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Research Protocol

Surgery Section

Evaluating Postoperative Healing of Skin Grafts With and Without Platelet Rich Fibrin at Free Flap Donor Sites in Oral Squamous Cell Carcinoma: A Research Protocol for a Randomised Controlled Trial

MAHENDRAKUMAR P PADSALA[1], NITIN BHOLA[2]

ABSTRACT

Introduction: Reconstruction of donor sites after harvesting radial forearm, fibula, and Anterolateral Thigh (ALT) flaps typically involves split-thickness free skin grafts. However, challenges such as necrosis and partial graft loss can arise. Studies show that optimising the wound bed with methods like negative-pressure wound therapy can improve outcomes, though these methods can be costly and time-consuming. A simpler, cost-effective alternative is the use of Platelet-Rich Fibrin (PRF) membranes, which enhance wound conditions and improve graft survival by releasing growth factors that promote angiogenesis and fibroblast migration. Additionally, PRF membranes act as a protective barrier for the skin graft, aiding in donor-site reconstruction.

Need of the study: Donor site closure is done with Split-Thickness Skin Graft (STSG) that requires proper regeneration for the best possible outcome after surgery. It is imperative to comprehend the relative effectiveness of STSG alone and in combination with PRF to assist clinicians in determining the most effective reconstruction method following microvascular surgery in oral cancer patients. Both STSG and PRF have shown promise in enhancing wound healing and tissue regeneration; however, to develop evidence-based guidelines for clinical practice, a direct comparison through a rigorous comparative study is essential.

Aim: To evaluate and compare the postoperative healing of skin grafts with and without PRF at free flap donor sites in oral squamous cell carcinoma.

Materials and Methods: The present Randomised Controlled Trial (RCT) will be conducted on 40 patients in the Department of Oral and Maxillofacial Surgery at Siddharth Gupta Memorial Cancer Hospital (SGMCH), DMIHER, Sawangi, Wardha, Maharashtra, India, from August 2025 to January 2027. A detailed history of the patient with written informed consent will be obtained from patients in their language before enrolment. The present single-blinded RCT with a parallel group design will randomly assign patients using an odd-even method into two groups: Group A (STSG without PRF) and Group B (STSG with PRF). The study population includes oral cancer patients undergoing surgical resection followed by microvascular free flap reconstruction, like anterolateral thigh, free fibula, and radial forearm. A Southampton Wound Assessment Scale (SWAS) will be utilised for assessing the healing. Patients will be monitored for graft survival, re-epithelialisation, and complications such as necrosis, infection, or tendon exposure over a structured follow-up period. Statistical analysis will be done by using descriptive and inferential statistics, specifically the Chi-square test, Student's paired and unpaired t-test, with p-value <0.05 considered significant.

Keywords: Angiogenesis, Donor site, Improved graft survival, Reconstructive surgery

INTRODUCTION

Radial Forearm Flaps (RFFF) and free fibula flaps are widely utilised techniques for reconstructing tissue defects in the head and neck region, boasting success rates exceeding 95% due to their adaptability and reliability [1]. As a fascio-cutaneous microvascular flap, the RFFF is particularly well-suited for intraoral reconstruction. Donor site closure, typically achieved via free skin grafting, remains a standard component of the procedure [2]. However, complications such as delayed wound healing, skin graft failure, and tendon exposure have been reported in approximately 28% or more of RFFF donor sites [3].

Successful graft healing hinges on vascular ingrowth, which is often hindered by tendon mobility and suboptimal wound bed conditions. These factors can lead to partial graft failure and tendon exposure. Additional complications, including pain, infection, and graft adhesion to tendons, can further impede recovery [4]. Consequently, optimising the wound bed before grafting is essential for effective donor site closure.

Various strategies have been explored to enhance healing, including vacuum-assisted closure, negative-pressure wound therapy, and the use of full-thickness skin grafts [5]. Full-thickness grafts offer superior mechanical strength and tendon coverage compared to split-thickness grafts, although they carry a higher risk of compromised vascular supply [6]. Techniques that bolster mechanical integrity without impairing blood flow may significantly improve graft integration. Re-epithelialisation, primarily driven by stem cells from hair follicles and other dermal structures, facilitates healing of STSG donor sites. This regenerative process typically spans two to three weeks, enabling skin regrowth suitable for future grafting. The preservation of dermal appendages accelerates recovery and minimises long-term morbidity [7]. One promising adjunct is the application of PRF membranes between the wound bed and the skin graft, potentially addressing both mechanical and vascular requirements [8]. PRF is an autologous blood derivative obtained through centrifugation, rich in growth factors such as platelet-derived growth factor, vascular endothelial growth factor, and various interleukins, all of which promote angiogenesis and fibroblast migration [9]. It also contains inflammatory cells, including leukocytes, monocytes, and macrophages, that further support tissue repair [10].

Depending on its preparation, PRF can be administered in either a liquid injectable form or as a solid membrane. Both formats release comparable growth factors and inflammatory mediators. Owing to these properties, PRF is frequently employed in oral and maxillofacial surgery, particularly in complex bone augmentation procedures and cases of osteonecrosis [11]. Nonetheless, prospective clinical studies exploring its broader applications remain limited. Efforts to enhance wound bed conditions for improved graft outcomes have been documented, including a study by Clark JM et al., in 2019, which demonstrated that preconditioning significantly enhances graft survival and reduces complications [12]. Despite their efficacy, many of these methods are resource-intensive, technologically demanding, and time-consuming.

The PRF, when interposed between the skin graft and wound bed, may offer benefits comparable to vacuum-assisted or negative-pressure therapies. The sustained release of growth factors from PRF could enhance graft viability and vascularisation while mitigating risks such as necrosis, infection, and dehiscence. Moreover, solid PRF membranes may provide mechanical reinforcement against tendon movement, acting as a protective buffer that reduces stress and exposure [13]. This approach could improve surgical outcomes regardless of the graft type employed, full-thickness or split-thickness. As per the author's knowledge, the present study is the first investigation into the role of PRF in enhancing the survival and healing of free skin grafts used for donor site reconstruction following free flap harvest.

REVIEW OF LITERATURE

Successful reconstruction in head and neck surgery often depends on microvascular free flaps. While these flaps offer remarkable versatility, they are frequently associated with donor-site morbidity and postoperative complications. Over time, numerous studies have explored the nature of these challenges, surgical outcomes, and innovative approaches to improve healing and graft survival. Among the most promising developments in regenerative medicine are Platelet-Rich Plasma (PRP) and PRF, which have emerged as valuable adjuncts for enhancing wound healing and minimising complications.

Karimi A et al., (2007) introduced a novel technique for closing radial forearm free flap donor sites using a locally harvested, meshed full-thickness skin graft. Their retrospective study reported improved functional and aesthetic outcomes, with notably reduced donor-site morbidity compared to conventional split-thickness grafting methods [14]. Furthermore, Chen J et al., conducted a meta-analysis evaluating the role of PRP in skin graft procedures. Their findings highlighted PRP's ability to improve graft integration and reduce complications such as graft loss and haematoma formation, without increasing the risk of adverse postoperative outcomes. These results support PRP as a safe and effective adjunct in reconstructive surgery [15].

In a prospective clinical trial, Straub A et al., examined the impact of PRF membranes placed beneath free skin grafts during donor-site reconstruction following RFFF harvest. Patients treated with PRF showed better graft survival and fewer complications, including reduced rates of dehiscence and tendon exposure. The study suggested that PRF not only delivers growth factors that promote angiogenesis and fibroblast activity but also acts as a protective barrier against tendon movement, thereby creating a more favourable wound environment and improving early healing outcomes [16]. A study by Reksodiputro M et al., employed a multiple-measure design and general linear modelling to investigate the efficacy of PRF in enhancing donor site healing post-harvest. Participants were divided into two groups based on PRF application, with standardised wound care administered bilaterally at the femoral donor sites. Epithelialisation was quantitatively assessed on days 3, 7, 14, and 30 using ImageJ software. The results indicated a statistically significant acceleration in epithelialisation in the PRF-treated group ($p<0.05$). Additionally, inflammatory markers such as hyperemia, pain, hyperthermia, and oedema were notably reduced [17].

The observed benefits are attributed to the localised release of growth factors from PRF, which fosters a conducive wound microenvironment for epithelial regeneration. These findings support PRF as a cost-effective adjunct in donor site management and wound healing optimisation. Therefore, the present study will be conducted with the aim of evaluating and comparing the postoperative healing of skin grafts with and without PRF at free flap donor sites in oral squamous cell carcinoma.

Study Objectives

- To evaluate the healing of the free flap donor site with STSG with PRF.
- To evaluate outcomes of healing the free flap donor site with STSG without PRF.
- To compare outcomes of healing of free flap donor site with STSG with and without PRF.

Null Hypothesis (H_0): There is no significant difference in healing outcomes between the use of STSG with or without PRF.

Alternative Hypothesis (H_1): STSG combined with PRF are more effective than those without PRF in promoting healing at free flap donor sites in patients with oral squamous cell carcinoma.

MATERIALS AND METHODS

The present parallel-group, superiority, single-blinded randomised clinical trial will be conducted in the Department of Oral and Maxillofacial Surgery at Siddharth Gupta Memorial Cancer Hospital (SGMCH), DMIHER, Sawangi, Wardha, Maharashtra, India, from August 2025 to January 2027. The trial has been prospectively registered with the Clinical Trials Registry of India (CTRI No: CTRI/2025/06/089263). Institutional ethical clearance has been obtained before initiating the study (Reference number: DMIHER(DU)/IEC/2025/692). Informed written consent will be acquired from participants in their native language before the commencement of the study. The present trial is designed within a superiority framework to determine whether one intervention is more effective than the other. The present study will include patients diagnosed with oral cancer who are undergoing surgical resection of the lesion, followed by reconstruction with microvascular surgery using free flaps such as the anterolateral thigh, free fibula, and radial forearm free flap, among others.

Inclusion criteria:

- Biopsy-proven case of oral squamous cell carcinoma.
- All patients who test positive for the Allen test, as a prerequisite to radial forearm free flap with or without PRF.
- Patients undergoing free flap donor site closure requiring skin grafts.
- Patients who will provide informed consent.
- American Society of Anesthesiologists (ASA) I and II

Exclusion criteria:

- Any carcinoma other than oral squamous cell carcinoma.
- Patients who have undergone recurrence or chemotherapy.
- Patient who has undergone radiotherapy.
- Patients who are lost to follow-up.
- ASA III and IV.
- All patients who are not willing to undergo microvascular surgery.

Sample size calculation: Sample size was calculated using the following formula:

$n=z^2 (p\times q)/e^2$

Where:

- n=Sample size
- z=Standard error associated with the chosen level of confidence (Typically 1.96)

- p=Variability/Standard deviation
- q=1-p
- e=Acceptable sample error

Formula developed by William G. Cochran

Z=1.96

Power of the test=80%

Confidence interval=95%

P=Success Rate 95

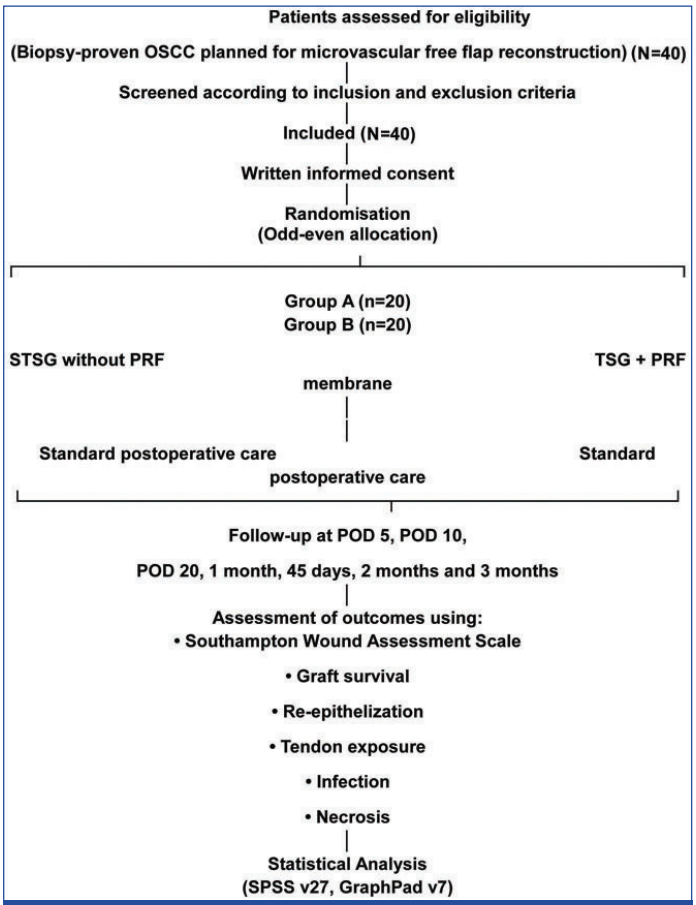
=95%=0.95 [16]

e=Desired error of margin=10%=0.10

$$n=\frac{1.96^2\times0.95\times(1-0.95)}{0.10\times0.10}$$

=18.24=20 patients needed in each group

A total of 40 patients will be recruited and randomly divided into two groups. Randomisation will utilise an odd-even method. An overview of the present study is demonstrated in Consolidated Standards of Reporting Trials (CONSORT) flowchart [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.
POD-Postoperative day OSCC-Oral squamous cell carcinoma

Group A (Split-Thickness Skin Grafting (STSG) Alone)

In Group-A, after harvesting the free flap, the donor site will be covered using a conventional STSG harvested from a secondary donor site, such as the thigh. The graft will be secured with sutures or staples and dressed with a bolster to ensure adherence and minimise graft movement. Standard postoperative wound care will include antibiotics, analgesics, and limb immobilisation to optimise healing.

Group B (Split-Thickness Skin Grafting (STSG) with Platelet-Rich Fibrin (PRF) Application)

In Group-B, after harvesting the free flap, PRF will be applied to the donor site before placing the STSG. PRF will be prepared by centrifuging the patient's blood to obtain a fibrin membrane rich in growth factors and inflammatory cells. These membranes will be placed over the wound bed to enhance angiogenesis, fibroblast migration, and mechanical stability before securing the skin graft with sutures or staples. The postoperative care and follow-up protocol will be identical to Group A.

Study Outcomes

Healing progress: A Southampton Wound Assessment Scale (SWAS) [18] will be utilised for assessing the healing.

Southampton Wound Assessment Scale (SWAS) [18]:

- Grade 0 → Normal healing
- Grade I → Normal healing with mild bruising/erythema
- Grade II → Erythema + other signs of inflammation
- Grade III → Clear/haemoserous discharge
- Grade IV → Pus
  - *IVa*: At one point only (≤2 cm)
  - *IVb*: Along wound (>2 cm)
- Grade V → Deep/severe wound infection with/without tissue breakdown; haematoma requiring aspiration

Patients will be monitored for graft survival, re-epithelialisation, and complications such as necrosis, infection, or tendon exposure over a structured follow-up period.

Graft survival will be assessed by visual clinical evaluation based on the presence or absence of tendon exposure. Complication rates will be expressed as the number and percentage of affected patients in each group, and healing time will be assessed on postoperative day 5th, 10th, 20th, one month, 45 days, two months and three months follow-up.

STATISTICAL ANALYSIS

The software used for analysis will be SPSS version 27.0 and GraphPad Prism version 7.0. Statistical analysis will be done using descriptive and inferential statistics, including the Chi-square test, student's paired and unpaired t-test. A p-value of <0.05 will be considered statistically significant.

Limitation(s)

The present study was a single-centre trial with limited sample size of 40 participants, although statistically calculated, may not be adequate to detect uncommon postoperative complications.

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REFERENCES

[1] Verhelst PJ, Dons F, Van Bever PJ, Schoenaers J, Nanhekhan L, Politis C. Fibula free flap in head and neck reconstruction: Identifying risk factors for flap failure and analysis of postoperative complications in a low volume setting. Craniomaxillofacial Trauma Reconstr. 2019;12(3):183-92.
[2] Boretto JG, Hohman MH, De Cicco FL. Fasciocutaneous flaps. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 July 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK562280/.
[3] Richardson D, Fisher SE, Vaughan DE, Brown JS. Radial forearm flap donor-site complications and morbidity: A prospective study. Plast Reconstr Surg. 1997;99(1):109-15.
[4] Jia Q, Chen D, Guo J, Luo X, Alimujiang A, Zhang J, et al. Risk factors associated with tendon adhesions after hand tendon repair. Front Surg. 2023;10:1121892.
[5] Zaver V, Marietta M, Kankanalu P. Negative pressure wound therapy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 July 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK576388/.
[6] Ramsey ML, Walker B, Marietta M, Patel BC. Full-Thickness Skin Grafts. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 July 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532875/.
[7] Braza ME, Marietta M, Fahrenkopf MP. Split-thickness skin grafts. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jan 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551561/.

[8] Naik B, Karunakar P, Jayadev M, Marshal VR. Role of Platelet rich fibrin in wound healing: A critical review. J Conserv Dent JCD. 2013;16(4):284-93.
[9] Johnson KE, Wilgus TA. Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair. Adv Wound Care. 2014;3(10):647-61.
[10] Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJJ, Mouhyi J, et al. Platelet-Rich Fibrin (PRF): A second-generation platelet concentrate. Part II: Platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):e45-e50.
[11] Miron RJ, Zucchelli G, Pikos MA, Salama M, Lee S, Guillemette V, et al. Use of platelet-rich fibrin in regenerative dentistry: A systematic review. Clin Oral Investig. 2017;21(6):1913-27.
[12] Clark JM, Rychlik S, Harris J, Seikaly H, Biron VL, O'Connell DA. Donor site morbidity following radial forearm free flap reconstruction with split thickness skin grafts using negative pressure wound therapy. J Otolaryngol - Head Neck Surg. 2019;48(1):21.
[13] Chang EI, Liu J. Prospective comparison of donor-site morbidity following radial forearm and ulnar artery perforator flap harvest. Plast Reconstr Surg. 2020;145(5):1267-74.
[14] Karimi A, Mahy P, Reychler H. Closure of radial forearm free flap donor site defect with a local meshed full-thickness skin graft: A retrospective study of an original technique. J Cranio-Maxillo-fac Surg. 2007;35(8):369-73.
[15] Chen J, Wan Y, Lin Y, Jiang H. The application of platelet-rich plasma for skin graft enrichment: A meta-analysis. Int Wound J. 2020;17(6):1650-58.
[16] Straub A, Brands R, Borgmann A, Vollmer A, Hohm J, Linz C, et al. Free skin grafting to reconstruct donor sites after radial forearm flap harvesting: A prospective study with Platelet-Rich Fibrin (PRF). J Clin Med. 2022;11(12):3506.
[17] Reksodiputro M, Harba'i H, Koento T, Harahap A. Platelet-rich fibrin enhances wound epithelialization in the skin graft donor site. Journal of Physics: Conference Series. 2018;1073:032046. Doi: 10.1088/1742-6596/1073/3/032046.
[18] Campwala I, Unsell K, Gupta S. A comparative analysis of surgical wound infection methods: Predictive values of the CDC, ASEPSIS, and Southampton Scoring Systems in evaluating breast reconstruction surgical site infections. Plastic Surgery (Oakv). 2019;27(2):93-99. Doi: 10.1177/2292550319826095.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of OMFS, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor and Head, Department of OMFS, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mahendrakumar P Padsala,
004, OMFS, SPDC, Wardha, Maharashtra, India
E-mail: mahendrapadsala44@gmail.com

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