

Original Article

Effect of Papain Urea versus EUSOL in Diabetic Foot Ulcer Management

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Background : Cases of Diabetes Mellitus (DM) are increasing day by day with a perpetual increase in diabetic foot ulcer among these patients. Most of the patients present with infected ulcers with slough and unhealthy tissue. Surgical debridement needed as a initial line of management and later slough removal by chemical debridement agents. In our study we compared the effectiveness of chemical wound debridement using papain urea dressing as against Edinburgh University Solution of Lime (EUSOL) in diabetic foot ulcer. Also we tried to study the associated risk factors involved in the outcome of an ulcer.

Materials and Methods : Patients diagnosed with Type 2 Diabetes Mellitus with a foot ulcer classified under Wagner's classification I and II were taken up for the study. They were randomly allocated into two groups of 51 members each. EUSOL was used in one group and Papain Urea in the other groups as dressing agent. The rate of healing and other factors related to the foot ulcer were compared between the two groups.

Results : It was observed that there was significant reduction in ulcer size and slough in ulcers where Papain Urea was used as dressing agent. There was also better and faster granulation tissue formation among the group of patients using Papain Urea as dressing agent. The observation was made by measuring the surface area of slough and granulation tissue.

Conclusions : In diabetic foot ulcer, Wagner's classification I and II Papain Urea dressings showed significant reduction in the duration of healing time and faster slough removal. It also helped in forming healthy granulation tissue, without any associated complications. Hence, Papain Urea dressings can be considered as a good option for chemical debridement and wound healing for diabetic foot ulcer.

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Key words : Papain urea, EUSOL, Diabetic foot ulcer, Diabetes Mellitus, Slough.

World wide there has been an increase prevalence of Type 2 Diabetes. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014¹. As per the current statistics number of individuals having Diabetes Mellitus can go up to 366 million by 2030. This disease could definitely turn into a threat to health and become a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease^{2,3}.

It is predicted that by 2030 Diabetes Mellitus may afflict up to 79.4 million individuals in India and there will be an increase in the sequelae followed by it^{4,5}. Among the foot problems associated with Diabetes Mellitus nearly 5-10% needs amputation. It has now

Editor's Comment :

- Diabetic Foot Ulcer treatment requires utmost care with proper debridement techniques.
- Papain Urea dressing provides effective debridement, promotes healing, causes very minimal pain and allergic reaction are very minimal.

been demonstrated that up to 50% of amputations and ulcerations could be prevented through early diagnosis and adequate treatment⁶. Almost 85% of the problems resulting from diabetic foot can be prevented through specialized care⁷.

There are many methods of slough removal, namely surgical debridement, biological, mechanical or chemical debridement. A range of chemical agents, including hypochlorite's such as EUSOL and Dakin's Solution (Sodium Hypochlorite), Hydrogen Peroxide and Iodine, have been used to promote debridement of wounds. One trial comparing enzymatic debridement with saline-soaked dressings reported that the enzyme-treated wounds healed faster⁸.

EUSOL is solution of chlorinated lime and boric acid, on exposure to the wound the nascent chlorine gets liberated and breaks down the di sulphide bond

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of the protein in the tissue hence aids in denaturing the slough. Papain, obtained from papaya fruit breaks down cysteine residues in proteins. Urea is combined to increase its proteolytic action⁵. Studies involving Papain Urea have shown faster granulation compared to other products^{9,10}. No studies have been done to compare EUSOL and Papain Urea chemical debridement agents, both which are easily available and economical to use. One of the main cause of non healing diabetic ulcer was development of osteomyelitis. Osteomyelitis in diabetic foot ulcers patients including ulcer size more than 2 cm and depth allowing visibly exposed bone or ability to probe to bone had lesser chance of healing and most of these cases needed amputation as an end measure¹¹⁻¹⁴. The presence of a sausage toe with erythema and non-pitting edema that obliterates the normal contour of the digit has been associated with underlying Osteomyelitis in diabetic patients but the frequency of this finding is not known¹⁵. To conclude once bone involvement sets in there is no use of any chemical debridement agents and patient will end up with amputation. So, early diagnosis and treatment is a must for all diabetic foot ulcers.

Hence, this study is done to compare two easily available chemical debridement agents and to see their effect of debridement on diabetic foot ulcers.

MATERIALS AND METHODS

The study involved only human subjects. This was a randomized control open clinical trial study of 18 months duration from November, 2016 to May, 2018.

The sample size for this study was 51 in each group, total of 102 patients.

Inclusion Criteria :

- Adults (above 18 years of age), both gender.
- Wagner's classification I and II.
- A wound in need of debridement (opinion of investigator).
- Patients under glycemic control.

Exclusion Criteria :

- Patients who were diagnosed to have vascular insufficiency.
- Clinical symptoms of osteomyelitis, inadequate nutrition, or uncontrolled diabetes.
- Clinically significant medical conditions that would impair wound debridement inclusive of renal, hepatic, hematologic, neurologic or immunological disease.
- Patients receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy within one month prior to study entry.

Discontinuation Criteria :

The patient required any treatment/therapy that would compromise the evaluation of the test product, such as surgical debridement or skin grafting.

Topical Agents Used :

Group 1 : Papain Urea ointment - Composition: Each gram contains Papain IP \geq 521700 units and Urea IP 100 mg.

Group 2 : EUSOL (Edinburgh University Solution of lime) Composition : 12.5 gm bleaching powder + 12.5 gm boric acid distilled water to make 1 liter (Fig 2).

Drugs are approved by the drug controller of India

Parameters to be studied :

- Duration of ulcer
- Wound size
- Wound site
- The proportion of slough completely debrided or maximum percentage of slough debrided according to surface area of the ulcer was studied
 - Periodical photographs of the ulcer was taken and was assessed for the amount of slough.
 - Blood sugar levels was recorded periodically, fasting and post prandial sugars were measured every 3rd day and recorded.

Study Design :

All patients diagnosed with type 2 diabetes mellitus and who have a diabetic foot ulcer reporting to the hospital between November, 2016 to May, 2018 falling into the inclusion criteria was subjected to the study using either EUSOL or Papain Urea dressings. All patients was brought under adequate glycemic control. Empirical antibiotic of choice was amoxicillin-clavulanate given orally at a dose of 625mg (500mg + 125mg) thrice a day to all patients and was changed according to their culture and sensitivity. Patients was randomly allocated to receive either Papain Urea (Group 1) or EUSOL (Group 2) dressings using computer generated random numbers.

Wound measurement was done by measuring the surface area of wound by mapping method. A transparent graft sheet was placed on the ulcer and areas of slough and total area of the ulcer was marked and recorded. Amount of slough present on the wound was measured and taken as percentage of total ulcer area (Fig 1).

Patient received once daily dressing according to the group they are placed in. Progress was monitored every 3rd day up to a period of 21 days. Periodic photographs was taken once at the end of every week and assessed for an objective assessment. The



Fig 1 — A-Graft sheet and the ulcer that needs to be measured. B-Graft sheet placed on the ulcer and outline marked. C-Area of slough marked. D-Total area of ulcer and slough area measured.



Fig 2 — A- Papain Urea debridement ointment. B- Edinborough University Solution of Lime.

progress in wound healing was assessed by a surgeon who was blinded from the study and chemical agent used.

Method of Statistical Analysis :

All the collected data was entered in Excel 2010, baseline characters (demography, clinical, biochemical, hemodynamic changes) of the study was measured using mean and Standard Deviation for continuous variables and percentage for dichotomous and categorical variables. Two groups was compared using independent 'T' test for continuous variables and Chi Square test for dichotomous and categorical variables

Outcome variables the time taken for wound debridement and the percentage of granulation tissue growth was compared using Independent 'T' test.

P-value of 0.05 was considered as statistically significant.

Ethical Consideration :

i) This trial was approved by the institute ethics committee – reference number IEC:RC/15/26

ii) This trial is registered under Clinical Trials Registry - India with Reference number REF/2015/10/009914

RESULTS

A total of 102 patients were included in this study. They were divided into two groups of 51 each. Group 1 patients received PAPAIN UREA ointment for wound treatment and Group 2 patients received EUSOL (*Edinburgh University Solution of lime*) for wound management. Mean age was 55.8 years with Standard Deviation of 12.8 years. Minimum and maximum age was 30 years and 94 years respectively. Mean age in EUSOL group was 57.55 and Papain Urea group was 54.73. Gender wise 99(97.1%) patients were male and 3(2.9%) females.

Group 1 had 37.3% patients under wagner grade 1 and 62.7% under wagner grade 2. Group 2 had 31% patients under wagner grade 1 and 69% under wagner grade 2. Both groups had comparable ulcers with equal distribution of Grade 1 (Erosion of epidermis) and Grade 2 (Involving muscle) ulcers. The ulcers were studied based on site. And both groups had an equal distribution of ulcers from all sites. Most common site present was on the plantar aspect followed by dorsum of foot (Fig 3.1). The mean difference in area of ulcer in the EUSOL group was – 0.69cm². The mean difference in area of ulcer in the Papain Urea Group was – 0.83cm². The mean difference in % area of slough in the PAPAIN UREA Group was – 1.61cm². The mean difference in % area of slough in the EUSOL group was – 1.01cm².

Papain urea method showed better slough removal after Day 6 of usage when compared to EUSOL. Papain urea also had a statistically significant faster presence of healthy granulation tissue (DAY-6) Papain Urea had a more number of subjects showing a faster granulation from day 6 onwards, all of which were statically significant (Chi-square value 20.4, p<0.001 – significant).

At the end of the study period, all 51 study subjects in the Papain Urea group showed healthy granulation tissue. In the EUSOL group 46 study subjects showed healthy granulation tissue, whereas 5 study subjects did not show healthy granulation tissue at the end of the study period.

All the parameters were statistically significantly better in the Papain Urea group when compared to EUSOL group. After assessing various parameters for wound healing in 51 patients in each group, it was observed that reduction in size of ulcer started with in minimum of 3 days, size of ulcers started reducing

faster in Papain Urea group after day 6 onwards when compared to EUSOL group. Reduction in area of slough was significantly faster in Papain Urea group from day 6 onwards and showed maximum reduction on day 18 (Fig 3.2).

Granulations were started to see in the ulcer within 6th day in the PAPAINE UREA group which was faster than the EUSOL group which was observed only from day 12. All the subjects in Papain Urea group had healthy granulation tissue at the end of the study period when compared to EUSOL dressings. Actual slough area as well as picture based slough area were in correlation with each other. Factors such as site, side, FBS, PPBS did not affect wound healing. Slough reduction in younger patients was much faster than older age group. There was a statistical significance between the age groups (Figs 4.1 & 4.2; Table 1).

DISCUSSION

One of the major complication and common reason for hospitalization in Diabetes Mellitus is diabetic foot ulcer. It occurs in majority of patients with diabetes. This has become the preceding cause for almost 84% of all lower limb amputations and upto



Fig 4.1 — A-Foot Ulcer Day 1 of EUSOL Dressing, B-Day 7, C-Day 14 and D Day 21.



Fig 4.2 — A - Foot ulcer Day 1 of Papain Urea Dressing , B - Day 7 , C - Day 14 and D-Day 21.

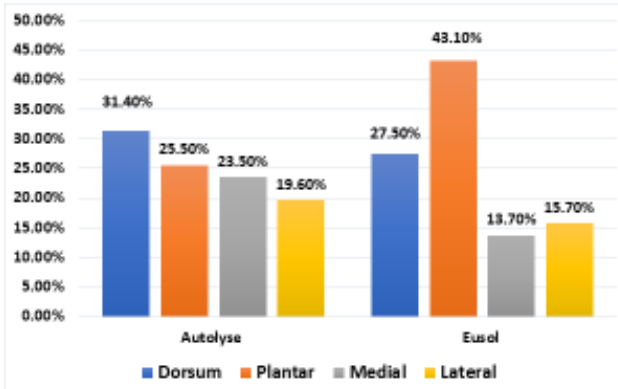


Fig 3.1 — Distribution of study subjects based on type of intervention and location of ulcer

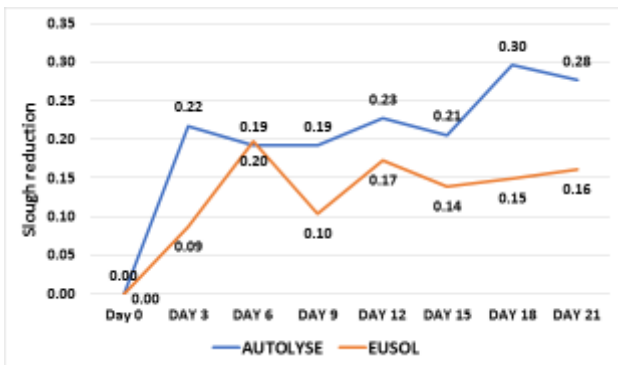


Fig 3.2 — Distribution of study subjects based on type of intervention and percentage area of reduction.

14% to 20 % of patients with diabetic foot ulcers to undergo amputation^{16,17}. There is a continuous search for an ideal method to accelerate wound healing which does not have any ill effects on the patient.

About 102 patients with diabetic foot ulcer were admitted under Surgery Department in Pondicherry Institute of Medical Sciences. Their wound condition at presentation was assessed and wounds were classified according to Wagner’s classification (grade 1 and grade 2 of Wagner’s classification). Their glycemic status were assessed by checking the biochemical parameters like FBS, PPBS and brought under control. The wounds that had slough and required debridement were brought under the study. The patients were randomized into two groups. Group 1 – Papain Urea and Group – 2 EUSOL respectively.

Healing of the ulcer was monitored every 3rd day on the based on following parameters like reduction in size of ulcer, reduction in percentage area of slough

Table 1 — Distribution of study subjects based on type of intervention and changes in variables from baseline to 21st day

Variables	Intervention	Number of subjects	Mean	Standard Deviation	t-value	p-value
Area of ulcer	PAPAIN UREA	51	0.8294	0.19929	3.94	<0.001 Significant
	EUSOL	51	0.6882	0.16081		
% area of slough	PAPAIN UREA	51	1.6157	0.55258	7.29	<0.001 Significant
	EUSOL	51	1.0118	0.21227		
% area of reduction	PAPAIN UREA	51	-0.2765	0.13355	-5.26	<0.001 Significant
	EUSOL	51	-0.1608	0.08265		
FBS	PAPAIN UREA	51	-12.5490	44.14083	0.003	0.998 Not Significant
	EUSOL	51	-12.5686	25.76607		
PPBS	PAPAIN UREA	51	0.6471	39.58577	-0.151	0.881 Not Significant
	EUSOL	51	1.6667	27.78393		
Picture	PAPAIN UREA	51	1.3980	0.47349	6.612	<0.001 Significant
	EUSOL	51	0.9255	0.19062		

showed that active treatment resulted in more rapid and effective removal of necrotic tissue from pressure ulcers, leg ulcers and partial thickness burn wounds. A comparison of collagenase and Papain Urea based ointments found faster removal of necrotic tissue in the Papain Urea group

and presence of granulation. All the ulcers were mapped and compared with a similar ulcer among both groups. The condition of ulcer at the time of presentation was assessed and recorded. The wounds were managed with once a day dressings with Papain Urea ointment or EUSOL solution. The wound was assessed on every 3rd day up to 21 days.

The mean age among the total study population was 56.14 years with Standard Deviation of 12.174 years. Minimum and maximum age were 30 years and 94 years respectively. The reduction in size of ulcer started within minimum of 3 days, size of ulcers started reducing faster in Papain Urea group after day 6 onwards. The reduction in area of slough was significantly faster in Papain Urea group from day 6 onwards and showed maximum reduction on day 18.

Granulation tissue were started to appear in the ulcer within 6th day in the Papain Urea group which was faster than the EUSOL group. All the subjects in Papain Urea group had healthy granulation tissue at the end of the study period when compared to EUSOL dressings. Actual slough area as well as picture based slough area were in correlation. Factors such as site, side, FBS, PPBS did not affect wound healing. Slough reduction in younger patients was much faster than older age group.

A study done by Alvarez, *et al*¹⁸ showed that Papain Urea significantly reduced the area of necrotic tissue at 4-weeks by comparison to Collagenase in ulcers. They also have shown that ulcers treated with Papain Urea had a greater degree of granulation than those treated with Collagenase at weekly periods during a 4-week assessment. However a strong scientific conclusion could not be made. A PubMed literature review by J Ramundo and M Gray¹⁹, a total of nine studies were included in the review: eight Randomized Controlled Trials (RCTs) and one cohort study with at least 320 patients were included. They

Morrison, *et al*²⁰ demonstrated that 27 of 30 patients with decubitus ulcers, previously resistant to topical therapy, were completely healed within two to 6 weeks of Papain Urea. There are many types of debridement methodologies for the removal of non-viable slough. Only when the slough is removed does the healing take place. Here, we compare two medical methods of wound debridement, EUSOL application and Papain Urea dressings and their effectiveness in debriding diabetic foot ulcers. These two debridement agents haven't been compared in previous clinical trials.

CONCLUSIONS

Diabetic foot ulcers are the most common complications in a diabetic patient. Debridement of an ulcer play a vital role in the healing of diabetic foot ulcers. Medical methods of debridement have an advantage where it can be used in patients who are unfit for anaesthesia and that it is painless. Also it can be done as an OPD basis. Papain Urea dressings has become one of the considerations as a debridement agent for various types of ulcers. It helps in wound healing by reducing the duration for wound healing by reducing the slough and also promoting granulation.

It was proved that Papain Urea ointment is a better again in debridement when compared to EUSOL. In the present study all 51 patients (grade 1 and grade 2 of Wagner's classification) started showing features of reduction in ulcer size, area of slough and presence of healthy granulation tissue. In diabetic foot ulcer, Papain Urea dressings help in wound healing by decreasing the duration of healing time and faster slough removal, also promotes granulation, without any complications. Hence, Papain Urea dressings are a good option for debridement and wound healing in diabetic foot ulcer.

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