Original Research Article

Comparative study of enzymatic debridement for ulcer healing by secondary intention by papain debridement versus using povidone iodine solution

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Abstract

Background: Ulcer care includes debridement of the necrosed tissue and a thorough cleaning and dressing of the wound. However, these methods of debridement differ as per the patient's condition. Present study was conducted to compare the effectiveness in wound healing using these two modalities for better patient compliance in the department of surgery of this medical college hospital. **Material and Methods:** Present study was single-center, prospective, comparative study, conducted in patients aged between 18 to 64 years with (nonhealing) ulcer, wound present over a bony prominence in a mobility compromised individual, full thickness or partial thickness wounds involving bone or muscle, wounds with nonviable tissue attached to the wound base. 101 patients were randomly divided into two groups each after matching for confounding factors Group 1 - 51 patients treated with papain-urea Group 2 - 50 patients treated with Povidone iodine. **Results:** The overall mean age of patients in both groups was 48.08 ±13.08, of Group A – 49.23±11.76 and Group B – 48.36±14.42. Statistically significant changes were noted in wound size, mean duration for Day of appearance of Granulation tissue, mean duration for day of appearance of Epithelialization, mean duration for day of Periwound Edema Resolution, the mean duration for day of Wound Disinfection, mean duration of hospitalisation between group A and group B ($p < 0.02$). There was a significant bivariate relationship between age, DM, group and wound procedures (debridement, fasciotomy) on wound healing outcomes. In Group A, patients in whom was Papain-Urea used and in patients who underwent procedures (debridement, fasciotomy), we found that there was earlier appearance of epithelialization, earlier resolution of periwound erythema and periwound edema and Early wound disinfection with rapid decrease in wound size significantly. **Conclusion:** Use of papain urea is highly recommended as compared to povidone iodine in management of non-healing ulcers.

Keywords: chemical debridement, papain urea group, povidone iodine, non-healing ulcers.

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INTRODUCTION

Wound management is an integral part of surgical practice, in depth understanding about the pathophysiology and the treatment options available will help the surgeon to achieve a better patient compliance. The devitalized tissue present in chronic ulcers increases the chances of microbial infection and decreases wound healing. Various local and systemic factors such as pressure, infection, necrotic tissue, age, nutritional status, and co-morbid diseases can impede healing of ulcers.[2] Devitalized tissue and exudates act as mechanical barrier to migration of cells and provide an

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environment ideal for bacterial proliferation,[3] thus there is excess production of pro-inflammatory cytokines and prolongation of inflammatory response.[4] Ulcer care includes debridement of the necrosed tissue and a thorough cleaning and dressing of the wound. However, these methods of debridement differ as per the patient's condition.[5] Papain-Urea is the combination of a proteolytic enzyme (papain) and a chemical agent, which denatures nonviable protein (urea).[6] Papain is a nonspecific cysteine protease, capable of breaking down a variety of necrotic tissue substrates. Urea's role is to facilitate papain's proteolytic action by altering the structure of proteins. Povidone iodine, along with hydrogen peroxide is commonly used for disinfection before and after surgery as well as wound healing Povidone iodine is a broad spectrum antiseptic for topical application having slow absorption via soft tissue and hence used to treat wound infections and prevent them. Bacteria do not develop resistance to povidone iodine.[7] This study will be conducted to compare the effectiveness in wound healing using these two modalities for better patient compliance in the department of surgery of this medical college hospital.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted in Department of Surgery, Dr Shankarrao Chavan Government Medical College, {GMC}, Vishnupuri, Nanded, India. Study duration was 18 months (January 2019 to June 2020). Study was approved by institutional ethical committee.

Inclusion criteria: Patients aged between 18 to 64 years with (non-healing) ulcer, wound present over a bony prominence in a mobility compromised individual, full thickness or partial thickness wounds involving bone or muscle, wounds with nonviable tissue attached to the wound base.

Exclusion criteria: Patients with age less than 18 and more than 64 years. Ulcers with severe active infection. Wounds with x-rays suggestive of osteomyelitis. Patients with systemic conditions impairing wound healing such as renal, hepatic and haematological causes. Patients on long term steroids, on chemotherapy and immunosuppressants

Study was explained to patients and a Informed Written Consent was taken from all patients. 101 patients.

randomly divided into two groups each after matching for confounding factors Group 1 - 51 patients treated with papain-urea Group 2 - 50 patients treated with Povidone iodine. The included patients were subjected to: Detailed clinical history, General Physical examination and local ulcer examination. Investigations (Routine blood investigations- Complete blood count, renal function tests, blood sugars), Radiological- X ray wherever indicated, Swab Culture sensitivity(C/S) form ulcer on Day 1 in all patients, and subsequent C/S on variable days. Assessments were done Debridement of slough/nonviable tissue, reduction in ulcer size, granulation noted. Discharge, odour, induration noted for overall response to treatment. Dressings were done using same technique – cleaning with saline and application of ointment (collagenase/papain – urea) and putting a dressing. Patients were assessed for wound size, appearance of granulation tissue, appearance of epithelization, resolution of peri wound erythema, resolution of peri wound edema, organisms isolated/growth on culture sensitivity duration of hospitalization and day of wound disinfection (culture negative) on day 1,7,14,21,28. All data collected was stored in MS Excel spread sheet and statistical analysis was carried out with the help of SPSS (version 20) for windows package (SPSS Science, Chicago II, USA) and EpiInfo application. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-square test. Quantitative data was represented using Mean +/- SD and t-test was applied. p value < 0.05 was considered as statistically significant.

RESULTS

The following observations have been made in the study. The overall mean age of patients in both groups was 48.08 ±13.08, of Group A – 49.23±11.76 and Group B – 48.36±14.42. The maximum number of patients were in the age group of 56-64 years in both Group A and Group B (19 and 22 patients respectively). In Group A, there are 36 male and 15 female patients. In Group B there are 33 male, 17 female patients in group B, with overall 68.31% male and 31.69 % female patients in both groups. Traumatic ulcers: 8 patients in Group A and 8 patients in Group B had history of trauma, in the form of thorn prick, road traffic accident. The total number of diabetics in the study included 101 patients (11.66%) in group A, while18.00%in group B. The total number of hypertensives in the study included 9.80% in group A and 6.00% in group B while patients having both DM and HTN 5.88% in group A, 6.00 % in group B. The most common site affected among group A subjects was left foot (23.53%) followed by right foot (21.57%), the least site affected was right thigh (1.96%) and right hand (1.96%). The most common site affected among the group B subjects was left leg(22.00%) and right foot (22.00%) followed by left foot (18.00%) The least site affected was left hand, right and left forearm (2.00%).

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Table 1: Age distribution

Age	Group A (PAPAIN-UREA)	Group B (PI)
18-25	2	6
26-35	6	3
36-45	8	11
46-55	16	8
56-64	19	22
Mean ± SD	49.23±11.76	48.36±14.42
Gender		
Male	36	33
Female	15	17
Co-morbidity		
Diabetes	6 (11.66%)	9 (18.00%)
Hypertension	5 (9.80%)	3 (6.00%)
Diabetes and Hypertension	3 (5.88%)	3 (6.00%)
No Co-morbidity	37 (72.55%)	35 (70.00%)

Table 2: Site affected

SITE OF ULCER	GROUP A		GROUP B	
	RIGHT	LEFT	RIGHT	LEFT
Foot	11 (21.57 %)	12 (23.53 %)	11 (22.00 %)	9 (18.00 %)
Leg	8 (15.69 %)	10 (19.61 %)	8 (16.00 %)	11 (22.00 %)
Thigh	4 (7.84 %)	1 (1.96 %)	1 (2.00 %)	3 (6.00 %)
Hand	1 (1.96 %)	3 (5.88 %)	3 (6.00 %)	1 (2.00 %)
Forearm	0	1 (1.96 %)	1 (2.00 %)	1 (2.00 %)

Wound size was measured at baseline-Day 1 for all patients. The change in wound size was calculated from baseline (Day 1) and last day of measurement, i.e.; Day 28 and in patients who underwent Split skin grafting (SSG) before 28 days it was calculated one day prior to SSG. The change in wound size from baseline (Day 1) was assessed and day28. There was significant change in wound size between Group A and Group B with greater decrease in wound size at day 28. In Group A (PAPAINUREA), the average percentage decrease in wound size at Day 28 was 36% compared to 20.6% in Group B (PI).

Table 3: Wound Size

INTERVENTIONGROUP	Wound size day 1 (in cms)	Wound size change	Wound size week4 (in cms)
Group A Mean ± SD	13.612 + 5.6762	5.294 + 2.312	8.317 + 3.633
Group B Mean± SD	16.706 + 5.629	3.46 + 1.511	13.246 + 4.443

In Group A (PAPAINUREA), the mean duration for Day of appearance of Granulation tissue was 3.529± 0.85 days. In Group B (PI), the mean duration for day of appearance of Granulation tissue was 7.26 ± 1.8 days, difference was statistically significant ($p < 0.001$). In Group A (PAPAINUREA), the mean duration for day of appearance of Epithelialization was 7.68± 1.80 days. In Group B (PI), the mean duration for day of appearance of Epithelialization was 13.32 ± 2.46 days, difference was statistically significant ($p < 0.001$). In Group A (PAPAINUREA), the mean duration for day of Periwound Erythema Resolution was 4.52 ± 1.10 days. In Group B (PI), the mean duration for day of Periwound Erythema Resolution was 7.72 ± 1.21 days, difference was statistically significant ($p < 0.001$). In Group A (PAPAINUREA), the mean duration for day of Periwound Edema Resolution was 6.60 ± 1.5 days. In Group B (PI), the mean duration for day of Periwound Edema Resolution was 10.52 ± 1.69 days, difference was statistically significant ($p < 0.001$). In Group A (PAPAINUREA), the mean duration for day of Wound Disinfection (Culture negative) was 7.56 ± 1.84 days. In Group B (PI), the mean duration for day of Wound Disinfection (Culture negative) was 10.16 ± 2.11days, difference was statistically significant ($p < 0.001$). In Group A (PAPAINUREA), the mean duration of hospitalisation was 10.64 ±2.65 days. In Group B (PI), the mean duration of hospitalisation was 13.16 ± 2.64 days, difference was statistically significant ($p < 0.001$).

Table 4: General characteristics

Characteristics	Group A (PAPAINUREA) (Mean ± SD)	Group B (PI) (Mean ± SD)	P value
Appearance of Granulation tissue (days)	3.529± 0.85	3.529± 0.85	<0.001
Appearance of Epithelialization (days)	7.68± 1.80	13.32 ± 2.46	<0.001
Day of Resolution of Periwound Erythema (days)	4.529 ± 1.10	7.72 ± 1.21	<0.001
Day of Resolution of Periwound Edema (days)	6.60 ± 1.51	10.52 ± 1.69	<0.001

Day of Wound Disinfection (days)	7.56 ± 1.84	10.16± 2.11	<0.001
Duration of Hospitalisation (days)	10.64 ± 2.65	13.16 ± 2.64	<0.001

The commonest organism on Culture sensitivity taken on day 1 for all patients was Staphylococcus aureus – 24 patients, Enterococci – 13 patients, no growth in 6 patients.

Table 5: Organism on C/S

Organism on Culture sensitivity	No. of Patients n= 101 (%)
Staph aureus	24 (23.76%)
Enterococci	13 (12.87%)
Pseudomonas	7 (6.93%)
Klebsiella	10 (9.90%)
E.coli	10 (9.90%)
Citrobacter	8 (7.92%)
Streptococcus	11 (10.89%)
Proteus	7 (6.93%)
Acinetobacter	5 (4.95%)
No growth	6 (5.94%)

In Group B (PI) 58.00 % of cases underwent SSG before 28days 42 % of subjects underwent SSG after 28 days. In Group A (PI), 78.43 % of cases underwent SSG . SSG before 28days 21.56 % of subjects underwent SSG after 28days. Difference between group A and group B was statistically significant (p = 0.02).

Table 6: Split skin Grafting

Split skin grafting	Group B (N=50)	Group A (N=51)
<28 days	29	40
>28days	21	11
Total	**50**	**51**

There was a significant bivariate relationship between age, DM, group and wound procedures (debridement, fasciotomy) on wound healing outcomes. In Group A, patients in whom was Papain-Urea used and in patients who underwent procedures (debridement, fasciotomy), we found that there was earlier appearance of epithelialization, earlier resolution of periwound erythema and periwound edema and Early wound disinfection with rapid decrease in wound size significantly.

Table 7: Pearson Correlations

	Epithelization	Periwound erythema	Periwound edema	Wound Disinfection	Wound size change D1- D21
Age					
Pearson Correlation	-0.019	-1.765	.755	2.357**	1.183
Sig. (2-tailed)	.980	.0165	.459	.000	.064
Sex					
Pearson Correlation	-.0.049	.089	.005	-.009	-.022
Sig. (2-tailed)	.106	.060	.901	.675	.348
DM					
Pearson Correlation	.003	-.024	.013	.022	-0.017
Sig. (2-tailed)	.91	.570	.697	.275	.710
Procedures (SS)					
Pearson Correlation	-.0006	.018	-.011	-.048**	.016
Sig. (2-tailed)	.833	.700	.765	.003	.483

**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

In present study the mean age of patients was 48.08 ±13.08. When this mean age compared in both groups A and B, the mean age in both groups was nearly same (Group A: 49.23 ± 11.76 and Group B: 48.36 ± 14.42). Gerstein AD *et al.*[8] stated in his study that age-related differences in wound healing have been clearly documented. Although the elderly can heal most wounds, they have a slower healing process. Eaglstein WH[9] mentioned in his study that the inflammatory response is decreased with age, and undoubtedly this bears on some of the alterations in healing. The proliferative phase traditionally includes cell migration, proliferation, and maturation, all of which are changed with age. In our study, when correlation of age with wound healing and decrease in wound size was calculated, there was positive correlation between in these factors which justify the statements of above mentioned studies. In present study, patients presented with co-morbidities in both groups were same (28% in group A and 30% in group B). And in both groups, Diabetes Mellitus

was most common co-morbidity noted (12 % in group A and 18 % in group B). Beyene RT *et al.*[10] mentioned in his study that preexisting diagnoses may significantly alter, delay, or inhibit normal wound healing. This is most commonly seen with chronic disorders, such as diabetes and renal failure, but also occurs secondary to aging and substance abuse. Less commonly, genetic or inflammatory disorders are the cause of delayed wound healing. In our study, when correlation of co-morbidities (DM) with wound healing and decrease in wound size was calculated, there was weak or no correlation and negative correlation respectively between in these factors. Mendiola-So M *et al.*70. mentioned about the sites of common foot ulcers in DM patients. Most common sites: plantar surface of foot (metatarsal heads and midfoot), toes (dorsal interphalangeal joints or distal tip). The Pathogenesis was DFUs frequently caused by repetitive injury to an insensate or vascular compromised foot. In our study also foot and leg is common site of ulcer occurrence and most common morbidity was DM. The mean decrease in wound size in Group A was 36% whereas 20.6% in Group B. Alvarez OM *et al.*, [1] mentioned in his study that Papain-urea also appeared to be more effective in promoting granulation tissue and in our study the mean duration (in days) for appearance of Granulation tissue in group A (Papain-urea) was less than PI. Dalla P *et al.*,[12] compared efficacy of SOS versus PI in post C- section wounds, showed that 88% had granulation by day 5 in SOS group compared to 80% in PI group and by day 10 there was granulation in all patients. In our study time taken for granulation tissue formation with PI treatment was less than the study conducted by Dalla P *et al.* The mean duration (in days) for appearance of Epithelial tissue in group A was 4.529 ± 1.10 days whereas in Group B was 7.72 ± 1.21 days. There was significant difference between Group A and Group B on for day of appearance of epithelial tissue. Dalla P *et al.*,[12] mentioned in his study that in 12% patients 5 days were required for resolution of erythema. Dalla P *et al.*,[12] conducted a study on 218 patients suffering from chronic diabetic foot ulcers 110 patients were treated with SOS and 108 patients with povidone iodine. The mean healing time in PI group was 58 ± 20 which is much higher than when compared to our study with both groups (group A and group B). The mean duration (in days) of stay at hospital stay in group A was 10.64 ± 2.65 days whereas in Group B 13.16 ± 2.64was. There was significant difference between Group A and Group B on for day of appearance of epithelial tissue. The overall most common organism found on bacteriological culture was Staphylococcus aureus (23.76%) followed by Enterococci (12.87%) (Table no. 13) which is similar to a study conducted Chittoria RK *et al.*[13] in which also Staph aureus was the commonest organism on culture. In patients where Papain urea was used and in patients who underwent procedures (debridement, fasciotomy), we found that there was earlier appearance of epithelialization, earlier resolution of periwound erythema and periwound edema and Early wound disinfection with rapid decrease in wound size significantly.

CONCLUSION

There was shorter duration of hospital stay, earlier wound disinfection and a greater number of patients who underwent earlier skin grafting in papain urea group. The results were statistically significant and in favour of papain urea. Thus we conclude that use of papain urea is highly recommended as compared to povidone iodine in management of non-healing ulcers.

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