EFFICACY OF AUTOLOGOUS PLATELET RICH PLASMA ON WOUND HEALING IN BED SORES

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Abstract

Introduction: Bed sores are a common complication in intensive care unit (ICU) patients who are sedated, ventilated, and/or bedridden for long periods with significant mortality and morbidity. There are many treatment options for treatment of bed sores. Platelet rich plasma (PRP) is considered to be advanced wound therapy. In this study we aimed to evaluate the clinical efficacy of autologous PRP gel in the topical treatment of bed sores.
Methods:100 patients with different grades of bed sores were included in this prospective study. Patients were randomly assigned into two equal groups: control group (n=50): Standard treatment was only applied to the wound, and study group (n=50): autologous PRP was directly applied to the wound in addition to the standard treatment. The primary objective of the present study was to follow-up and observe wound healing indices; wound surface area (WSA), healing time, proportion of ulcers healed within trial period (PUHTP), and the pressure ulcer scale for healing (PUSH Tool). Secondary objectives were to assess pain intensity with visual analogue scale (VAS), the frequency of dressing changes, the positive rate of bacterial cultures.
Results: The results showed that patients in study group exhibited statistically significant higher ratio of healed area, lower PUSH and VAS scores, and decreased frequency of dressing changes, after one week of treatment and throughout the follow up, in comparison control group. Regarding healing time, it was statistically significant shorter in study group in comparison to control group. In addition, there was statistical significance decrease in WSA and positive rate of bacterial cultures of bed sores in patients of study group after two weeks of treatment in comparison with control group.
Conclusion: The administration of topical autologous PRP gel accelerates wound healing with a definite effect in treatment of patients with different grades of bed sores in the ICU. It has proven its clinical efficacy in improvement of wound healing indices, pain intensity, and bacterial cultures.

Keywords: bed sores, platelet rich plasma, wound healing

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1. INTRODUCTION

Bed sores, also known as decubitus ulcers, pressure sores, injuries or ulcers, are a common occurrence in all health care settings, including acute care hospitals, long-term care facilities, rehabilitation centers, and subacute care centers. (1)
Bed sores are most commonly found on the lower half of the body, with two thirds occurring in the pelvic region such as the sacrum, coccyx, or hip areas and one third occurring on the lower extremities. (2)
Pressure ulcer formation is multifactorial (external and internal factors), but it all leads to ischemia and necrosis via a common pathway. External pressure must be greater than the arterial capillary pressure (32 mmHg) to obstruct blood flow and greater than the venous capillary closing pressure (8 to 12 mmHg) to obstruct venous blood return. If the pressure remains above these levels, it causes tissue ischemia and necrosis. (3)
Once a bed sore is identified, it should be staged and the wound size carefully documented. Additional evaluations of the ulcer include its location, the condition of the surrounding skin, the presence of tissue undermining and tunneling, and the amount of exudate, odor, and tenderness. (4,5)
Bed sores frequently result in complications. Infection is the most common issue. Microbial analysis revealed that the lesions contain both aerobic and anaerobic bacteria. If the infection spreads, it can cause periostitis, osteomyelitis, septic arthritis, sinusitis, and even septicemia. (6)
Offloading the offending pressure source, adequate drainage of any areas of infection, debridement of

devitalized tissue, and regular wound care to support the healing process are the mainstays of bed sore treatment. (5)

Platelet Rich Plasma (PRP) is a biological product defined as a portion of the autologous blood plasma fraction with a platelet concentration greater than the baseline (before centrifugation). (7) PRP contains not only a high concentration of platelets, but also the entire complement of clotting factors, which typically remain at their normal, physiologic levels. It contains a variety of GFs (PDGF AB, EGF, TGF-β, IGF-1, VEGF-a), chemokines, cytokines, and other plasma proteins. (8,9)

PPR or regenerative therapy has many applications in different aspects of medicine. (10).

2. PATIENTS AND METHODS

This prospective randomized study was conducted on one hundred patients with bed sores in the ICU over two years after getting approval from local research ethical committee of faculty of medicine, Cairo university.

Our Inclusion criteria were ICU patients with different grades of bed sores. While Exclusion criteria were patients with bleeding disorders, Patients on therapeutic anti-coagulant therapy and anti-thrombotic, Patients on systemic corticosteroid therapy and patients with surgical potential for reconstruction.

The eligible 100 patients were randomly assigned into two equal groups:

• **Control group (n=50):** Standard treatment was only applied to the wound.

• **Study group (n=50):** Autologous PRP was directly applied to the wound in addition to the standard treatment.

Study population was subjected to patient basic demographic characters including age, gender and medical history (hypertension, heart diseases and diabetes mellitus).

Empirical anti-microbials (cephalosporins), nutrition support and other symptomatic treatment were given in both groups.

WOUND CARE

The wounds in the control group patients were all thoroughly debrided using normal saline and 10% povidone-iodine, and all of the skin that had disintegrated was removed. Then, standard treatment including glycerin magnesia and bivatracin spray was applied to the wound by external compression bandages, and then covered with sterile gauze dressing. Until the wound healed, this external dressing was changed repeatedly. On the other hand, those in the study group had the same debridement procedures as patients in the control group. In addition to this standard treatment, PRP gel was used twice weekly to the wound until it healed.

PREPARATION OF PRP

Through the side valve, one mL of sodium citrate solution was permitted to enter the 10 ml vacuumed tube. The patients' 9 mL of blood sample was then withdrawn using an 18-gauge needle. To properly combine the anticoagulant with the blood, samples were gently shaken. This tube was centrifuged, and the upper plasma layer was removed, leaving the PRP behind. The gel was made by mixing PRP with calcium chloride. Within 30 minutes, this preparation should be finished in an aseptic environment. (11)

WOUND MONITORING

Differences between two groups were compared as regards to wound healing indices. Also, the bacterial cultures were collected from the ulcers of patients weekly.

Primary outcome parameters: The primary objective of the present study was to follow up and observe wound healing indices as follows:

1) Healing time: The wound healing standard was reduction in wound size by more than 50%, or formation of fresh granulation tissue.

2) Wound surface area (WSA): It was recorded before start of treatment, and then twice weekly throughout the follow up. For regular wound surfaces, the maximum diameters of the length and width of the wound were measured with a centimetre ruler for calculation by multiplying them to obtain an estimate of surface area in square centimetres (cm^2). For irregular wounds, different lengths and widths were measured for calculation.

3) Proportion of ulcers healed within trial period (PUHTP): The ratio of healed area was calculated as follows: (the area of the healed surface/the initial wound area) x 100%.

4) The pressure ulcer scale for healing (PUSH Tool): PUSH Tool categorized the ulcers with respect to wound surface area (0-10), exudate (0-3), and type of wound tissue (0-4) recording a sub-score for each of these ulcer characteristics, and then adding these sub-scores to obtain the total score of 17 points. (12)

SECONDARY OUTCOME PARAMETERS:

1) Visual analogue scale (VAS): It was used to assess pain intensity from 0 to 10 points (0 = no pain and 10 = the worst imaginable pain). Wound pain was evaluated before start of treatment, and then twice weekly until end of the follow up

2) The frequency of dressing changes: They were documented from the start of treatment twice weekly throughout the follow up.

3) The total number of dressing changes was also recorded.

4) Positive rate of bacterial cultures: At the end of each week of treatment, the secretions were collected from the wounds of patients in the two groups to perform bacterial cultures, and the positive rate of wound bacterial cultures was compared between them.

STATISTICAL METHODOLOGY:

The Statistical Package of Social Science (SPSS) application for Windows was used to analyze the data (standard version 26). The Kolmogorov-Smirnov test was initially used to determine whether the data were normal. Number and percentage were used to describe qualitative data. Using the Chi-square test, associations between categorical variables were investigated. Continuous variables were given as mean ± standard deviation for normally distributed data, and independent student t-test was used to compare the two groups. The level of significance for the mentioned statistical tests was set at 5%. When P ≤ 0.05, the results were considered significant. The results were more significant as long as the obtained P value was smaller.

3. RESULTS

A-Patients characteristics:

•100 patients who met the inclusion criteria were enrolled and analyzed.

•Patients in the both groups were comparable with respect to the age, gender, medical history and number of platelets (P > 0.05).

Table (1): Demographic and clinical data of our study population

Data	Control group (n=50)	Study group (n=50)	Test of Significance	P value
Age (years)	47.02±12.92	46.62±14.03	t=0.148	0.882
Sex				
Male	29 (58.0%)	24 (48.0%)	χ 2 =1.004	0.316
Female	21 (42.0%)	26 (52.0%)		
Medical history				
Yes	28 (56.0%)	27 (54.0%)	χ 2 =0.04	0.841
No	22 (44.0%)	23 (46.0%)		
Platelet number before treatment	264.24±67.41	242.78±58.06	t=1.71	0.091
Platelet number after treatment	224.92±49.90	207.60±42.53	t=1.86	0.065

* Significant P ≤ 0.05, t: student t test, X^2: Chi square test

B-Comparison between both groups regarding healing indices:

•Regarding healing time, it was statistically significant shorter in study group (16.72 ± 2.24 days) in comparison to control group (21.52 ± 1.96 days) (P ≤ 0.001).

•There was statistical significance decrease in wound surface area (WSA) of bed sores in patients of study group after two weeks of treatment until the end of follow up in comparison with control group (P ≤ 0.05). Table (2).

•Moreover, patients in study group exhibited statistically significant higher ratio of healed area (PUHTP) after one week of treatment and till end of the follow up when compared to control group (P ≤ 0.001). Figure (1)

•According to pressure ulcer scale for healing (PUSH Tool), there were statistically significant lower values after one week of treatment and throughout the follow up in study group relative to those in control group (P ≤ 0.001). Figure (2)

Table (2): Wound surface area (WSA) (cm^2) in both groups through study period
(Data were expressed as mean ± standard deviation)

WSA	Control group (n=50)	Study group (n=50)	Test of significance	P value
Basal	10.88±4.68	10.76±4.35	t=0.133	0.895
Mid 1st week	9.99±4.30	9.77±3.98	t=0.271	0.787
End 1st week	9.28±4.00	8.75±3.65	t=0.683	0.497
Mid 2nd week	8.42±3.64	7.57±3.23	t=1.22	0.223
End 2nd week	7.64±3.31	6.34±2.68	t=2.15	0.033 *
Mid 3rd week	6.61±2.77	5.39±2.35	t=2.37	0.019 *
End 3rd week	5.15±2.14	3.99±1.70	t=2.98	0.004 *
Mid 4th week	3.74±1.56	2.84±1.24	t=3.18	0.002 *
End 4th week	2.67±1.15	1.42±0.70	t=6.53	≤ 0.001 *

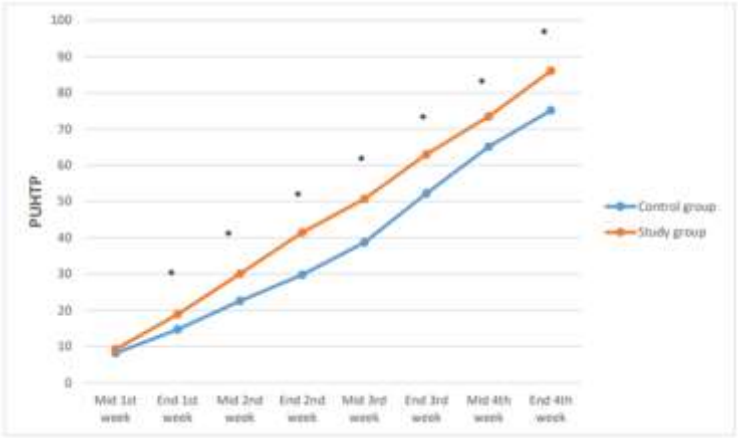

Figure (1): Proportion of ulcers healed within trial period (PUHTP) (%)

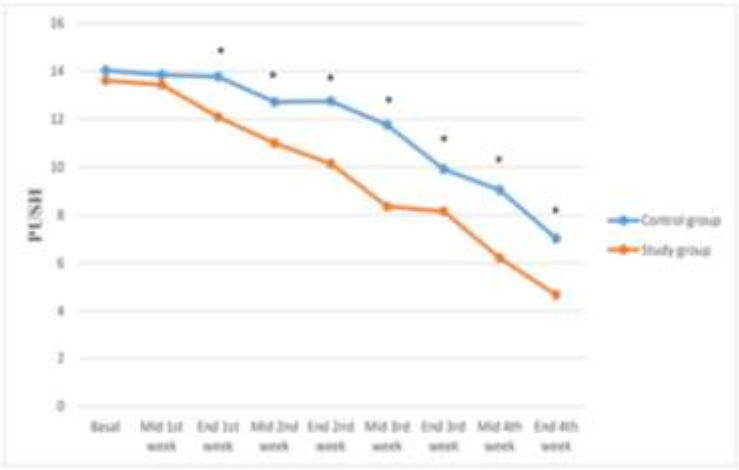

Figure (2): Pressure ulcer scale for healing (PUSH Tool)

•In addition, frequency of dressing changes in control group was statistically significant less than that of control group after one week of treatment till end of follow up ($P \leq 0.001$). Total number of dressing changes was decreased with statistical significance in study group (9.90 ± 0.92) as compared to control group (18.14 ± 1.48). Table (3)

Table (3): Frequency of dressing changes in control and study group
(Data were expressed as mean ± standard deviation)

	Control group (n=50)	Study group (n=50)	Test of significance	P value
Mid 1st week	2.74±0.44	2.38±0.49	t=3.21	0.061
End 1st week	2.54±0.50	1.52±0.50	t=10.11	≤ 0.001 *
Mid 2nd week	2.52±0.50	1.00±0.00	t=21.29	≤ 0.001 *
End 2nd week	2.44±0.50	1.00±0.00	t=20.30	≤ 0.001 *
Mid 3rd week	2.42±0.49	1.00±0.00	t=20.13	≤ 0.001 *
End 3rd week	2.38±0.49	1.00±0.00	t=19.90	≤ 0.001 *
Mid 4th week	1.56±0.50	1.00±0.00	t=7.89	≤ 0.001 *
End 4th week	1.54±0.50	1.00±0.00	t=7.58	≤ 0.001 *
Total frequency of dressings	18.14±1.48	9.90±0.92	t=36.34	≤ 0.001 *

•As regards to visual analogue scale (VAS), scores in the study group were statistically significantly lower than those of control group after one week of treatment and throughout the follow up ($P \leq 0.001$).

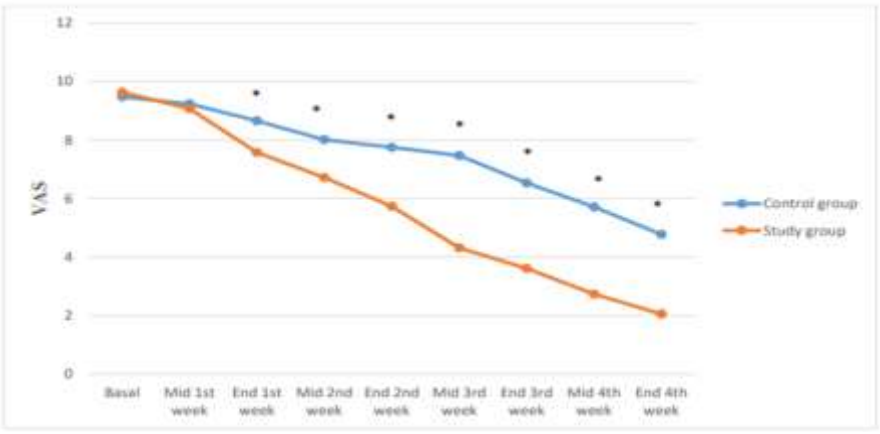

Figure (3): Visual analogue scale (VAS) scores

C-Comparison between both groups regarding rates of bacterial cultures

•Patients in control group showed statistically significant higher positive rate of bacterial cultures in comparison to study group only after two and three weeks of treatment ($P \leq 0.05$). Figure (4)

•The organisms most commonly isolated from pressure ulcers were proteus mirabilis, escherichia coli, enterococci, staphylococci, and pseudomonas species. Anaerobic isolates included peptostreptococcus species, bacteroides fragilis, and clostridium perfringens.

•According to results of these cultures, they were sensitive to cephalosporins, amoxicillin-clavulanate, piperacillin, tazobactam, imipenem, meropenem, ciprofloxacin, ofloxacin, gentamycin, clindamycin, tobramycin, amikacin, metronidazole and vancomycin.

• No other complications were documented in our study.

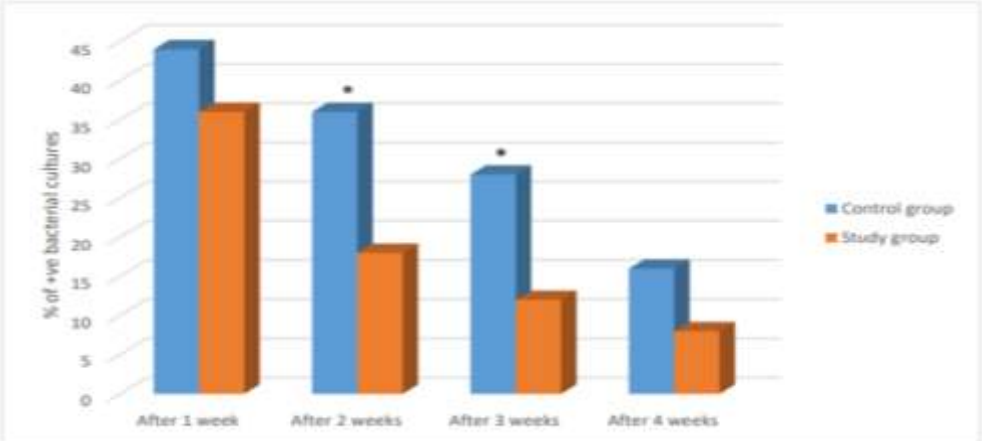

Figure (4): Rates of bacterial cultures

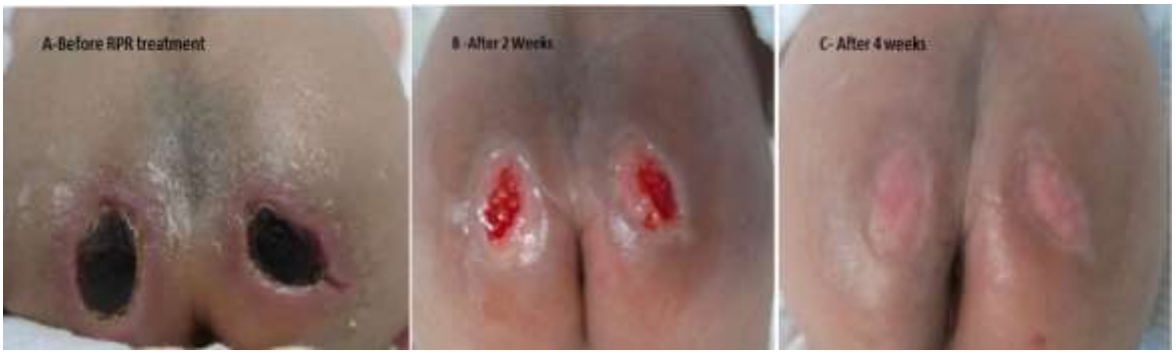

Figure (5): Wound healing in one of our patients treated with RPR

4. DISCUSSION

Pressure ulcers are a serious health issue that causes severe pain and discomfort in patients, as well as prolonged hospital stays, lengthy and complex treatment and care practices, increased health-care costs, decreased life quality, and an increased mortality rate. (13)

Although the etiology, pathology, prevention, early diagnosis, and treatment methods are well understood, this problem remains clinically and surgically significant. (14) There are several methods for providing pressure ulcer healing, which is a dynamic and complex process. Gas dressing with serum physiology is the most widely used and least expensive of them. (15)

In recent years, significant progress has been made in wound healing techniques, with autologous platelet-rich gel receiving the most attention. Platelets have been shown to initiate wound healing by releasing locally active growth factors. (16,17)

Growth factors can generate granulation tissue and induce epithelialization through neovascular formation, fibroblast and mesenchymal cell attraction, collagen fiber secretion, and keratinocyte proliferation. PRP may also reduce inflammation by inhibiting cytokine production. (18)

The present study was designed to look into the clinical efficacy of autologous platelet rich plasma gel in the treatment of bed sores. One hundred patients with bed sores were divided into two groups in the current study. The study group received autologous PRP treatment, while the control group received standard treatment over the wound of bed sores. There was no statistically significant difference between the two groups in terms of mean age, gender distribution, or chronic diseases, indicating that the process was effective. In the current study, patients in the study group had a statistically significant decrease in WSA of bed sores after two weeks of treatment when compared to the control group ($P \leq 0.05$). Furthermore, when compared to the control group, patients in the study group had a statistically significant higher ratio of healed area (PUHTP) after one week of treatment until the end of follow up ($P \leq 0.001$).

This was consistent with the findings of Megahed and his colleagues, who included 28 patients with nonhealing ulcers of various etiologies. Nine patients were treated with saline gauze dressings on alternate days, while 19 were treated with PRP at weekly intervals for a maximum of seven treatments. At day 28, the mean percentage of improvement in ulcer area and volume was 44-100% (73.32±23.77) in the study group and 17-37% (26.89±7.51) in the control group ($P \leq 0.001$). (19)

A recent meta-analysis that included 20 randomized controlled trials and five observational studies backed up these current findings. PRP therapy significantly increased complete wound closure in the lower extremity and reduced wound area and depth when compared to control managemen. (20)

Parallel to this study, Volakakis et al. also included 36 patients with a median age of 62 years (38-88 years), 64 pressure ulcers with an initial median surface area of 20 cm^2 (range of 1 cm^2 - 180 cm^2), a median diameter of 6.3 cm (range of 1.3 cm - 18.6 cm), and a median circumference of 16.8 cm (range of 4 cm - 68 cm). After PRP treatment, reductions in median surface area (63% vs. 41%), median maximal diameter (33% vs. 20%), and median circumference (38% vs. 21%) were significantly ($P \leq 0.001$) greater than conventional treatment. (21)

Likewise, 35 patients with foot ulcers were treated with autologous PRP gel or saline gel within a control group in a prospective, randomized, controlled, and blinded multicenter study. Patients treated with PRP gel healed significantly more wounds [13 (81.3%) of 16 patients] than patients treated with control gel [eight (42.1%) of 19 patients]. (22)

The number of clinical studies on the role of PRP in chronic wound healing is growing. Serra and his colleagues investigated the effect of platelet-rich gel on 32 patients who served as controls. Healing rates in patients who received platelet-rich gel were 96.15% compared to 59.37% in patients who did not receive platelet-rich gel. (23)

Also, Ahmed and his colleagues published a randomized controlled trial on the use of PRP on diabetic foot ulcers in 56 patients in 2017 and discovered a statistical difference in the rate of complete healing after PRP treatment (86 vs. 68%, $P \leq 0.05$). (24)

In agreement, Martinez-Zapata et al. investigated whether autologous PRP promotes chronic wound healing. The average duration of treatment was 12 weeks. The authors concluded that the results were inconclusive as to whether autologous PRP improves chronic wound healing in general when compared to standard treatment. Autologous PRP may improve the healing of diabetic foot ulcers when compared to standard care, but it is unclear whether autologous PRP has an effect on other types of chronic wounds. (17)

On the other hand, the results of current study disagreed with Singh et al., who included 52 patients with pressure ulcers of grade III/IV who were randomized into two groups of 26 each. Hydrogel dressing was used on patients in group A, while freshly prepared PRP was used on patients in group B. Three weeks after starting the intervention, mean baseline surface areas of 36.38 cm^2 in group A and 37.04 cm^2 in group B were reduced to 23.45 cm^2 and 25.91 cm^2, respectively. This surface area change was statistically significant. A significant reduction in surface area was also observed after six weeks. This demonstrates the effectiveness of both modalities in

reducing the ulcer's surface area. However, no significant difference in surface area reduction was observed between the two treatment modalities during the study period. Furthermore, there was a significant improvement in the PRP group compared to the other control group in terms of epithelization, granulation, and neovascularization. (25)

According to the present study, healing time was statistically significantly shorter in the study group than in the control group ($P \leq 0.001$). The findings were compatible with Megahed and his colleagues, who found that the mean duration of ulcer healing (days) was (49.84±22.23) in the study group and (108.6 ±5.64) in the control group. The duration was significantly shorter in the PRP group ($P \leq 0.001$). (19)

Parallelly, Upadhyay and his colleagues reported that the mean time duration to wound healing was (6.33 ±2.16) weeks. A statistically significant difference ($P \leq 0.05$) was observed between the baseline parameters and mean wound areas after PRP injection after 7 sessions (28 days of therapy). (26).

In the same vein, Singh et al conducted an experimental study with 25 patients in 2014, applying serum physiology and PRP to pressure sores. This study found that patients who received PRP dressing healed faster than those who received serum physiology dressing. (27)

Regarding the scores of PUSH Tool, the study group had statistically significant lower values after one week of treatment and throughout the follow-up period when compared to the control group ($P \leq 0.001$).

Uçar and Çelik in 2020 found no statistically significant difference in the mean PUSH scores of the pressure ulcer after the first dressing (1st observation) between the control and study groups ($P > 0.05$). In the 20th observation, however, the study group's score was statistically significantly lower. In the PRP gel dressing, there was a statistically significant difference between the mean PUSH scores at the first observation and at the end of the second month ($P \leq 0.001$). In the same study, the mean scores of the pressure wound area, exudate, and tissue type decreased significantly ($P \leq 0.001$) in the 20th observation of the dressing performed with PRP gel. (28)

Concerning VAS scores, our results showed that they were statistically significantly lower in the study group than those in the control group after one week of treatment and throughout the follow up ($P \leq 0.001$).

This was supported by Megahed and his colleagues, who demonstrated that after treatment, all patients' pain levels decreased and their quality of life improved significantly. They discovered that patients who received topical autologous PRP (group A) experienced a significant reduction in pain, keloids, and hypertrophic scar formation, as well as improved wound healing after starting PRP ($P \leq 0.001$). (19)

This finding copes with Everts and his colleagues who used platelet-leukocyte gel on 40 patients scheduled for open subacromial surgery, and found that it reduced the VAS score for pain. They also showed a significant reduction in recovery time and analgesic usage during the six-week follow-up, which was similar to the current study, whereas the mean VAS in the PRP group showed a dramatic reduction in pain compared to the control group, where oral analgesic was prescribed after dressing. (29)

In accordance to current results, Liu and his colleagues found that the total efficacy rate in the PRP group (92.16%) was higher than that in the control group (76.47%) ($P \leq 0.05$). The PRP group exhibited lower VAS and PUSH scores, than the controls after 21 days of treatment ($P \leq 0.05$). (30)

In the present study, the frequency of dressing changes in the control group was statistically significantly lower than that of the treatment group after one week of treatment until the end of follow up ($P \leq 0.001$). This was consistent with Ma et al., who successfully treated 11 patients with diabetes mellitus (11 wounds) with combined vacuum-assisted dressings with PRP therapy. There were no complications noted. The average size of wounds decreased to $3.1 \pm 1.9\ cm^2$ ($p \leq 0.01$). The average length of stay in the hospital was (39.3±5.4) days. At the time of discharge, all wounds had healed completely. (31)

Current results showed that only after two and three weeks of treatment, patients in the control group have a statistically significant higher positive rate of bacterial cultures than patients in the study group ($P \leq 0.05$). This agreed with Abd El-Mabood and Ali who included 80 diabetic foot wounds. Patients were randomly assigned to one of two groups: group A received standard ordinary dressing (N=40) and group B received PRP dressing (N=40). The average period of follow-up was 12 weeks. Antibiotics were used more frequently in group A due to pronounced infection, according to their findings. (32)

This effect could be attributed to high lipoxin A4 concentrations. Furthermore, platelets' anti-inflammatory effect could be explained by the fact that PRP may suppress cytokine release and limit inflammation. (33)

Indeed, the PRP improves wound healing by promoting the healing process through its GFs. PDGF AB, EGF, TGF-β, IGF-1, and VEGF-a are examples of these. For tissue regeneration, these GFs promote mesenchymal cell recruitment, proliferation, extracellular matrix degeneration, and cell differentiation. These factors are released from the granule in response to platelet activation by platelet aggregation inducers. (34)

LIMITATIONS OF THE STUDY:

The current study is limited by the small number of included cases and the fact that it is a single-center study, which may reduce the power of the obtained results. Therefore, well designed and adequately powered large-scale multi-center clinical trials are warranted to validate PRP as an ideal therapy for enhanced wound healing in bed sores.

5. CONCLUSION

The administration of topical autologous PRP gel accelerates wound healing with a definite effect in treatment of patients with different grades of bed sores in the ICU. It has proven its clinical efficacy in improvement of wound healing indices, pain intensity, and bacterial cultures. Meanwhile, with the advantages of simple preparation, biocompatible safety and low cost, PRP local application seems to be a promising beneficial technique for this clinical practice.

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