

Study of efficacy of autologous Platelet Rich Plasma in enhancing the healing of acute ulcers

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Abstract: Background: Autologous Platelet Rich Plasma (PRP) is a modern modality for healing of wounds. But there is paucity in the studies demonstrating the efficacy of PRP with no consensus about its efficacy in healing as compared to conventional methods. As healing of acute ulcers is mainly dependent on local therapy, we performed to this study to study the efficacy of PRP in healing of acute ulcers

Aims and objectives: Aim of the study is to study the efficacy of PRP in healing of acute ulcers. Objectives: to assess the healing rate, to assess the time taken for complete healing/ ulcer eligible for grafting and to note complications or adverse effects during the study.

Materials and methods: a single arm prospective clinical study which included patients 18-80 years with acute ulcers of maximum area 10 x 10 cm². Venous ulcers, diabetic ulcers, pressure sores, burn wounds, arterial ulcers were excluded. Ulcer characteristics like dimensions, area, slough, discharge, edge along with clinical photograph were noted during the start of the study. Ulcers underwent weekly PRP dressings after preparation of autologous PRP and ulcer characteristics were noted at the time of dressing along with pain score and clinical photograph. The end point of study was completely healed ulcer/ ulcer fit for skin grafting.

Results: 28 ulcers were included. 23 healed by re-epithelisation while 5 healed by grafting. The healing rate calculated as percentage reduction in area/ week had significant increase over the weeks ($p < 0.0001$). No difference was noted in the healing rates of ulcers with diabetes and ulcers without diabetes ($p = 0.45$). The mean duration of healing was 5.1 ± 1.85 weeks for complete re-epithelisation while it was 3 weeks for ulcers eligible for skin grafting. Only 3 ulcers (11%) had persistent slough after 1st PRP application. No complications of wound infection or adverse effects were noted. Pain score had a decreasing trend over the weeks.

Conclusions: PRP is an efficacious treatment modality for treatment of acute ulcers which is cheap, affordable and easily available. Due to reduced dressing frequency and pain, it positively impact quality of life of patients. It is not associated with any adverse effects or complication of wound infection and can be easily combined with traditional methods of wound healing to augment the process of healing.

Key words: Acute ulcers, Platelet rich Plasma, wound healing.

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I. Introduction:

Wounds and ulcers have been an age-old health problem affecting human lives not only in terms of health but also socially and economically. Throughout history, different cultures and civilisations have used different principles like debridement, wound irrigation and different dressing materials like lint, honey, wine etc to cover the wound and enhance wound healing [1,2,3]. The dawn of 19th and 20th century revolutionised the concept of wound care by introduction of asepsis and antibiotics [4]. Recently, we have been able to decode the pathophysiological basis of wound healing to the molecular levels, identifying the importance of growth factors in this process.

Wounds or ulcers are classified as acute or chronic depending on their ability to heal. Acute wounds heal in pre-determined way and are able to heal completely [5]. Chronic wounds on the other hand fail to heal and persist, being a major burden on human health [6]. In India, the prevalence of acute wounds was 10.5 per 1000 and of chronic wound was 4.5 per 1000.[7]

To deal with this problem, more than 5000 dressing methods are now available in armamentarium including tulle dressings, foams, hydrocolloids bioactive dressings etc but there is no single ideal local wound care modality and the search for this is still on. Autologous PRP is one such recently developed treatment modality, which has been tried in the area of wound healing since almost 3 decades.

Autologous PRP is obtained by subjecting patient's venous blood to double centrifugation based on principle of double centrifugation. There is no consensus on the standard method of PRP preparation and PRP application and many commercial kits are available [8]. The obtained PRP acts as drug delivery system wherein the platelets deliver the numerous growth factors stored in their α granules like PDGF, EGF, FGF, TGF- β , VEGF PDEGF, IGF etc by degranulation [9]. These growth factors then promote wound healing by stimulating macrophages, fibroblasts, keratinocytes for angiogenesis, granulation tissue and ECM synthesis, thus promoting wound healing in a physiological way.

Many RCTs and case series have demonstrated the benefit of PRP in chronic wounds but a recent Cochrane meta-analysis 2016 [10], demonstrated no significant advantage of PRP for healing of wounds. The healing of chronic ulcers has a multidimensional approach which includes local dressings as well as systemic therapy like adequate vascularisation (arterial ulcers), compression (venous ulcers), control of diabetes etc. For this very reason the healing process of chronic ulcers depends on all these factors and not just the local dressing therapy. In this study, we choose only acute ulcers (traumatic, post-surgery) in whom the healing is dependent only on the local dressing modality.

In this study, we aim to analyse the efficacy of autologous PRP in the treatment of acute ulcers/wounds by assessing the wound healing rates, time required for wound healing and assessing for complications or adverse effects during the study.

II. Materials and methods:

This was a prospective single centre, single arm interventional study conducted over a period of 2 years from 2018-2020 at MGM medical College and Hospitals, Aurangabad. Study was initiated after approval from the local ethics committee.

Inclusion criteria:

Patients visiting the centre on OPD or IPD basis between 18-80 years of age, of both genders suffering from ulcers (traumatic, iatrogenic) with maximum size of 100 cm² and who were willing to participate in study were include in the study.

Exclusion criteria: patients with screening platelet count <100000 / ml (thrombocytopenia due to any cause), patients on antiplatelet drugs, patients suffering from CRF, Anaemia, malnutrition, immunosuppression, ulcers with cellulitis/ spreading infection, osteomyelitis, and ulcers like venous ulcers, arterial ulcers, diabetic ulcers, burn wounds, pressure sores were excluded.

Methodology:

After written informed consent, the patients included in the study underwent thorough clinical examination and local examination of ulcer, noting its clinical characteristics and dimensions along with clinical photograph. Necessary laboratory investigations and wound swab were sent.

Preparation of Autologous PRP: PRP was prepared by drawing venous blood from patient using wide bore needle with aseptic precautions in sterile sodium citrate bulbs to prevent clotting of blood. This collected blood was 1st centrifuged at 5000 rpm for 15 mins to separate the RBC from plasma. The collected plasma in plain sterile tubes was subjected to 2nd centrifugation at 2000 rpm for 5 mins. The upper 2/3rd of the centrifuged plasma was discarded (Platelet poor plasma) and lower 1/3rd was collected as PRP.

After PRP preparation, the wound if necessary was debrided and washed with normal saline and PRP was applied over the wound. The wound was covered with paraffin gauze and dressed with aseptic precautions. The 1st application of PRP was considered as the 0th day of the study and patients were followed up weekly at 7th, 14th, 21st and so on till the end point of study was reached. At every follow up, the wound's clinical characteristics were noted along with dimensions and area and clinical photograph and next application of PRP would be done. Area of the ulcer was calculated as length x breadth x 0.7854 as wounds closely resemble an ellipse rather than other shapes. During the study no antibiotics were given to patients.

End point of study: complete healing by re-epithelisation or ulcer fit for skin grafting (for ulcers > 6 cm in length).

Statistical analysis was carried out using the Graphpad PRISM 9 software

III. Results:

Out of the 28 patients, 23 patients (82.1%) underwent healing by complete re-epithelisation while 5 patients (17.9%) underwent healing of ulcer by split thickness skin grafting. (figure 1)

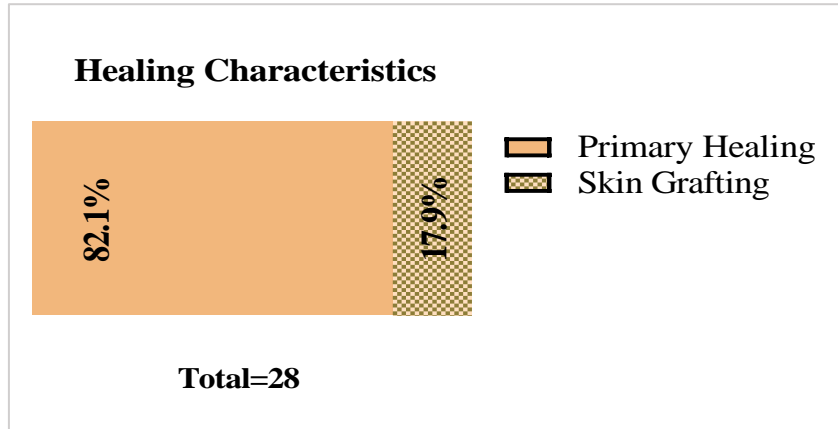


Figure 1 : healing characteristics of ulcers

The male : female ratio was 3: 1 (21: 7).

In our study, the mean age of the patients was 50.24 ± 18.75 years. Maximum number of the patients belonged to the age group of 51-60 years with 8 patients in that group. 61% of the patients belonged to elderly population (>50 years). (figure 2)

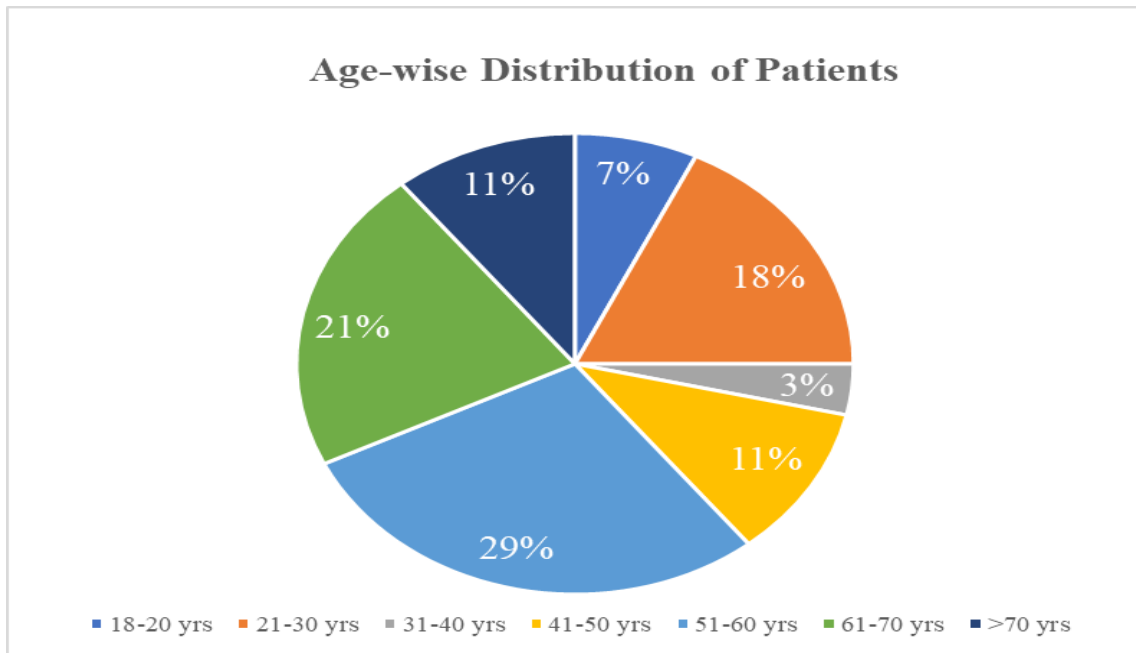


Figure 2 : Age wise distribution of ulcers

The age of the youngest patient was 18 years while that of the eldest patient was 80 years.

Overall, 14(50%) patients had co-morbidities. 7 patients (25%) had diabetes mellitus type II only while 5 patients (18%) had hypertension. 2 patients (7%) had both DM and hypertension. All the patients were on oral hypoglycaemic drugs with controlled blood sugar levels.

In the present study the highest number of the ulcers were post debridement ulcers with 9 cases (32%) and traumatic ulcers with 9 ulcers (32%). These were followed by post-operative wound gap/dehiscence wounds with 8 patients (28.5%) and post fasciotomy ulcers with 2 patients (7%) had the least ulcers. (figure 3)

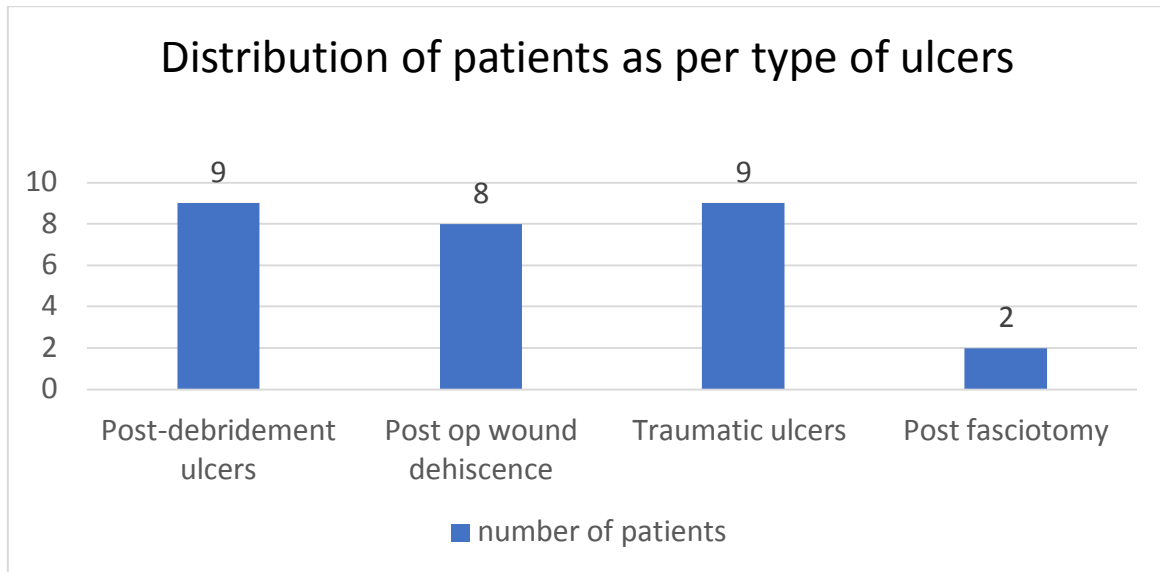


Figure 3: distribution of ulcers as per type of ulcers

16 ulcers (57.1%) were located in the lower limbs making lower limb the most common location of ulcers in this study. (figure 4)

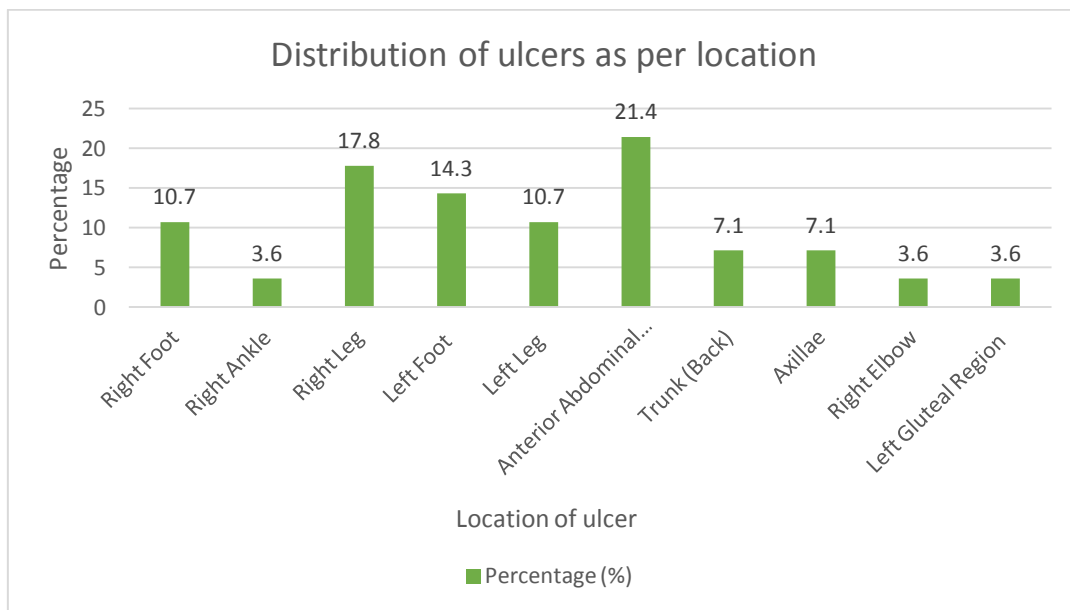


Figure 4 : distribution of ulcers as per location

The mean duration of the ulcers at the time of presentation was 17.5 ± 9.8 days. The shortest duration of the ulcer was 3 days while the longest duration of ulcer was 45 days. (figure 5)

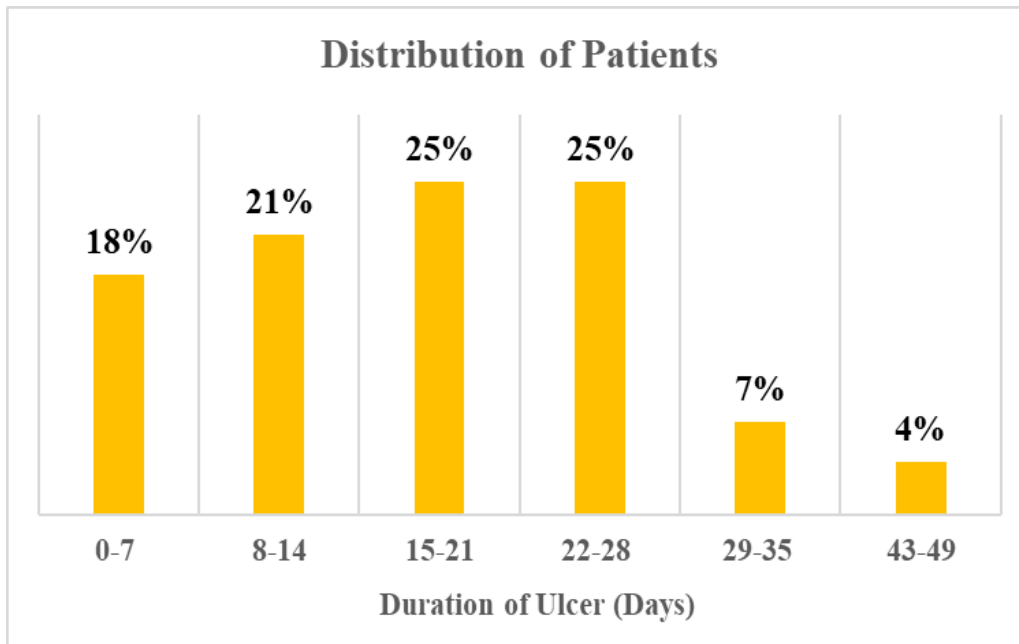


Figure 5 : distribution of ulcers as per duration at time of presentation

The mean initial area of the ulcers who underwent healing by complete re-epithelisation was $16.7 \pm 10.7 \text{ cm}^2$. In this group, the smallest area of the ulcer was 3.86 cm^2 while the largest area of the ulcer was 41.42 cm^2 . Highest number of ulcers belonged to $21-27.99 \text{ cm}^2$ group with 6 ulcers (26.1%) followed by 5 ulcers (21.7%) in the $0-6.99 \text{ cm}^2$ and $7-13.99 \text{ cm}^2$ group each. (figure 6)

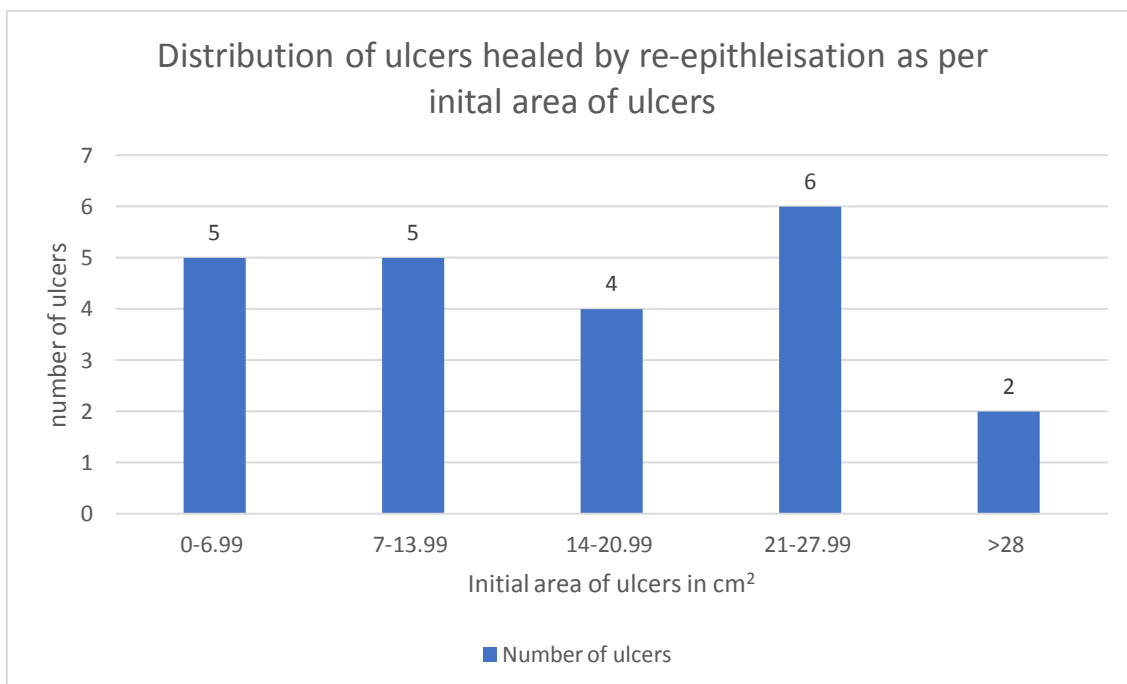


Figure 6: Distribution of ulcers as per initial area of ulcers.

In the 5 ulcers that healed by skin grafting, the largest area of ulcer included was 81.68 cm^2 while the smallest area of ulcer included was 50.56 cm^2 . The mean initial area of this group of ulcers was $68.5 \pm 12 \text{ cm}^2$. We classified ulcers as presence of slough, minimal slough and no slough at the time of presentation. 8 ulcers (29%) had slough, while 9 ulcers (32%) had minimal slough and 11 ulcers (39%) had no slough. 6 ulcers (21%) had seropurulent discharge, while 22 ulcers (79%) had serous discharge. None of the ulcers had frank pus discharge. 9 ulcers had healthy granulation tissue, 18 ulcers had unhealthy granulation tissue while 1 ulcer had

no granulation tissue (acute traumatic ulcer) (figure 7). All ulcers with unhealthy granulation underwent debridement.

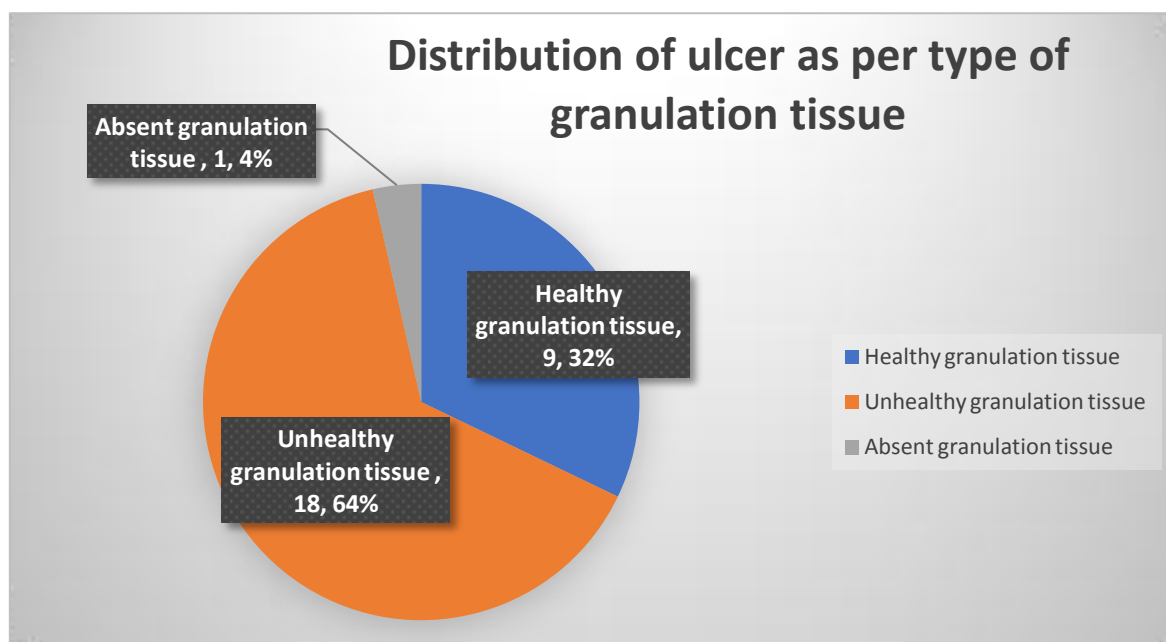


Figure 7 : Distribution of ulcer as per type of granulation tissue

The 23 ulcers that healed by complete re-epithelisation, the mean duration of healing was 5.1 ± 1.85 weeks. The shortest duration of healing was 2 weeks and the longest duration of healing was 8 weeks. Maximum number of ulcers i.e. 8 number of ulcers healed in the 7th week. (figure 8) In the 5 ulcers that healed by split thickness skin grafting, all the 5 ulcers were eligible for skin grafting after 3 weeks of time.

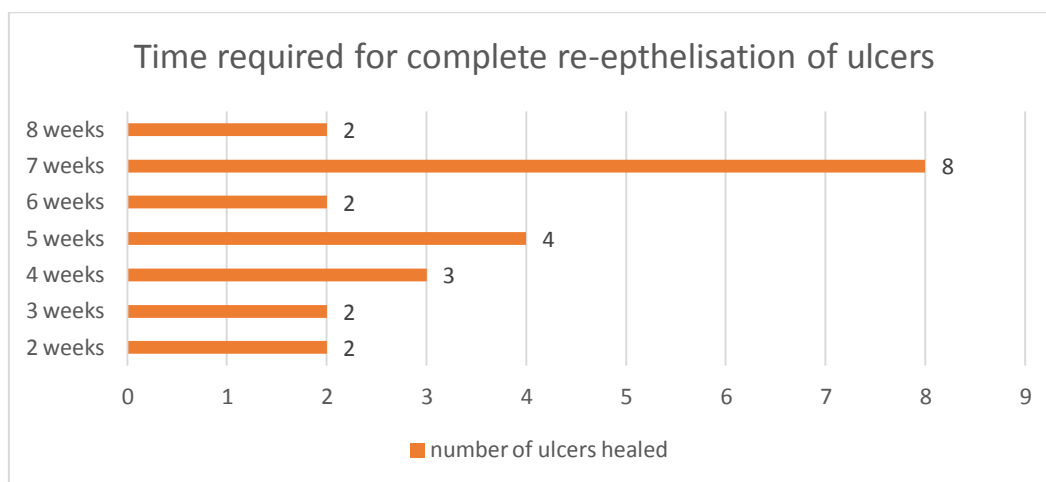


Figure 8: time required for healing of ulcers by re-epithelisation

Time period	Total area of ulcers per week in cm ²	Decrease in total area in cm ²
0 th week (start of study)	387.99 (baseline area)	Not applicable
1 st week	320.95	63.07
2 nd week	240.09	80.86
3 rd week	166.60	73.49
4 th week	109.52	56.48
5 th week	62.24	47.24
6 th week	33.82	28.42
7 th week	6.90	26.92
8 th week	0	6.9

Table 1: Reduction in total area of ulcers per week

In the 23 ulcers that healed by complete re-epithelisation, the total area of all the ulcers and its reduction per week is displayed in table 1. (figure 12)



Figure 9: healing by re-epithelisation



Figure 10: healing by re-epithelisation



Figure 11: healing by skin grafting after PRP dressings

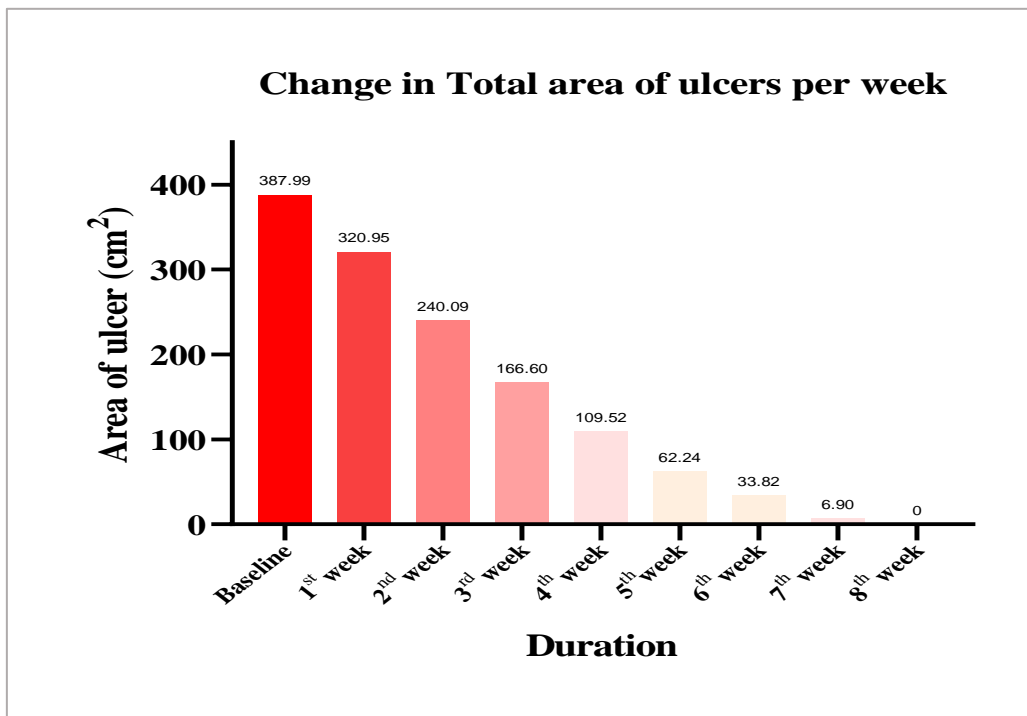


Figure 12 : reduction in total area of ulcer

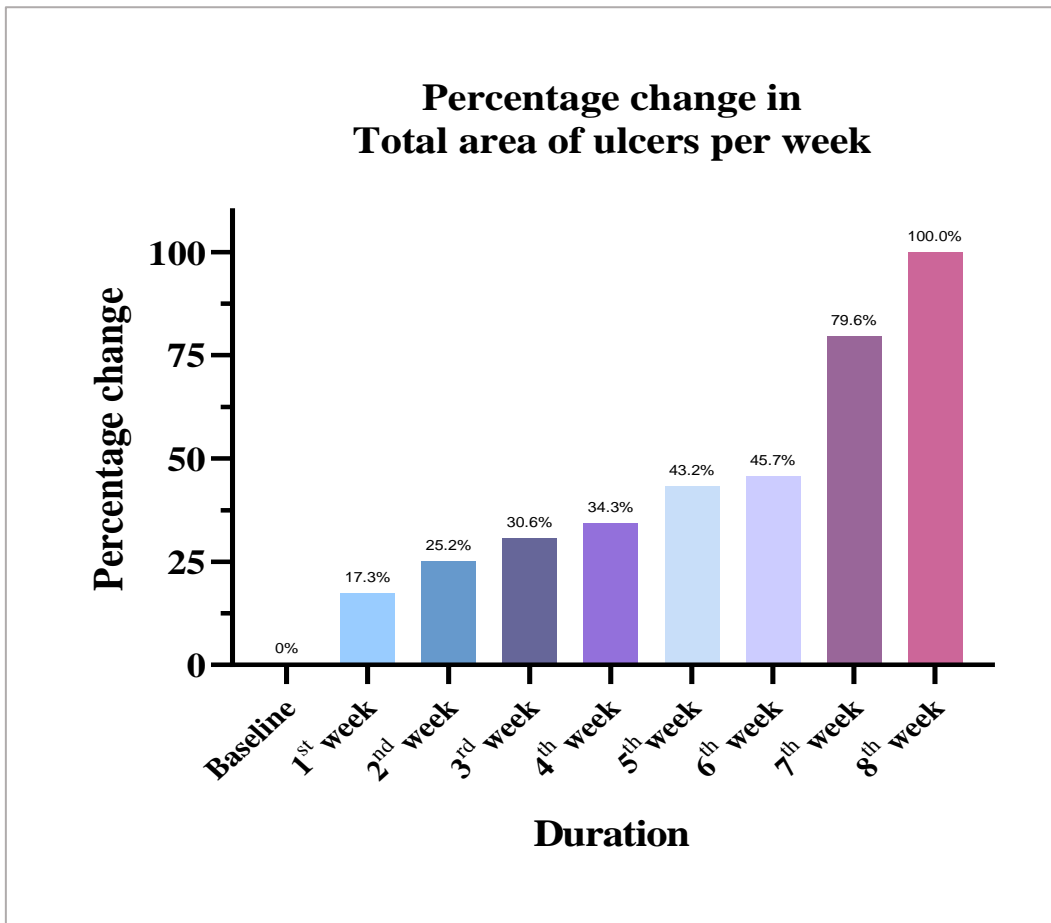


Figure 13 : Percentage reduction in the area of ulcers per week (healing rate/ week)

The average rate of healing per week was indicated by the percentage change (reduction) in total area of ulcers per week. It was calculated as the difference of the initial total area of ulcers and the total area of ulcers after 1 week divided by the initial area of ulcer and multiplied by 100. In the first week the percentage change in area of ulcer was the least i.e. 17.3 %, from 1st to the 8thweek. (figure 13) The percentage reduction in area of ulcer had an increasing trend with the highest changes in the 7th week of 79.6% and 8th week of 100. The one-way ANOVA test showed statistically significant percentage reduction in total area of ulcers per week ($p < 0.0001$) as the weeks advanced.

In comparing the percentage reduction in total area of ulcers in patients with and without diabetes, no significant difference was found ($p = 0.4454$) after applying unpaired T test with Welch’s correction. (figure 14)

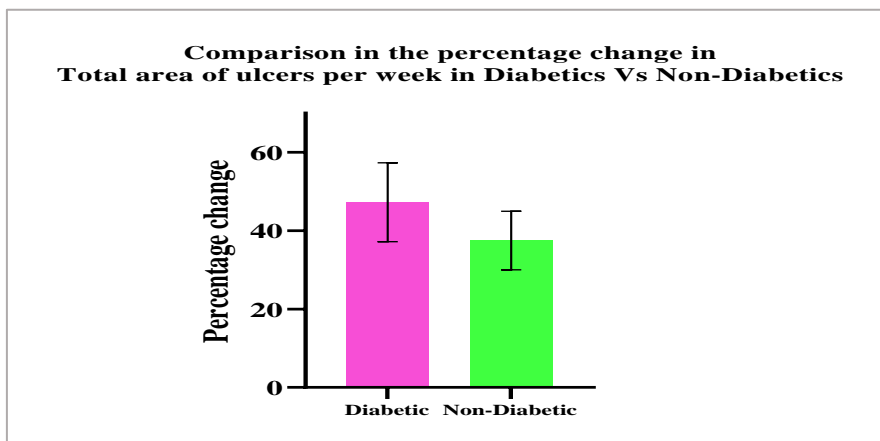


Figure 14 : comparison in healing rates of ulcers with diabetes and ulcers without diabetes 5 ulcers which underwent healing by skin grafting had mean percentage reduction in area by 30.1 ± 5.1 %.

Out of the 28 ulcers, 3 ulcers had persistent slough at the 1st week after starting the PRP application and were associated with lower healing rates (3.4 %, 8.14 %, 5.30 %). These 3 ulcers were subjected to sharp debridement again and started on oral antibiotics as per wound swab. Subsequently over the next week the ulcers had no slough with improved healing rates. No other complication of wound infection, non-healing ulcers were noted. No adverse effects of PRP like disease transmission, graft vs host reaction, anaphylaxis were noted. Pain score was highest at the 1st PRP application i.e 5.47 ± 0.37 standard error of mean and eventually reduced as shown in figure. All patients had pain score of < 2 after 3rd week. (figure 15)

Using Pearson's coefficient formula, the correlation between the initial area of ulcers that healed by epithelisation and their healing duration was calculated. In this study the initial area of ulcer and the duration of healing of ulcer were found to be strongly co-related $p=0.84$

Using Pearson's coefficient formula, the correlation between the duration of ulcers on presentation and total duration of healing by re-epithelisation was calculated. In this study there was no correlation found in the duration of ulcer and duration required for healing with $p=0.06$.

Average pain score per week

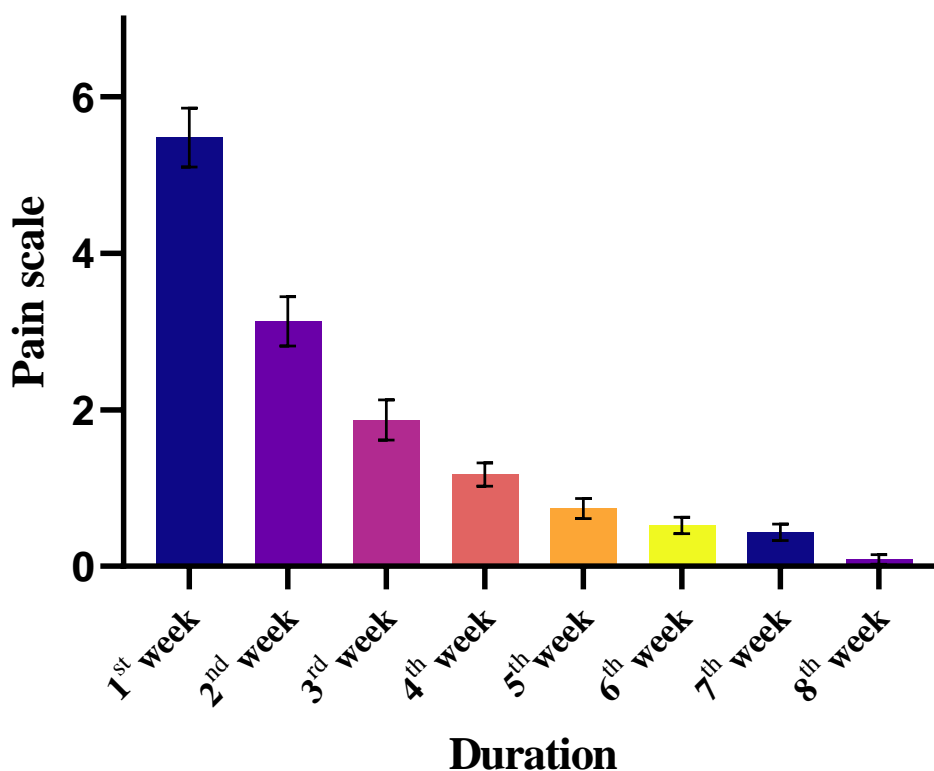


Figure 15: Pain score at every PRP application

Out of the total 28 ulcers, 15 ulcers had sterile wound swab culture sensitivity report while 13 ulcers flagged growth. The most common flagged bacteria was Staphylococcus Aureus (4 ulcers) followed by E coli (3 ulcers). (figure16)

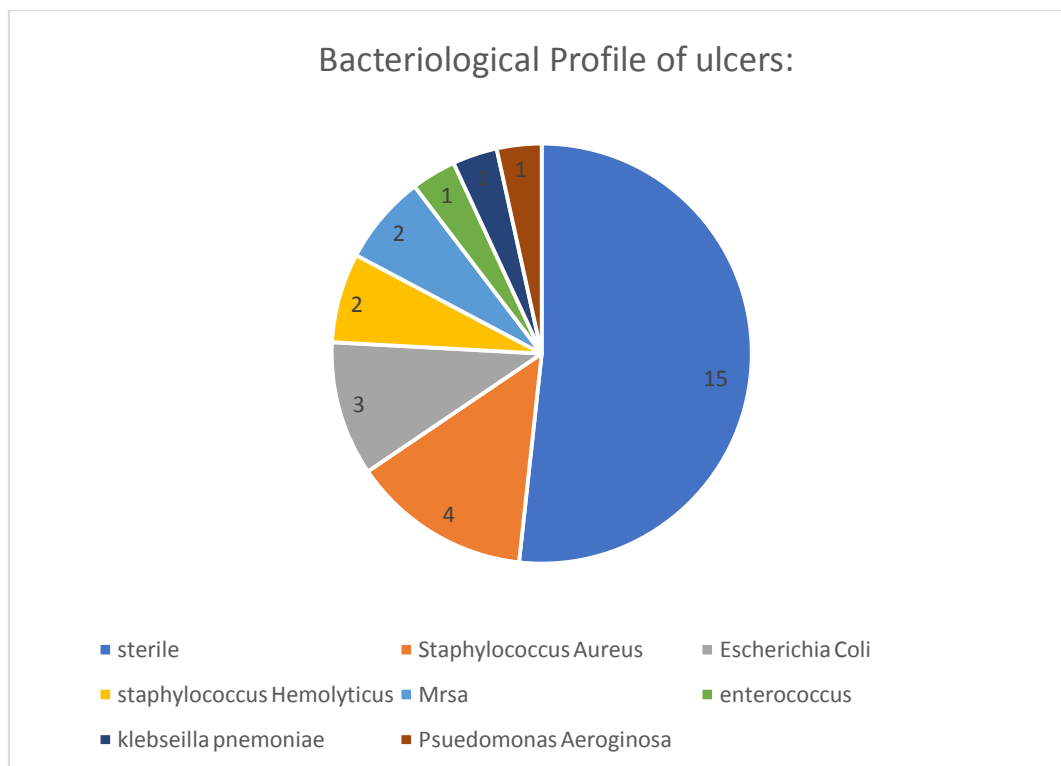


Figure 16: Bacteriological profile of ulcers

IV. Discussion:

In this study, 60 % of patients were > 50 years of age. Acute ulcers which maybe traumatic / post-surgery are more prevalent in younger groups while chronic ulcers are more common in the elderly population due to increased incidence of co-morbidities which contribute to impaired healing. Male: female ratio of 3: 1. This can be attributable to the fact that acute wounds are more likely to occur in men owing to increased risk of road traffic accidents, occupational injuries, assault injuries. Lower limbs are the most common site of acute as well chronic ulcers which is a finding supported in our study.

Debridement is considered as a standard in wound management to remove slough, devitalised tissue and to augment wound healing by stimulating angiogenesis, granulation tissue formation. [11] All the ulcers with presence of slough/minimal slough and unhealthy granulation tissue were subjected to sharp debridement prior to start of PRP dressings. In this study, the acute ulcers with slough had a history of improper local wound care and follow up before being included in study.

In the study by Kazakos et al [12], the time required for wounds in PRP group to be eligible for plastic reconstructive surgery was 3 weeks (mean 21.26 days) while in the control group of conventional dressing it was 40.59 days which was statistically longer than PRP group ($p < 0.001$). In a study by Spyridakis et al [13], complete healing of the surgical wound required about 24 days for PRP group while the control group patients needed more than 30 days to completely heal ($p < 0.01$). In a study conducted by Hom et al [14], the average time for the APG treated wounds to achieve 100% closure was 29.75 days compared with 35.38 days for the control wounds. (table 2)

Study	Type of ulcer in study	Mean time required for healing of ulcers (weeks/days)
Present study	Acute ulcers	5.1 ± 1.85 weeks for complete re-epithelisation 3 weeks for skin grafting eligibility
Kazakos et al	Acute ulcers	3 weeks (mean 21.26 days) for plastic reconstructive surgery eligibility
Spyridakis et al	Acute ulcers	24 days for healing by re-epithelisation
Hom et al	Acute ulcers	29.75 days for healing by re-epithelisation

Table 2: time required for healing of acute ulcers in different studies

Considering the healing rates i.e. the percentage reduction in area of ulcer per week, there was a significant increase in the rate as the week advanced. In the 7th week the percentage reduction increased to 80 %. This is because 8 ulcers healed in this week, which individually had 100% reduction in area of ulcer. Similarly, in the 8th week the percentage reduction is 100 % as the remaining 2 ulcers completely healed in this week. The increase in healing rates can be attributed to the increase in healthy granulation tissue, reduction in

discharge and slough. Platelets, being a storage of multiple functional granules containing growth factors are one of the first cells to participate in wound healing process primarily to achieve haemostasis and release factors for cellular chemotaxis to continue the process of healing. They do so by releasing the functional secretory granules. These properties of platelets can be used to accelerate the process of wound healing by making them act as a “growth factor delivery system” on the wound and is the basis of development of concept of PRP. The platelets undergo degranulation after coming in contact with the wound and secrete proteins like PDGF(AA, BB, AB isomers), TGF- β , platelet factor 4, VEGF, EGF, PDEGF, epithelial cell growth factor (ECGF), insulin like growth factor (IGF), osteocalcin, osteonectin, fibrinogen, vitronectin, fibronectin, thrombospondin-1 [15-23]. All these growth factor proteins then stimulate the macrophages, endothelial cells and fibroblasts to undergo mitosis, angiogenesis, ECM production and epithelialisation upon application to the wound to promote wound healing in a physiological way.

Study	Present study	Kazakos et al
1 st week	17%	12.3 %
2 nd week	25 %	24.3 %
3 rd week	30 %	36.30 %
4 th week	34.3%	NA

Table 3: healing rates in our study vs Kazakos study.

In study by Spyridakis et al the rate of wound healing was calculated as difference in mean volume between 2 consecutive time periods of 5 days intervals and expressed as dv/dt . The healing rates were 0, 5, 12, 6, and 6 in $cm^3/5$ days as seen on 5th, 10th, 15th, 20th 25th day respectively while in a study by Hom et al the PRP treated wounds healed faster with a steeper healing slope ($p=0.001$). the differences in the healing rates in different studies can be attributable due to the differences in preparation and application of PRP, ulcer profile, and methods of calculating healing rates

There was no significant difference in the healing rates of ulcers in diabetics vs non-diabetics due to controlled blood sugar levels and absence of angiopathy/ neuropathy in diabetic patients.

In our study inly 10% of ulcer for 1 week had persistent slough. No other complications or adverse effects were noted. Kazakos et al, Spyridakis et al, Hom et al, Raslan MM et al [24], Suryanarayana et al[25], Reddy et al [26], Suthar et al [27], in their studies have noted no complications of PRP. Till date no study has reported any adverse effects of autologous PRP.

Pain score scores during PRP dressings had a decreasing trend. it was highest at 1st PRP application due to prior debridement. Kazakos et al, Suryanarayan et al, Suthar et al noted significant decrease in pain scores with improved quality of life.

V. Conclusion:

PRP is an efficacious treatment modality for treatment of acute ulcers as demonstrated by significant increases in healing rates.it can be combined with traditional principles of wound healing to augment the process of healing. It is cheap, affordable and easily available modality requiring basic laboratory tools. It may have antibacterial effects due to low rates of wound infections seen. Due to decreased frequency of dressings (weekly) and reduced pain during the procedure, PRP can positively impact quality of life of patients with ulcers.It can be safely used in wound treatment with no adverse effects of disease transmission, antibody formation, graft vs host reaction due to its autologous nature. We feel a need for establishing a universally acceptable method of PRP preparation and PRP application to reduce the differences in the results of clinical studies. Also, there is a need to carry of Randomised controlled trials including acute and chronic ulcers comparing it with conventional methods to conclude the efficacy of PRP in healing of ulcers.

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