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The use of platelet-rich plasma, a simple and cost- effective way in decreasing pain, promoting epithelialization, angiogenesis and collagen synthesis in a split thickness skin graft donor site

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Introduction

The split-thickness skin grafting (STSG) is performed daily in plastic surgery and is an indispensable part of many plastic surgery procedures. Majority of the primary and secondary defects during flap harvest, posttraumatic, and postburn raw area almost always require STSG. The skin harvest creates a donor site wound. The donor site after STSG harvest is treated with multiple treatment options of which paraffin gauze dressing is mostly used. Studies have shown that as many as half of all donor sites show signs of infection and that patients often experience pain and delayed healing at the donor site[i ii]. Infection, pain, and discharge from wound are factors that can complicate and slow the rate of healing and result in a hypertrophic scar and either hypo- or hyper-pigmentation. A lot of factors that have deleterious effect on wound healing like smoking, being underweight or overweight, taking steroids, having autoimmune diseases [iii] and a lot of chronic diseases. Patients in whom healing is delayed are often subjected to cumbersome and costly wound care procedures. Delayed healing of the donor site can result in a prolonged hospital stay and may cause the patient more problems than the original injury or disease. A donor site should, under optimal conditions, be healed within 7–21 days [iv]. The ideal dressing should help quick re-

epithelialization without infection, inhibit discharge, and be painless, adjustable for different sites, easy to use, and cost-effective. Currently, it is recommended that we use dressings that provide a moist environment [v]. Autologous platelet-rich plasma (PRP), is used in many specialties for the treatment of chronic neuropathic wounds [vi], maxillofacial bone defects [vii] and cosmetic[viii], spinal [ix], and reconstructive surgery [x]. In this study, we had used autologous PRP to treat soft-tissue wounds created by STSG harvest. This study aims to assess if topical PRP can reduce the pain following an STSG harvest from the donor site and to access the potential of PRP to accelerate the soft-tissue wound healing by increasing epithelialization, collagen deposition and angiogenesis at the split-thickness skin graft donor site.

Materials and Methods

This was a prospective study conducted on 30 patients at Gauhati Medical College and Hospital attending the Department of Plastic Surgery from March 2020 to December 2021.

Inclusion criteria

- Any patient above the age of 18 years requiring split thickness skin grafting, after taking proper consent for procedure, study and photography.
- The donor site should be a minimum of 15*7 cm up to a maximum of 40*20 cm in size.
- Both the males and females are included.

Exclusion criteria

- Medical history of chronic pain at the donor site.
- Diabetes mellitus
- Traumatic, chemical or degenerative causes of altered mental sensorium
- Any allergy to Calcium Gluconate
- Patients having platelet and other bleeding disorders.
- If the donor area is being used for the second time for harvesting skin graft.

Methods

- It is a prospective study.
- Prior approval for research work was obtained from the institute ethical committee.
- Informed consent and detailed history was obtained for each study.
- Assessment of donor area was made by clinical evaluation.
- Data were analysed on the patient's age, gender, aetiology, previous treatment history and modality, complications, recurrences, and clinical photograph.
- Subjective assessment of pain in donor area outcome is measured with clinical evaluation, Wong-Baker visual pain scale.
- Microscopic evaluation of the increase in epithelialization, angiogenesis and collagen synthesis measured using Haematoxylin and Eosin stain and Van Gieson's stain
- The final results are judged during the post-procedure and follow up period.

Procedure used for study

- Autologous platelet rich plasma is derived from patients own blood after centrifugation at 3000 rpm per 15 mins in a semi-automatic centrifuge machine.
- Platelet rich plasma is activated using cacl2/ calcium gluconate 10% after separation of PRP from cells just before administration.
- This activated PRP is injected dermally and sub-dermally at one part of donor site at the time of operation using a 1ml insulin syringe.
- Remaining portion is dressed with paraffin gauge and left as control.

- On day 5 donor site dressing is opened for visually inspection and also to assess the pain in the study and control areas using Wong-Baker faces pain rating scale (subjective pain scale).
- On day 13 a 3 mm biopsy is taken from study, control and normal skin area under local anaesthesia, and observed under microscope after staining with above mentioned stains for detecting the epithelialization, angiogenesis and collagen synthesis.

Results

Site of Donor area used

- Of the 30 patients in the study majority of the cases 14 (46.66%) cases used right thigh as donor area, 10 (33.33%) cases used left thigh, followed by 2 (6.66%) cases used bilateral thighs and left thigh and left leg, followed by 1 (3.33%) case of bilateral legs and back and right thigh and back.

Pain on the fifth day

- The donor site was opened on the fifth post-operative day and pain during removal of bandage was assessed using Wong-Baker visual analogue pain scale.
- Of 30 cases in study population, 28 (93.3%) cases showed a decrease in pain at test area. Only 2 (6.6%) cases showed no change in pain compared with test and control area of donor site.
- Fig 3 shows the pain difference between test and control groups on post operative day 5 when removing dressing based on Wong-Baker faces pain rating scale (fig 5). Statistics showed a significant P value of <0.0001, indicating a significant reduction in pain in test area where PRP is injected compared with control area.

Skin biopsy on day 13

- Skin biopsy is taken on day 13 from test site, control site and a biopsy from normal skin just adjacent to the donor area using a size 11 blade or 4mm biopsy pen.

After Staining

On Haematoxylin and Eosin staining

Epithelialization

- 5 (17%) patients did not show any change in epithelialization.
- 25 (83%) patients showed an increase in epithelialization comparing to control site.
- Statistical analysis showed a significant P value of 0.0001 for epithelialization, indicating that there is a significant increase in epithelialization in PRP injected test area compared to control area.

Angiogenesis

- 23 (77%) patients showed an increase in angiogenesis at the test site.
- Only 7 (23%) patients of total population in study showed no change in angiogenesis when compared to control site, showing a significant P value of 0.0001.

On Elastica Van Giesons staining

Collagen deposition

- 27 (90%) cases out of 30 total cases, showed an increase in collagen deposition when observed under elastica van giesons staining.
- Only 3 (10%) cases did no show any change in collagen deposition.
- Statistical analyses shows that P value is 0.0001 for the study on collagen deposition, indicating significant increase in collagen synthesis in PRP injected area compared with the control area.

Discussion

Pain

- In this study conducted on 30 patients the mean pain in test site is 4.53 and mean pain at control site is 7.2 on Wong-Baker visual pain scale showing a decreased pain at test site compared to control site showing a significant p value < 0.0001.

- This is in correlation with the study conducted by Natsuko kakundo et al [xi] showing a decrease in pain on PRP treated site compared to control site on removal of paraffin guage,
- This is in correlation with study conducted by Miller JD et al,[xii] Donor site pain was reduced from an average of 7.292.6 to 393.7. The average reduction in pain with PRP was 4.2 with a standard error of 1.1.
- This is in correlation with the study conducted by Kuffler DP [xiii], showing that the application of PRP to the refreshed end of peripheral nerves evoking neuropathic pain, including excruciating pain, results in the reduction/elimination of that pain.
- This study is contradicting with the study conducted by Fang Z, Yang X et al[xiv], which shows that Pain intensity was evaluated during each dressing process with the use of the Visual Analogue Scale (VAS) until the donor sites were fully healed and the gauze naturally fell off. At 3 and 21 days postoperatively, there were no significant differences in the total VAS score (p ¼ 0.21 and p ¼ 0.27) between the two groups, indicating that the difference in pain intensity during the dressing process was not significant.
- This study is correlating with the study conducted by Mojtaba Vaheb et al[xv], showing, there was no statistically significant difference between the mean pain scores of PRF and control groups on the first day of surgery (P = .181). However, the mean pain score in the PRF group was significantly reduced compared with the control group on days 8 and 15 (P < .001 and P < .001, respectively).
- This is in correlation with the study conducted in India by Samarth Gupta[xvi], showing that Pain at t[xvii]he donor site was measured at 6, 10, 16 hours post operatively by the use of VAS Scales. Further, pain was also measured at the time of first dressing.
- This is also in correlation with another study conducted in India by RK Jain and Samarth Gupta[xviii], showing that the Mean VAS Score was also significantly lower with a p value < 0.05 at 6 hours in the cases group. At 10 hours and 16 hours the VAS score was similar because of the rescue drug being given to patients who complained of pain. The pain scores were significantly less at the time of first dressing.

Parameters wound healing

Epithelialization

- Of 30 cases in this study 83% (25) show an increase in epithelialization in test site compared to control site was confirmed microscopically. Statistical analysis shows that the P value is 0.0001 for epithelialization, which is <0.05. But macroscopically there is no significant change.
- This study is in correlation with study done by Danielsen et al[xix], they observed no significant differences in macroscopic epithelialization between PRP and control dressing for graft harvest wound.
- This is in correlation with the study done by Natsuko kakundo et al [xi] showing that the control site showed no evidence of epithelial budding and demonstrated immature fibroblasts and macrophages. In contrast, the PRP-treated site showed mature epithelial budding and a mature dermis.
- This is in correlation with the study done by Etulain J, Mena HA, Meiss RP, et al[xx]. Histological analysis of biopsies revealed the notable presence of a hypertrophic neo-epidermis, granulation tissue, and immature blood vessels in ASA-PRPr-treated wounds.
- This study is in correlation with the study done by Fang Z, Yang X et al [xiv], The mean wound healing time

was 13.89 ± 4.65 days in the PRP group and 17.73 ± 5.06 days in the petrolatum gauze group, and the difference was statistically significant ($p < 0.05$). The PRP group showed significantly higher wound healing rates.

- This is in correlation with the study done by Igor Slaninka et al[xxi] which shows that In 17 patients, healing of the donor site was faster on the side where PRP was applied (on average 14.2 days with PRP versus 18.8 days without PRP).
- This is in correlation with the study done by Mojtaba Vaheb et al [xv].The mean wound healing time in the PRF was significantly lower than the control group. The PRF group showed significantly higher wound healing rates than the control group at 8- and 15-days dressing.
- This is in correlation with the review done by Paula One to and Julia Etulain[xxii] showing evidence of repair of epithelial tissue when treated with PRP.
- This is in correlation with the study done by RK Jain and Samarth Gupta [xviii] . It was observed that the patients in the PRP group had significantly higher fasted wound healing rates as compared to the controlled group.

Angiogenesis

- Of the 30 patients in this study, 23 (77%) patients showed an increase in angiogenesis at the test site compared with control site. Statistical analysis shows the P value as 0.0001 for angiogenesis which is <0.05 and is significant.
- This is in correlation with the study done by Natsuko kakundo et al [x] showing an increase in angiogenesis at the PRP treated site. On α-SMA immunostaining, the number of blood vessels in the dermis was clearly greater on the PRP treated side.
- Another study conducted by Natsuko Kakundo et al [xi], showed results that indicate that PRP induces angiogenesis in vitro and in vivo.
- This is in correlation with the study done by Kuffler DP [xiii], showing that PRP induces angiogenesis both in vitro and in vivo.
- This is in correlation with the study done by Etulain J, Mena HA, Meiss RP, et al [xx].

Collagen deposition

- There is an increase in collagen deposition in test area compared to control area in 27 (90%) cases out of 30 total cases, when observed under elastica van giesons staining. Statistical analyses shows that P value is 0.0001 for the study on collagen deposition, which is <0.05 and is significant.
- This is in correlation with the study conducted by Natsuko kakundo et al [x] showing the tissue observed immediately below the thickened epidermis on the PRP-treated side consisted only of collagen fibres, which were stained red with elastica van Gieson. In contrast, normal skin and control side was a mixture of collagen and elastic fibres, which were stained black.
- This is in correlation with the in vitro study done by Kuffler DP [xiii],showing for horses, PRP induces more rapid epithelial differentiation and increased collagen presence, and the dense collagen bundles are oriented parallel to each other and to the overlying epithelium, contrary to what is seen for control tissue, showing wound healing.
- This study is in correlation with the review done by Paula One to and Julia Etulain [xxii] showing that PRP induces the migration, proliferation and biosynthetic activity of dermal fibroblasts, promoting extracellular matrix restoration as well as the differentiation of human dermal fibroblasts in myofibroblast.

Conclusion

- The author concludes the discussion by stating that the results proved in this study are supported by various research studies all over world, showing that PRP is safe and cost-effective treatment in reducing pain and increasing the rate of wound healing when used on skin graft donor sites.

Figure Legends

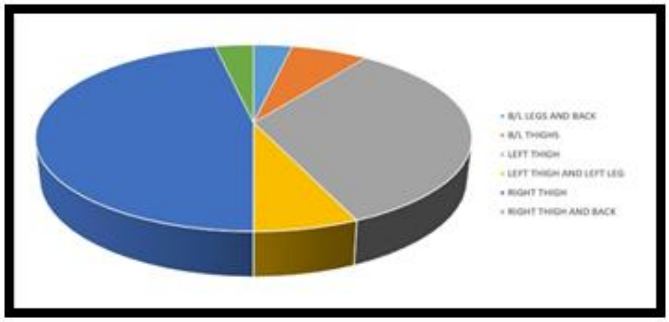

Figure 1: Pie chart showing the donor areas sites used in the study group.

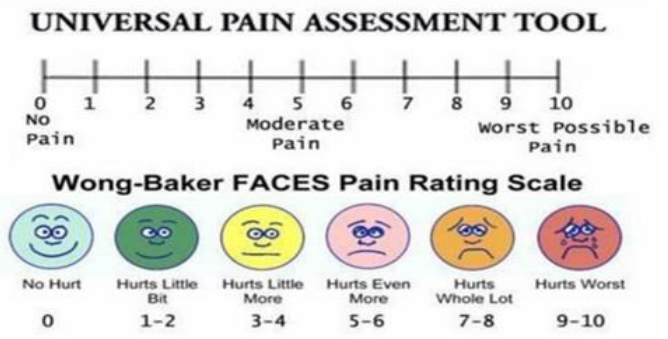

Figure 2: Wong-Baker visual analogue scale used for the study.

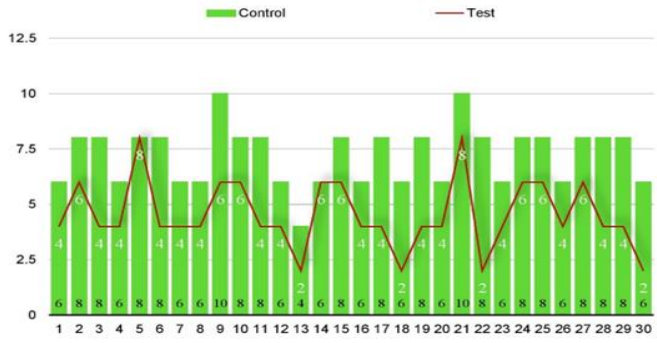

Figure 3: Graph depicting pain in test and control area of all subjects in study on post operative day 5.

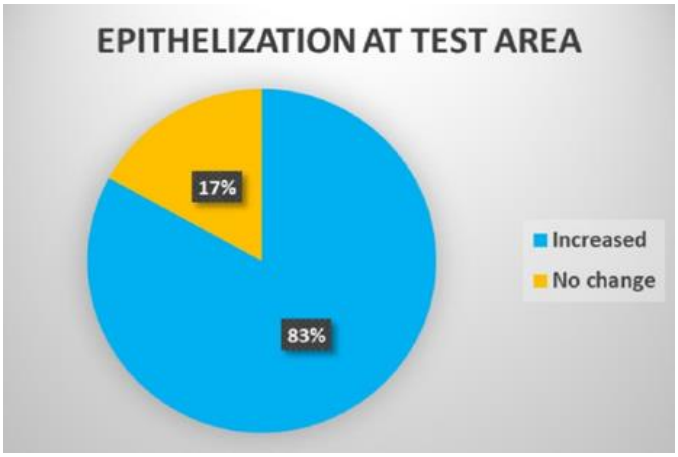

Figure 4: Pie chart showing epithelialization in the study group on test site compared with control site.

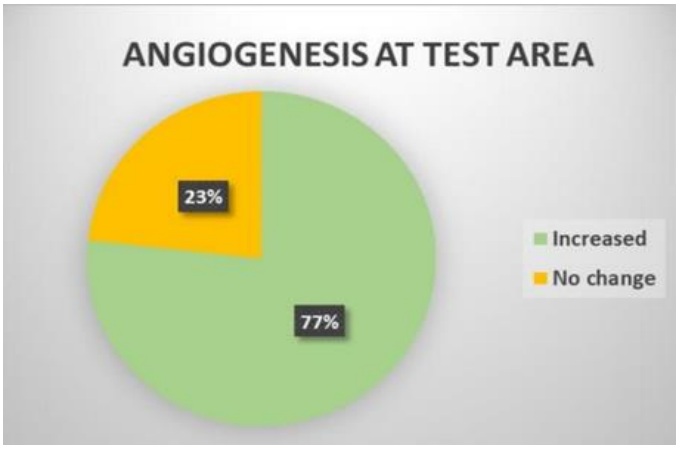

Figure 5: Pie chart showing angiogenesis in the study group on test site compared to control site.

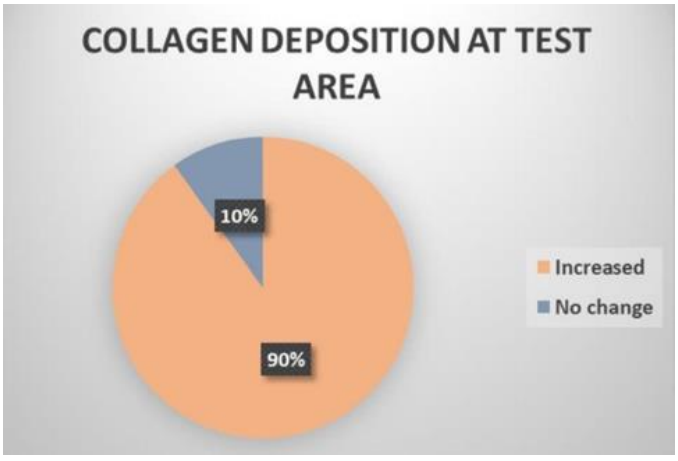

Figure 6: Pie chart showing collagen deposition in the study group on test site compared to control site.

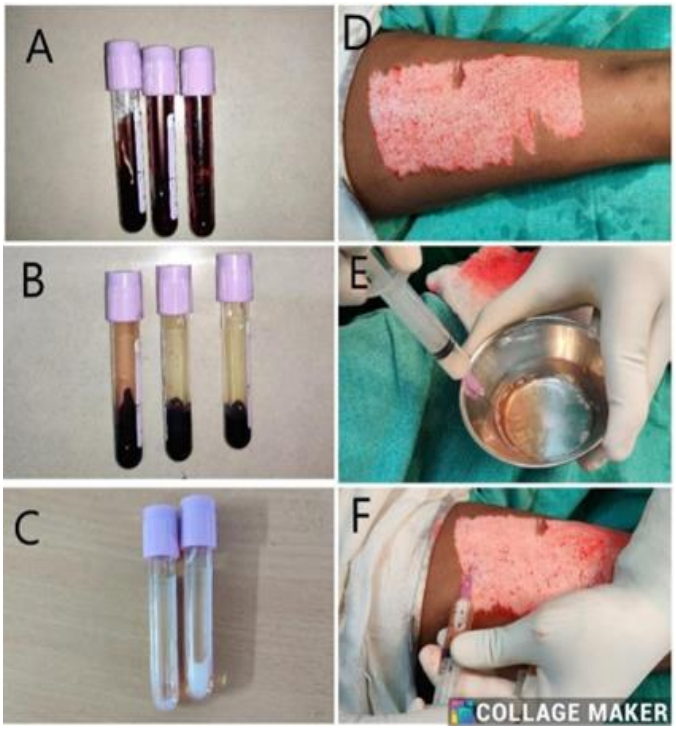

Figure 7: A, B, C: Showing extraction of PRP from patient blood. D, E, F: Showing injection of PRP at donor site after skin harvest.

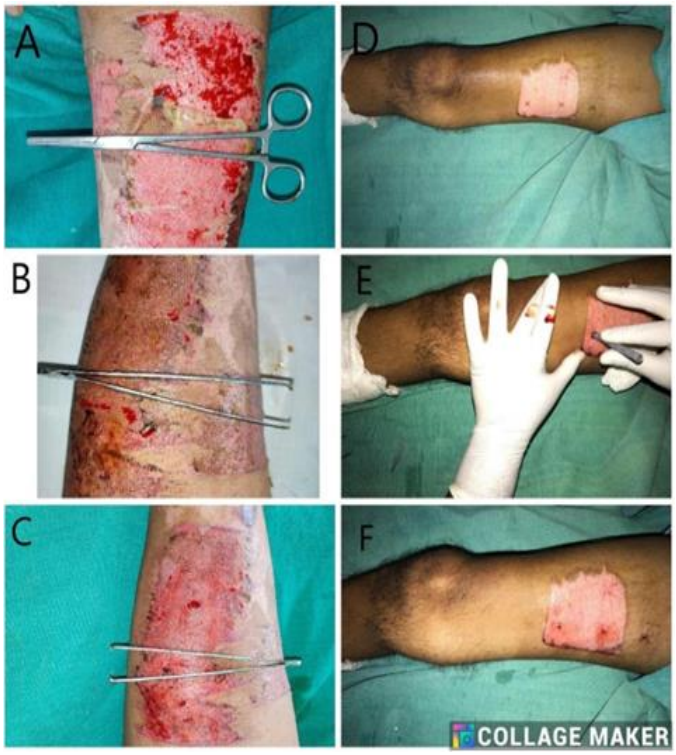

Figure 8: A: Showing the site on post operative day 5. B, C: Post operative day 13. D, E, F: Taking skin biopsy on post operative day 13.

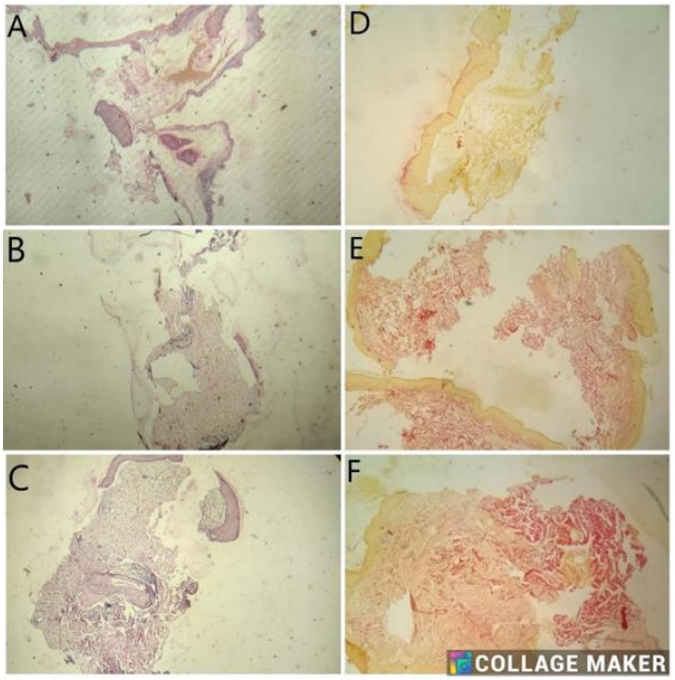

Figure 9: Scanner view on haematoxylin and eosin staining: A: control site, B: normal skin, C: test site. On Van giesons stain: D: control site, E: normal skin, F: test site.

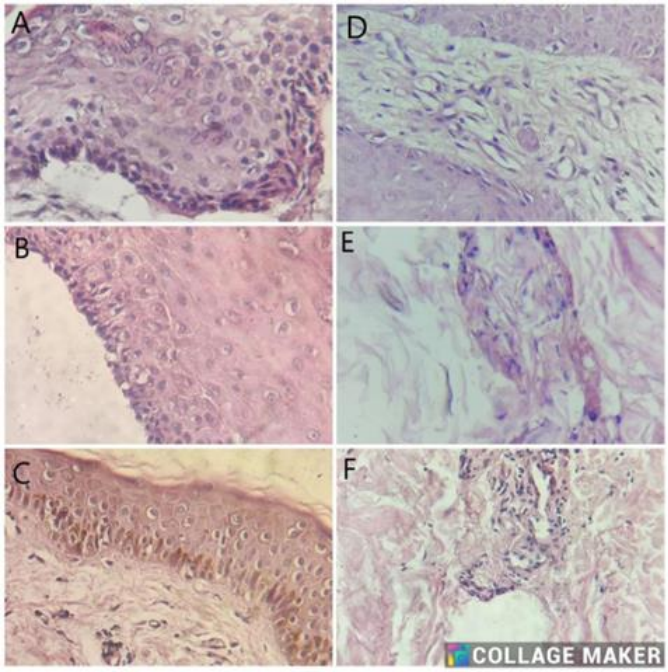

Figure 10: On H and E stain, A: increase in epithelialisation on test site, B: no increase in epithelialisation at control site, C: normal skin showing melanocytes. D: increase in angiogenesis at test site,

E:no increased angiogenesis at control site, F: normal skin.

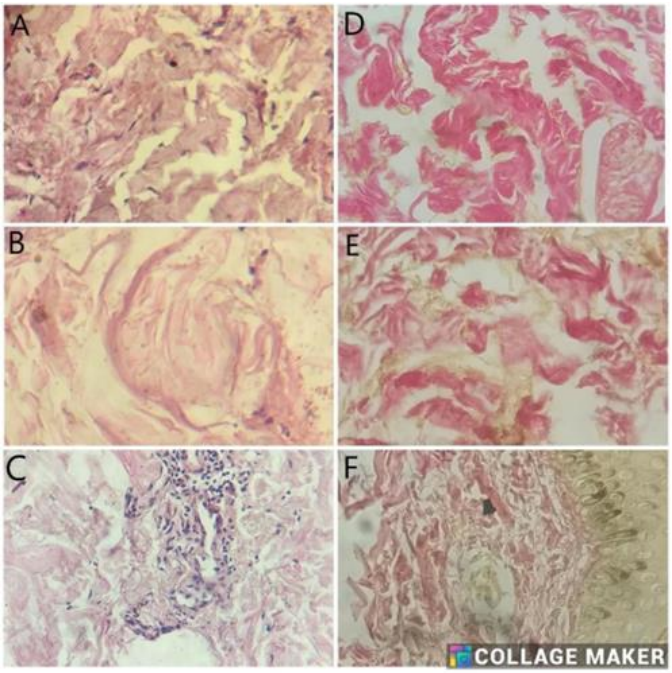

Figure 11: On H and E stain showing collagen deposition A: increased at test site, B: control site, C: normal skin. On Van giesons stain, D: increased collagen at test site, E: control site, F: normal skin.

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