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Research International Journal of Skin and Plastic Surgery

Research Article

Received: 25 January, 2024
Accepted: 19 February, 2024
Published: 20 February, 2024

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Citation: Abhishek Sharma (2024) Comparative Study of Epidermal Grafting (Blister graft) versus STSG (Split-thickness skin grafting) in wound healing. Our experience. Re Int J Skin and Plastic Surg. 1(1): 001-005. DOI: 10.37179/rijsps.000001

Comparative Study of Epidermal Grafting (Blister graft) versus STSG (Split-thickness skin grafting) in wound healing. Our experience

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Abstract

Background: Split-thickness skin grafting (STSG) is one of the basic modalities for wound cover. Sometimes donor site becomes painful and leaves a second wound or scar which may take longer time to cure than the primary graft site itself. Epidermal grafting (Blister graft/Suction graft) is an alternative method of skin grafting in which we apply continuous negative pressure on the skin to harvest the epidermal layer of the skin. This procedure leaves minimal donor site morbidity or scar and is relatively less painful. It can be done on an outpatient basis. In our study, we try to compare STSG and Epidermal grafts and the mechanism by which each technique achieves wound healing.

Introduction

Epidermal Grafting

Epidermal Grafting for wound healing is not a new concept, and several case reports have reported a good wound healing outcome; however, it is not known if the healing rate is comparable to Split Thickness Skin Grafting, a mainstay of treatment for wounds that cannot be closed primarily [1-5].

This study is to investigate the efficacy of epidermal graft against split-thickness skin graft. We hypothesize that epidermal graft has the same wound healing outcome as split-thickness skin graft but with lower donor site morbidity. In this trial design, we try to evaluate the wound-healing mechanism by epidermal graft and split-thickness skin graft to promote further understanding and compare the mechanism of healing at the cellular level. It is postulated that epidermal grafting stimulates wound healing by acting like a bioengineered skin by expressing growth factors, thereby encouraging the wound bed to regenerate, and initiating keratinocyte migration from the edges of the wound [19] In vitro studies showed that the migrating keratinocytes from the grafts synthesize several growth factors, namely the vascular endothelial growth factor, hepatocyte growth factor, granulocyte colony-stimulating factor, platelet-derived growth factor, and transforming growth factor α [6]. The migrating keratinocytes also deposit a variety of extracellular matrix components, such as laminin, fibronectin, and type IV collagen [6, 19] The wound exudate analysis in this trial demonstrated the expression pattern of the growth factors expressed by the grafts in vivo [20]. The effect of the growth factors

on the wound bed and the edge of the wound is further confirmed by the punch biopsies. The punch biopsy taken from the center of the wound was used to identify the expression pattern of the keratinocyte and other markers of proliferation before and after treatment, which could suggest the activation of the wound bed with treatment. The skin biopsy from the wound edges is used to study the migratory activity of the keratinocytes by determining the expression pattern of the Connexin proteins [19, 7, 8].

The Connexin proteins are gap junctional proteins which are channel-forming proteins enabling adjacent cells to communicate and play a vital role in coordinating cell proliferation and migration **[13]**. It is known that the downregulation of Connexin protein at the edges of the wound correlates with increased keratinocyte migratory activity, resulting in accelerated wound healing **[19]**. As the Epidermal Graft is postulated to stimulate the keratinocytes at the wound edges to proliferate and migrate onto the wound bed, downregulation of the Connexin protein is expected at the wound edges **[13, 20-21]** This, in turn, indicates that the keratinocytes have increased migratory properties. This will also be correlated with the proliferation markers of keratinocytes **[13, 19]** This study is expected to define the efficacy of Epidermal Grafting and further understand the mechanism of wound healing by Epidermal Grafting compared to Split Thickness Skin Grafting. These results can be used further to enhance the current best practice for wound care.

Methods/Design

This study is conducted in our center. In our study, we compare the efficacy and wound-healing mechanism of the epidermal graft with a split-thickness skin graft. The primary outcome measures are the proportion of wounds healed in 6 weeks and the donor site healing time. The secondary outcome measures include the mean time for complete wound healing, pain score, patient satisfaction, health care utilization, cost analysis, and incidence of adverse events [5].

Study Design

This study is a randomized, control trial that includes 26 patients, with two parallel groups. Eligible patients are randomized to epidermal grafting or split-thickness skin grafting using a computerized randomization method. Participants were admitted to our hospital from March 2021 to March 2023.

Eligibility criteria

Patients who visited our department (Plastic and cosmetic surgery) for skin grafting were eligible for this study. During enrolment, patients are subjected to screening for inclusion in the trial and a patient information sheet was given to each of them explaining aims, techniques of skin grafting and subsequent wound management, anticipated benefits, and potential risks of the procedure. Patients are given sufficient time to decide whether they wish to participate. Informed consent was obtained. Treatment was given within a week of patient enrolment [4].

Inclusion criteria are as follows

Age ≥ 14 years

Wound measuring > 2 cm x 2 cm and less than 20 cm.

Clean, healthy granulating bed

All Patients were explained to understand and be willing to participate in the study and be able to comply with the weekly visits and follow-ups.

The exclusion criteria are as follows

Infected wound

Wound at the plantar aspect of the foot.

Not suitable for split-thickness skin grafting

Previous history of excessive bleeding associated with trauma or surgical procedure or co-morbid medical conditions including hepatic, renal, and active autoimmune diseases.

Uncontrolled diabetes mellitus, (as measured by HbA1c ≥ 8 %)

Pre-immune or immune disease, hematologic diseases.

Use of systemic steroid or immunosuppressant

Not fit for surgery by any means.

Interventions

Wound bed preparation

All wounds are prepared as per guidelines of normal clinical practice, which is either using appropriate wound dressings or negative pressure wound therapy (NPWT) to achieve a healthy granulating wound [11, 14]. Wound swabs are used to rule out any bacterial infection or bacterial growth. During the preparation of the wound bed, the patient was referred to our research team. When the wound, bed is ready for procedure, patients are then screened and offered a patient information sheet for inclusion in the trial. Once the patients were ready for intervention, informed consent was taken.

Epidermal graft

Before the grafting procedure, the wounds are cleaned using normal saline solution by the surgeon and debrided if required. The 50 cc and 20 syringes were applied in the reverse direction over the epidermal graft area to be harvested and the mouth of the syringes was fixed with another syringe through a silicon tube and negative suction was maintained for 30 to 40 minutes [17, 18] The harvested epidermal grafts are then transferred onto the wound using a non-adhering silicone dressing. The wound is then dressed with NPWT, or gauze dressing deemed appropriate based on the type of the wound. The dressing is then secured with a crepe bandage and the use of Tegaderm is considered over the wounds that are more exudative or had previous infections. The wound and donor site were reviewed after a week post-grafting (Figure 1).

Split-thickness skin graft

Patients underwent this procedure in the operating theatre under general or local Anesthesia. The wound was debrided initially in a similar manner to the epidermal graft group. Skin is harvested from the thigh using a dermatome or skin grafting knife and meshed by 1:1.5 and 1;2 ratio. The wound is then grafted and dressed in gauze, and a Med pore or crepe bandage,

depending on the site of the graft. The donor site is dressed with Alginate dressing 3 cm beyond the wound margins and secured with adhesive tape as per standard clinical practice, the grafts are checked after a week (Figure 2).

Wound exudate sampling and biopsy

Wound exudate sampling was performed by applying a filter paper on the wound for 1o to 20 minutes until it is absorbing enough exudates and become moist. The filter paper is then stored in a sterile vial and transferred to the laboratory. The wound fluid sampling is performed before skin grafting and at each review or after 7 days. After administering adequate local Anesthesia (2 % lidocaine). Skin punch biopsies (5 mm) are taken from two locations, one from the center of the wound and the other at the wound edge. This procedure is done before skin grafting and repeated after a week post-grafting. The specimens are then placed in a sterile vial containing 4 percent Paraformaldehyde and sent to the laboratory.

Laboratory studies methodology summary

The methodology is summarized as follows

1. The wound exudate samples are used to determine the pre-grafting and post-grafting concentration of a type of growth factor, using an enzyme-linked immunosorbent assay (ELISA) [6].
2. The skin biopsies are used to compare the pattern of expression of keratinocyte proliferative markers and Connexin protein (gap junctional proteins) before and after skin grafting at the wound edge and wound center. Tissues are cryo-sectioned and stained with haematoxylin and eosin (H&E) and analyzed for immunohistochemistry [13].

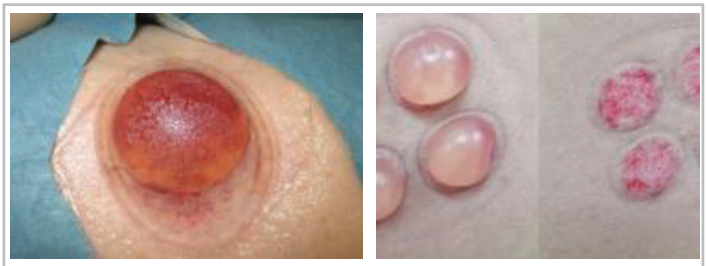

Figure 1: Epidermal graft harvesting.

Figure 2: Split-thickness skin grafting.

Study outcome

Most of the wounds or their proportion were healed completely at 6 weeks post-grafting and the time for donor-site healing varies from two weeks to 6 weeks. Complete wound healing is defined as 100 % re-epithelialization [10] The assessment of wound healing was done through wound measurement at each review. The photographs of the wounds and the donor sites were taken at each weekly visit using a high-quality camera with accurate, and standardized images for digital measurement of the wound surface area and angiogenesis [8] These images were stored in the patient's digital photo diary. An independent blinded analysis of the photo diary was carried out by us from time to time.

The secondary endpoints were the pain score mean time for complete wound healing; as noted by patients' complaints using a numerical rating scale (scale of 0–10); patient satisfaction measured by using a validated patient questionnaire related to their satisfaction [10, 12] Cost analysis healthcare utilization, measured by the consumables item used, the incidence of adverse events and frequency of visits. The incidence of adverse events includes mortality of any cause within the 3-month duration from the time of initial therapy [12], the incidence of wound-related adverse events (WAEs), and the incidence of device-related adverse events (DAEs), occurring within the study duration. The patient questionnaire related to skin graft satisfaction was completed by the participants at the 6-week and 3-month visits [12].

Furthermore, we determined the mechanism of wound-healing of epidermal grafting compared to STSG by analyzing the type and concentration of growth factors expressed by the grafts, as well as the expression of Connexin proteins (gap junctional protein) and keratinocyte proliferative markers at the wound edge and the center of the wound before and after grafting [19-21].

Participant timeline

The study was conducted between March 2021 to 2023 March. Each patient is followed up weekly for one and a half months or until the wound heals. The final follow-up was at the end of the third month from the initiation of the treatment. In case of failing the primary intervention within 6 weeks, re-grafting and a repeat of the biopsy were performed as per protocol after discussing with the patient. Failed intervention is defined as increasing wound size or failure of 50 % reduction in wound size at week 6 or more **[3].**

Brief study protocol of patient's journey

1. Patient referred by various hospitals for our center.
2. Wound bed preparation done.
3. Patient screening is done, and a patient information leaflet is given to them.
4. Patient consent for procedure and enrolment done.
5. Patients randomly distributed (n=13) for epidermal grafting and (n=13) For split-thickness skin grafting

6. The patient undergone for wound exudate sampling and 5 mm punch biopsies samples were sent to the laboratory. Followed by procedures.
7. Patient reviews after a week for sampling and biopsy
8. Patient followed up weekly for 6 weeks.
9. Last and final review at the end of 12 weeks.

Sample size

Our study revealed that both techniques offer the same healing rate after 6 weeks post-grafting procedure; however, the donor site morbidity is present in 38 % of the patients with split-thickness skin graft while only 4 % is seen in patients with the epidermal graft. Morbidity of donor site includes discoloration, Pain, scarring, and risk of infection.

Given a significance level of 0.045 for 70 % power, a sample size of 13 patients per group is yielded. In consideration of a potential dropout rate of 14 %, adjustments have been made to the sample size, with an increase to 16 patients per treatment arm. A total of 26 patients are recruited into the study. The timeline for recruitment was 24 months.

Randomization, allocation concealment, and blinding

After obtaining consent, patients are randomly assigned to one of the treatment groups. A random allocation sequence is computer-generated. The allocation sequence is sealed in identical envelopes and given to the enrolling investigator upon receipt of patient consent. None of the surgical team members, clinical staff, and patients are blinded to the intervention status.

Data collection and management

All data collected are recorded on paper and digitally. Data collected by the surgical team. Accuracy of the data collection and sample assessments done at regular intervals. Any adverse events are recorded and reported to the primary investigators and ethical committee. Wounds are assessed and recorded in a wound assessment form at each follow-up visit. Data related to patients' co-morbidities, wound duration, and type, and previous wound bed-preparation methods are recorded. The photographs are used to measure the wound surface area digitally. The cost and number of outpatient visits are recorded, and the cost and type of dressings used are documented [22].

Data storage

The data extracted for this study purpose are anonymised. All personal data extracted are stored in the computers, which are password protected with avoided access to unauthorized individuals. Access to the computers is via a secure login.

Statistical analysis

Patients are assessed for analysis if they received treatment during the study. If the clinical course cannot be fully evaluated, the last point of the visit is considered the last data analyzed [9, 16]. The baseline characteristics of both groups are recorded. The categorical variables are compared using Pearson's chi-square depending on the number of events. The proportion of wounds healed with each treatment is compared using a chi-square test, depending on the number of events. Mean time to wound healing was determined based on the number of days until complete re-epithelialization. Secondary outcomes are compared in both groups using a chi-square test for categorical variables. Non-normally distributed continuous variables are compared using a Mann-Whitney U test. A *p-value* of less than 0.05 will be considered significant [9, 16], and all tests will be two-sided.

Discussion

This study defines the efficacy of epidermal graft and encourages further understanding of the mechanism of wound healing by epidermal graft compared to split-thickness skin graft. The results of this study could be used to make aware of the current best practice for wound care. Split-thickness skin grafting (STSG) is a current basic standard of care for wound cover for non-healing wounds. STSG involves excision of the epidermis and part of the dermis, leaving behind the reticular dermis in the donor site, which enables the skin to heal by secondary intention [1, 15]. Despite STSG being an important modality for wound closure, the donor site leaves a second, often painful wound, which may take more time to heal than the graft site itself and holds the risk of infection and scarring [2] (Figure 3a&b), Epidermal grafting is an emerging and promising option to overcome these challenges. Epidermal grafting is a method of autologous skin grafting that harvests only the epidermal layer of the skin from the donor site by applying gentle heat and continuous negative pressure on the normal skin to raise blisters [3]. The roof of the blister, which is the epidermis, is then excised and transferred onto the wound. As the dermis in the donor site dermis remains untouched, the skin regenerates itself without scarring. This procedure also causes less pain as the pain fibres in the dermis are unstimulated, allowing autologous skin grafting in the outpatient setting without the need for local Anesthesia [2] (Figure 4a&b).

This study evaluates the efficacy of epidermal grafts using syringes to create negative pressure. This study was carried out in our center using the method we described. Epidermal graft is observed to be an effective method of autologous skin grafting with complete wound healing achieved in two-thirds of selected

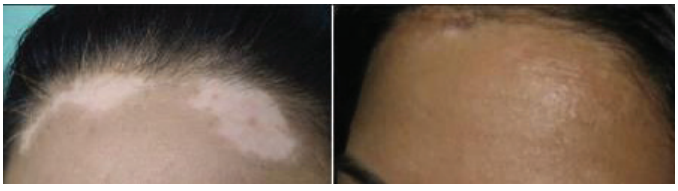

Figure 3: Epidermal Grafting Forehead.

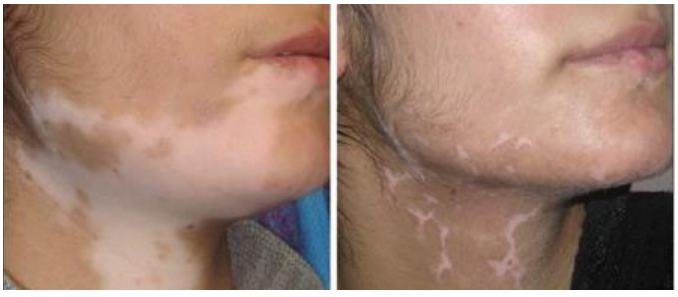

Figure 4: Epidermal Grafting Neck.

patients with minimal or no pain and a scar-free donor site [3]. The ability to perform epidermal grafting in outpatient settings eliminates the need for an operation theatre and a hospital stay and it has better patient satisfaction [3] (Figure 5a&b).

However, it is not known if epidermal grafting is an effective clinical alternative to split-thickness skin grafting [3]. The mechanism of wound healing by epidermal graft may be different compared to split thickness skin grafting and epidermal grafting is postulated to promote. wound healing by expressing growth factors that accelerate wound healing and encourage keratinocytes to migrate from the wound edge (Barrandon Y 1987). We observed that epidermal grafting has similar wound healing rates to split-thickness skin grafting at 6 weeks but with minimal donor site morbidity [3]. We wish to promote the importance of epidermal graft as an alternative to split-thickness skin grafting and to further investigate the mechanism by which each technique achieves wound healing (Figure 6a&b).

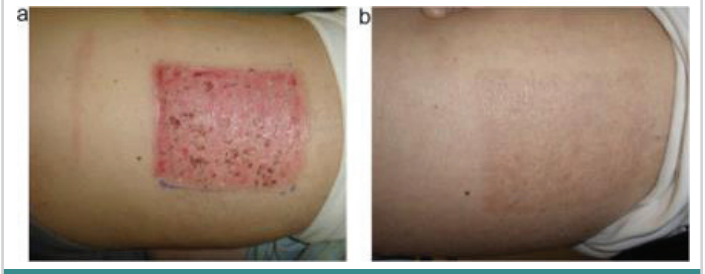

Figure 5a&b: Donor site scarring after STSG.

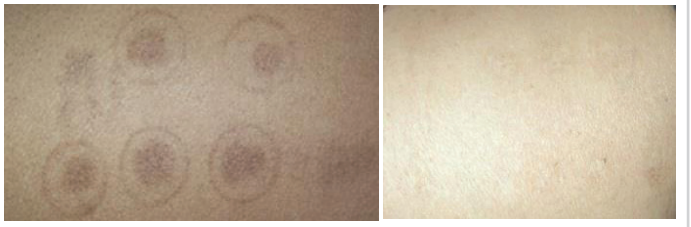

Figure 6: Donor site scarring after epidermal grafting.

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