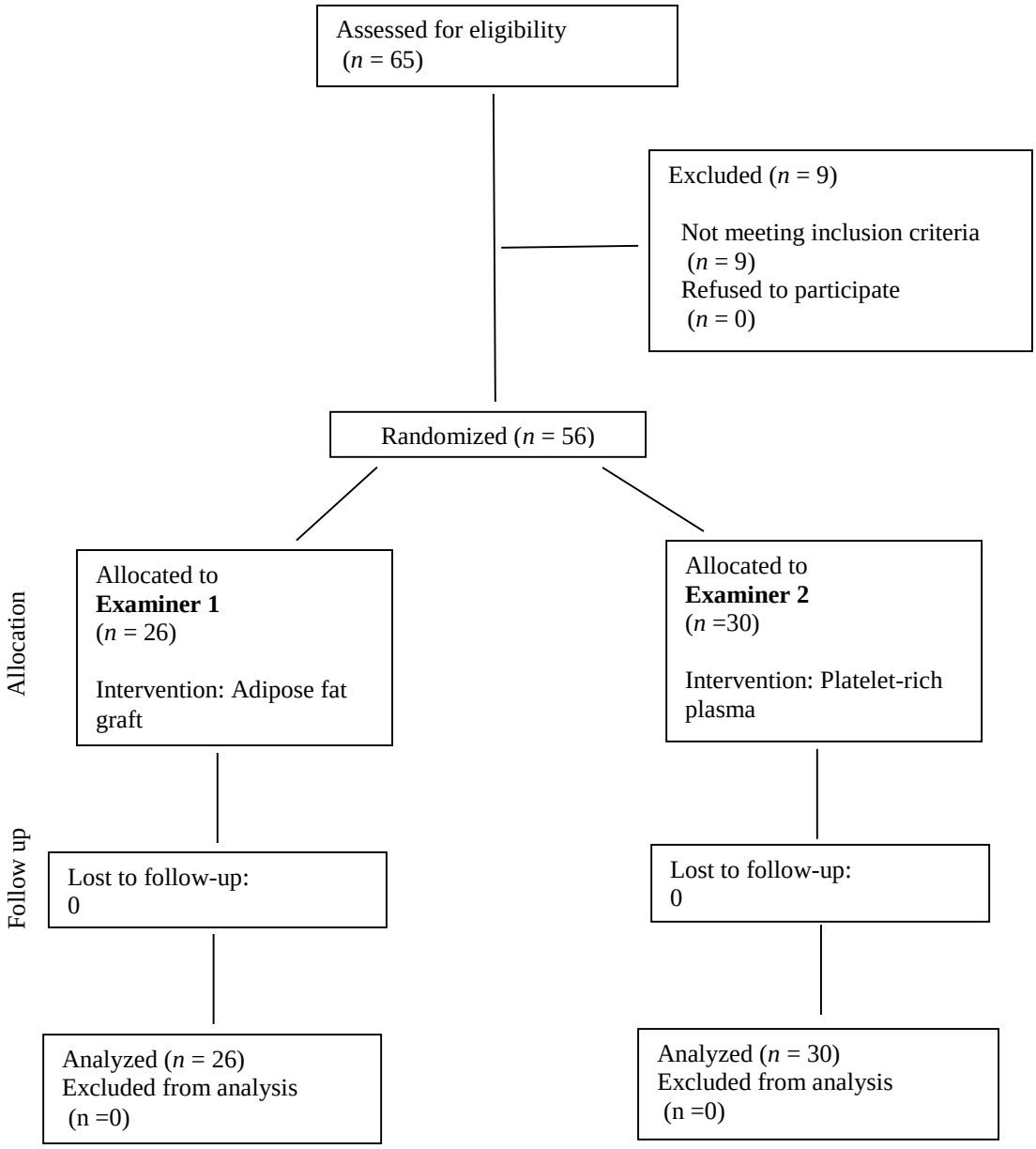
Ethical approval was sought from the KnH-ERC review committee (P695/10/2016). All data were collected after approval and procedures conformed to the World

Medical Association Declaration of Helsinki (June 1964) and subsequent amendments. Informed consent was sought from all the participants. Participation in this study did not attract extra cost to the medical care of the participants.

Results

Per-protocol analysis was done. All patients enrolled were followed until day 28, none dropped out. The majority of the patients were male (67%).

PATIENT FLOW DIAGRAM



The majority of the patients were between 30 and 40 years of age (40%), followed by those 20–30 years of age (34%), with the ages ranging from 21 to 75 years. The types of chronic wounds in this study were distributed as follows: arterial 35%, diabetic 40%, and hematological wounds (sickle cell) 25%.

Percentage of Granulation

In the two different groups, granulation was noted to increase from days 0 to 28 (Table 1). From days 0 to 14, the AFG group registered higher percentages than the PRP group; however, from days 21 to 28, the PRP group registered higher values.

Table 1: Comparing the effect of AFG versus PRP in wound contraction, granulation, epithelialization, pain, and infections

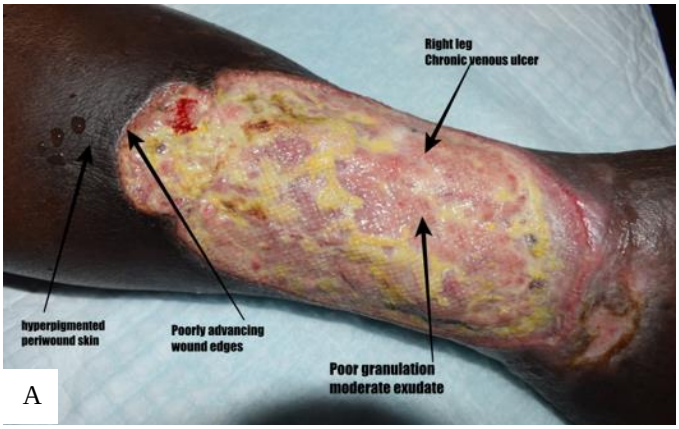
	DAYS	0	3	7	14	21	28
VARIABLE	Procedure						
WOUND CONTRACTION	PRP	10–20	10–20	10–20	10–20	0–10	0–10
	AFG	10–20	10–20	10–20	10–20	10–20	0–10
	p value	0.075	0.015	0.004	0.221	0.090	0.332
GRANULATION PERCENTAGE	AFG	33	34	52	69	78	88
	PRP	31	33	51	67	81	91
	p value	0.033	0.072	0.056	0.002	0.002	0.080
PAIN	PRP	6	4	2	1	0.8	0.2
	AFG	7	4	3	2	1.0	0.6
	p value	0.098	0.088	0.132	0.225	0.894	0.996
INFECTIONS	AFG	None	None	None	None	None	None
	PRP	Infection	Infection	None	None	None	None
	p value	0.056	0.213	0.074	0.058	0.356	0.289
EPITHELIAL PERCENTAGE	PRP	3	4	7	14	22	34
	AFG	1	1	5	22	19	25
	p value	0.080	0.074	0.090	0.122	0.231	0.556

Abbreviations: *AFG*, autologous fat graft; *PRP*, platelet-rich plasma.

Table 2: Granulation and epithelialization based on type of wound

GRANULATION			
	Arterial	Diabetic	Hematologic
Day 0	25	10	40
Day 3	25	10	40
Day 7	45	20	40
Day 14	65	40	60
Day 21	70	70	60
Day 28	85	96	88
EPITHELIALIZATION			
	Arterial	Diabetic	Hematologic
Day 0	0	0	0
Day 3	0	1	0
Day 7	0	0	0
Day 14	7.5	5	5
Day 21	12	10	5
Day 28	18	29	19

The differences between the two groups in all the days observed were statistically significant on days 0, 14, and 21 (*p* values = 0.033, 0.002, and 0.002, respectively). As regards wound types, granulation was noted to occur fastest in diabetic wounds (Table 2).



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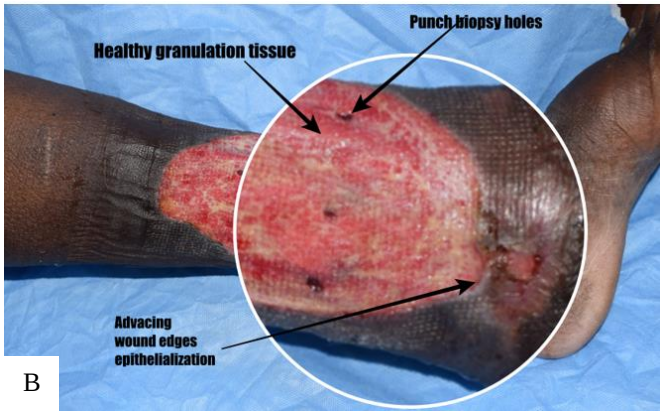

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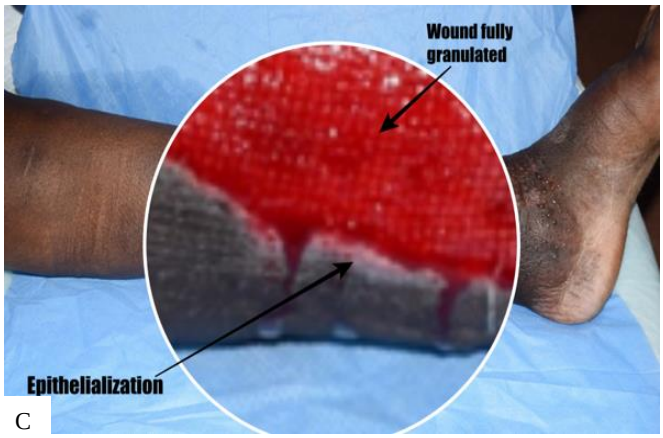

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Figure 1. Chronic wound managed using AFG. (A) Day 0; (B) Day 14; (C) Day 28.

Percentage of Epithelialization

Percentages of epithelialization were noted to increase between the two groups gradually from days 0 to 28 (Table 1). From days 0 to 7 and 21 to 28, the PRP group registered higher percentages than the AFG groups, which had higher levels recorded only on day 14. The differences noted were not statistically significant. As regards wound types, epithelialization was noted to occur fastest in diabetic wounds (Table 2; Figures 1 and 2).

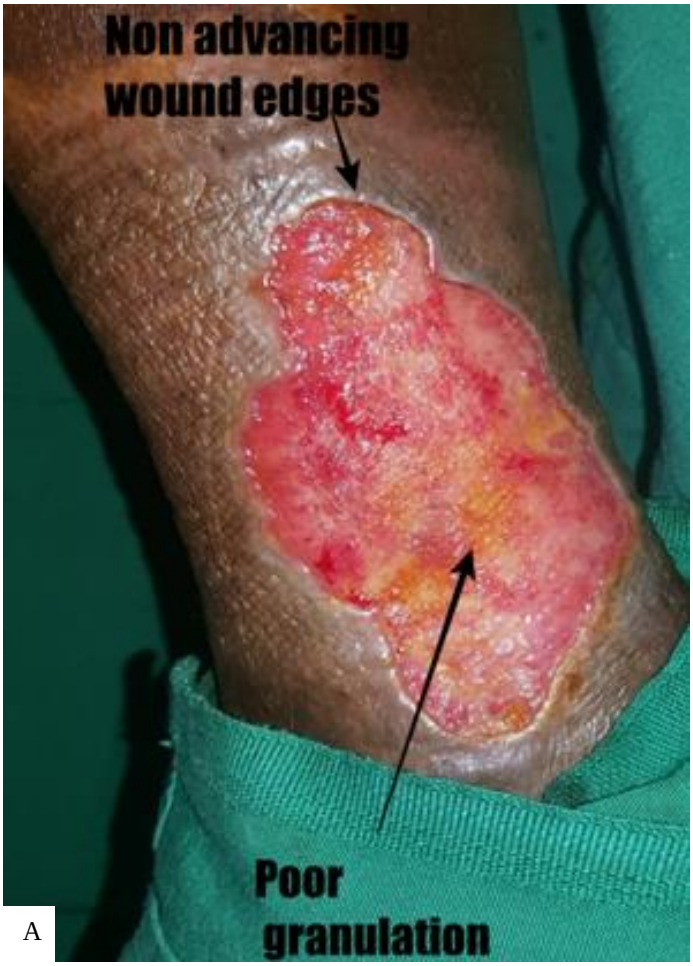
Size of the Ulcers/Contraction of the Ulcer Size

On all the days observed, and in the two groups, the ulcer was noted to decrease in size from days 0 to 28 (Table 1). When compared with the AFG group, patients in the PRP groups were noted to have smaller mean size of ulcers on all days observed. Statistical significant difference was noted on days 3 and 7 (p value = 0.015 and 0.004, respectively).

Complications

The major complications recorded during the duration of the experiment were infection and pain. Data from the results showed a gradual reduction in the scale of pain from days 0 to 28 in both AFG and PRP (Table 1). In all the days noted, the PRP group recorded lower pain scales as compared with the AFG group. The differences were, however, not statistically significant.

As for the infections, out of the 56 patients, 8 were infected, all of whom were in the PRP group. The rest of the patients did not suffer any infections. Most of the infections that were noted were mostly by Gram-positive bacteria, which were all treated with sensitive oral antibiotics for 7 days; the patients recovered. None of the patients needed extra medical attention after the dose of the oral antibiotic. There were no patients who opted out of the studies due to their infections.



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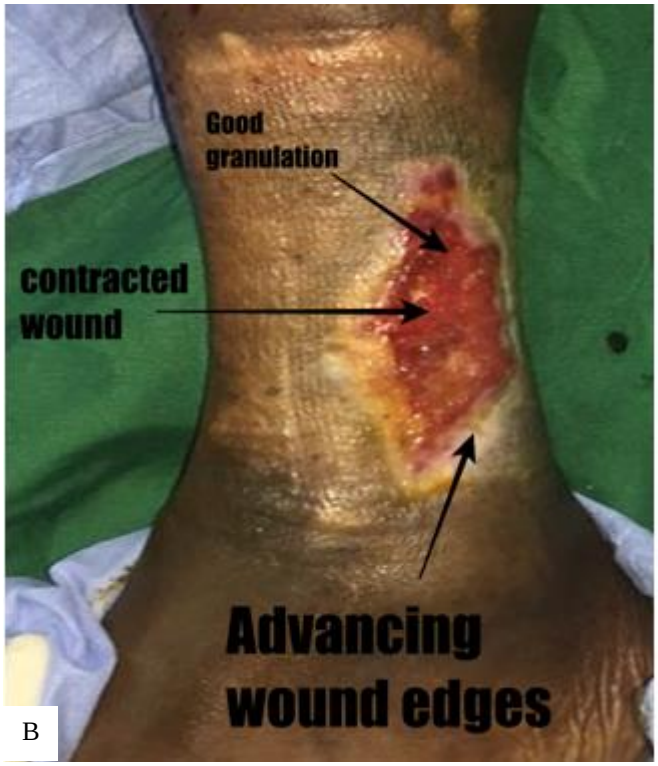

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Figure 2. Chronic wound managed using PRP. (A) Day 0; (B) Day 14; (C) Day 28.

Discussion

Healing: granulation, epithelialization

Our study showed an increase in granulation and epithelialization from days 0 to 28 in both groups. The AFG group had higher granulation levels in the earlier days (days 0–21) compared with the PRP group. As regards epithelialization and contraction, our findings showed that the PRP group had higher percentages.

The use of AFG in increased tissue granulation, epithelialization, and contraction has been shown in previous studies (13). Ebrahimian et al. (14) noted significant faster granulation when he treated irradiated mice with AFG. His findings were similar to that of Knighton et al. (15), who also reported better wound healing of chronic ulcers versus placebo group and Driver et al. (16), who reported significant tissue granulation in diabetic foot ulcers. Biribwa et al. (17) while investigating the difference in healing of chronic ulcers following AFG vs standard dressing also noted faster rates of granulation and epithelialization following AFG. Senet et al. (18), in his study on chronic venous ulcers, however, noted no difference in tissue granulation when compared with placebo.

The differences observed between his study and the rest might be because of the low sample size of 15 that he employed, as compared with other studies.

Studies have also documented the use of PRP in increased tissue granulation as well as epithelialization and contraction. A study by Badis et al. (19) showed that PRP reduced inflammation during the first 3 days post-surgery and promoted epithelialization in 3 weeks of healing when compared with placebo. Similar findings were noted by Abdullah et al. (20) in his study on full thickness wounds in rabbits.

AFG facilitates wound regeneration by promoting angiogenesis, immunomodulation, differentiation, and proliferation (21). The cells present in a lipoaspirate are adipocyte precursors, mesenchymal stem cells, and endothelial cells that release cytokines such as VEGF and TNF that are involved in the regenerative process. These same properties allow the infiltrated AFG to survive and proliferate. The modulation of the extracellular matrix (ECM) promotes the migration of cells, contributing to angiogenesis (22). The synergistic

movement, differentiation, and immunomodulation enhances cell survival and tissue regeneration, reducing the fibrosis in the wound bed and increasing healthy granulation tissue.

The mechanism underlying the increased granulation and epithelialization as noted, following AFG augmentation, may be due to their role in the production of KGF-10, which is a growth factor that has been shown to stimulate the wound healing process in vivo and in vitro, thereby enhancing healing. Furthermore, AFG has been reported to support angiogenesis as evidenced by a study by Ebrahimian et al. (14), where intravenous and local injection of AFGs increased the vessel density by 2.22- and 1.85-fold, respectively, compared with control animals.

PRP, on the contrary, has been shown to enhance tissue granulation, epithelialization, and contraction by releasing vascular endothelial factor, which promotes angiogenesis, platelet-derived growth factor, and transforming growth factor-β (23). These factors contribute to the migration of leukocytes to the site of the wound as well as to the proliferation of fibroblasts in myofibroblasts and to the synthesis of the constituents of the ECM.

The differences noted between the two groups in our case though may be due to the adipokines that are released by adipocytes (21). Adipokines have a profound impact on the immune and inflammatory response. The negative influence of adipokines on the systemic immune response may influence the healing process, although the direct proof for this is lacking. Impaired peripheral blood mononuclear cell function, decreased lymphocyte proliferation, and altered peripheral cytokine levels have also been reported (21). Since, during the preparation of AFG, adipocytes may be infused and these may in turn release adipokines, the better granulation, epithelialization, and wound contraction in PRP versus AFG may be attributed to the negative effects of adipokines in AFG.

This does not suffice to say that other systemic factors may impede wound healing such as obesity, non-steroidal anti-inflammatory drug (NSAID) use, and glucocorticoids. In our case particularly, patients were put on either paracetamol or NSAID use following the procedure. Its use may have impeded wound healing.

Difference noted in granulation and epithelialization among the different wound types

The results from our study showed that diabetic wounds had faster granulation, as well as epithelialization rates among the wound types. Our findings were similar to those of Wilcox et al. (24), who reported faster healing rates among diabetic wounds as compared with arterial, in his study. The differences may be attributed to the fact that in most cases, the reduced perfusion in arterial wounds impairs wound healing worse when compared with diabetic and hematological wounds, whose underlying factors can be managed easily to facilitate wound healing.

Complications: Pain and Infection

The complications noted in our study were pain and infection. Pain was reduced in both groups with more analgesic effect among PRP compared with the AFG group. The reduction in pain following augmentation is similar to the findings of Manneli et al. (25).

On infections, similar studies have reported infection rates following either AFG or PRP augmentation. A systematic review and meta-analysis on the "Use of platelet rich plasma gel on wound healing" shows that in patients augmented with PRP (26), infection rates are lower than other methods. As for the AFG, infection rates have also been reported to occur commonly (27). In our case, the discrepancy on the infection rates between the groups could be attributed to the low sample size employed, and as a result, chance. Similarly, it might be that in those with infections, these had occurred prior to the augmentation and were not picked up since biopsies before the augmentation were not done.

Limitations

Tissue cultures were not taken at day 0 of the study, thus the onset of infection was difficult to discern.

Owing to the study duration, our study utilized a small sample and thus the findings might not fully represent the general population.

Conclusion

AFGs and PRP are useful adjuvants in the management of chronic wounds, as demonstrated in the study with PRP-treated wounds having a slightly faster rate of healing and better pain control. PRP is also relatively easier to harvest; however, both groups have significant and similar clinical outcomes.

Suggestion for Further Studies

RCT studies to investigate the mechanism of action including molecular and histological changes to a chronic wound treated with either intervention.

Despite our small sample, our findings are hypothesis-generating and prove that a larger, multicenter trial is possible.

Author contributions

All authors equally contributed to conceptualization, formal analysis, data curation, funding acquisition, investigation, methodology, visualization and in writing, reviewing and editing of the original draft.

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