

Original Research Article

Effect of papain urea versus hydrogen peroxide in diabetic foot ulcer management

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Received: 20 February 2023

Revised: 20 March 2023

Accepted: 31 March 2023

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ABSTRACT

Background: Diabetic foot ulcers are the most common complications in diabetic patients. Debridement of an ulcer play a vital role in the healing of diabetic foot ulcers. Medical methods of debridement have an advantage as it is also painless and can be done on OPD basis. Aim of this study was to compare the effectiveness of debridement using papain urea dressing as against hydrogen peroxide in diabetic foot ulcer management.

Methods: Patients who have a diabetic foot ulcer reporting to the hospital were studied using either hydrogen peroxide or papain urea dressings. All were brought under adequate glycemic control. Empirically oral antibiotics are started to all patients and changed according to culture and sensitivity reports after three days. Patients was randomly allocated to receive either H₂O₂ or papain urea dressings, 63 per set. Statistical analysis was done using the SPSS software. Significance level was fixed at p value of p<0.05.

Results: It was seen that PAPAINE UREA ointment is a better agent in debridement when compared to hydrogen peroxide. All 63 patients started showing features of reduction in ulcer size and area of slough. This difference was statistically significant.

Conclusions: In diabetic foot ulcer, papain urea dressings help in wound healing by decreasing the duration of healing time and by faster slough removal. It promotes granulation, without any complications. Hence papain urea dressings are a good option for debridement and wound healing in diabetic foot ulcer.

Keywords: Diabetes, Hydrogen peroxide, Papain urea, Wagner's grade

INTRODUCTION

Over the past few decades there has been an alarming rise in 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 2014. Its prevalence has been rising more rapidly in middle and low-income countries.¹ This disease could definitely turn 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}

Foot problems such as ulceration, infection and gangrene are quiet common in diabetic subjects. Uncontrolled diabetes delays wound healing as a result of reduced inflammation, angiogenesis and collagen synthesis. However once the slough has been removed, the formation of granulation tissue can take place unhindered. It has now been demonstrated that up to 50% of amputations and ulcerations could be prevented through early diagnosis and adequate treatment.⁴ It also has been well established that 85% of the problems resulting from diabetic foot can be prevented through specialized care.

There are many methods of slough removal, namely sharp or surgical debridement, biological, mechanical or chemical.^{5,6} A range of chemical agents, including hypochlorites 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 were cleaned more quickly.

This study was done to compare two chemical debridement agents, namely Hydrogen peroxide and papain-urea combination.^{5,6} Papain, obtained from papaya fruit breaks down cysteine residues in proteins. Urea is combined to increase its proteolytic action.⁷ They aid in digesting necrotic tissue without damaging healthy tissue. No studies have been done to compare Hydrogen peroxide and papain-urea chemical debridement agents, both of which are easily available and economical to use.

METHODS

The objectives of this study were to assess the effectiveness of debridement using papain urea dressing as against hydrogen peroxide in diabetic foot ulcer and to study the risk factors involved in the outcome of ulcer(8). It was an observational study for one year in the Department of General Surgery in government medical college, Kottayam, Kerala during 2020-2021. Sample size was calculated to be 63 in each group. Statistical analysis was done using the SPSS software. Significance level was fixed at p value of $p < 0.05$.

Adults above 18 yrs of age from both genders with Wagner's classification I and II, wound in need of debridement and patients under glycemic control were included. Patients with vascular insufficiency, Wagner stage III and above, clinical osteomyelitis, inadequate nutrition, or uncontrolled diabetes, clinically significant medical conditions that would impair wound debridement inclusive of renal, hepatic, hematologic, neurologic, or immunological disease and patients receiving

corticosteroids, immunosuppressive agents, radiation or chemotherapy within one month prior to study entry were excluded.

Study procedure

Wound was measured by mapping method. A transparent graft sheet was placed on the ulcer and areas of slough and total area of the ulcer were marked and recorded. Amount of slough present on the wound was measured and taken as percentage of total ulcer area. Patients received once daily dressing and progress monitored every 3rd day up to a period of 21 days and assessed for improvement. Independent T test was done to compare the mean. The topical agents used were papain urea ointment -(each gram contained papain IP >521700 units and UREA IP 100mg.)(3) and 2% hydrogen peroxide. Parameters studied included duration of ulcer, wound size, proportion of slough completely debrided or maximum percentage of slough debrided according to surface area of the ulcer. Fasting and post prandial sugar blood sugar levels were recorded periodically.

RESULTS

There were 126 patients including both male and female with diagnosis of diabetic foot ulcer included. Their wounds were classified according to Wagner's grading (grade 1 and grade 2). Their glycemic status was brought under control. The wounds that had slough and required debridement were brought under the study. The patients were randomized into two groups 1 - papain urea and 2 - hydrogen peroxide.

The condition of ulcer at the time presentation was assessed and recorded. The wounds were managed with once a day dressings with papain urea ointment or Hydrogen peroxide solution. Healing of the ulcer was monitored every 3rd day up to 21st days based on reduction in size of ulcer, reduction in percentage area of slough and presence of granulation. All the ulcers were mapped and compared with ulcer among both groups.

Table 1: Type of intervention and change in parameters at 21st day.

		N	Mean	Std. Deviation	t	P value
Area ulcer diff	Papain Urea	63	0.817	0.2311	3.501	0.001
	Hydrogen peroxide	63	0.695	0.1529		
Area slough diff	Papain Urea	63	1.5794	0.55740	7.314	0.000
	Hydrogen peroxide	63	1.0032	0.28339		
Area reduction diff	Papain Urea	63	-0.276	0.1353	5.902	0.000
	Hydrogen peroxide	63	-0.159	0.0816		
Epithelization diff	Papain Urea	63	1.00	0.000	2.784	0.006
	Hydrogen peroxide	63	0.89	0.317		
FBS diff	Papain Urea	63	-11.22	40.923	0.038	0.970
	Hydrogen peroxide	63	-11.46	27.670		
PPBS diff	Papain Urea	63	0.29	41.681	0.299	0.766
	Hydrogen peroxide	63	2.14	26.409		

Table 2: Type of intervention and change in parameters at 21st day in different age groups.

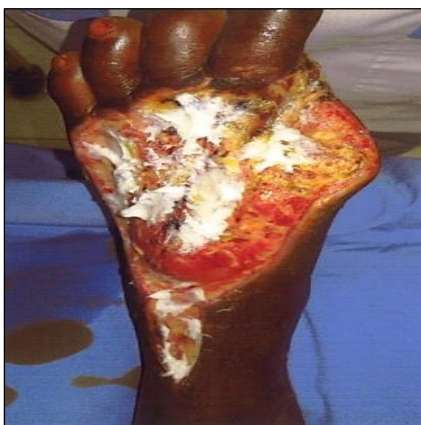
Group		Age (in years)					Total	χ^2	P value
		41 to 50	51 to 60	61 to 70	70 to 80	>80			
Papain urea	Count	9	20	22	10	2	63	14.978	0.005
	%	14.3	31.7	34.9	15.9	3.2	100.0		
Hydrogen peroxide	Count	4	9	21	28	1	63		
	%	6.3	14.3	33.3	44.4	1.6	100.0		
Total	Count	13	29	43	38	3	126		
	%	10.3	23.0	34.1	30.2	2.4	100.0		

Table 3: Type of intervention and change in parameters at 21st day in different sex groups.

Group			Sex		Total	χ^2	P value
			Male	Female			
Group	Papain urea	Count	59	4	63	0.896	0.344
		%	93.7	6.3	100.0		
	Hydrogen peroxide	Count	56	7	63		
		%	88.9	11.1	100.0		
Total		Count	115	11	126		
		%	91.3	8.7	100.0		

Table 4: Type of intervention and change in parameters at 21st day in different ulcer locations.

Group		Location				Total	χ^2	P value
		Plantar	Dorsal	Medial	Lateral			
Papain urea	Count	16	20	16	11	63	2.097	0.553
	%	25.4	31.7	25.4	17.5	100.0		
Hydrogen peroxide	Count	15	27	14	7	63		
	%	23.8	42.9	22.2	11.1	100.0		
Total	Count	31	47	30	18	126		
	%	24.6	37.3	23.8	14.3	100.0		

**Figure 1: Papain urea day 1.**

The 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. The reduction in area of slough was significantly faster in papain urea group from

day 6 onwards and showed maximum reduction on day 18 (Table 1).

Granulation tissue started to appear in the ulcer within 6th in the papain urea group which was faster than the hydrogen peroxide group.

All the subjects in papain urea group had healthy granulation tissue at the end of the study period when compared to hydrogen peroxide dressings (Figure 1 and 2 vs Figure 3 and 4).

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. There was a statistical relation between the age groups. Papain urea was effective in decreasing the slough area in all age groups compared to hydrogen peroxide $p=0.005$; which is statistically significant (Table 2).



Figure 2: Papain urea day 21.



Figure 3: Hydrogen peroxide day 1.



Figure 4: Hydrogen peroxide day 21.

Majority of patients in both groups were men. 115 men and 11 ladies patients were involved in study. Sex of the patient has no role in outcome of the study ($p=0.344$). (Table 3).

The ulcers were studied based on site. Both the groups had an equal distribution of ulcers from all sites. Site of the ulcer has no role in determining the outcome of the study ($p=0.553$) (Table 4).

Both the groups had an equal distribution of ulcers from both the sides. Side of the ulcer has no role in determining the outcome of the study ($p=0.722$).

DISCUSSION

Diabetic foot ulcers are the most common complications in a diabetic patients. 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. It is painless and also can be done on OPD basis.

One of the major reasons for hospitalization in diabetes mellitus is diabetic foot ulcer, and it occurs in majority of patients with diabetes. This has become the preceding cause for almost 84% of all lower limb amputations and up to 14% to 20% of patients with diabetic foot ulcers to undergo amputation.

Diabetic foot ulcers are managed predominantly debridement and suitable dressing with antiseptic solutions.

Non healing ulcers are managed by adequate debridement and suitable dressing with antiseptic solutions and topical applications which enhance wound healing. There is a continuous search for an ideal method to accelerate wound healing which does not have any ill effects on the patient.

Papain urea dressings has become one of the considerations as a debridement agent for various type of ulcers. It helps in wound healing by reducing the duration for wound healing by reducing the slough and also promoting granulation.

A study done by Alvarez et al showed that papain urea significantly reduced the area of necrotic tissue at 4-weeks by comparison to collagenases in ulcers.⁹ They also have shown that ulcers treated with papain urea had a greater degree of granulation than those treated with collagenases at weekly periods during a 4-week assessment. However a strong scientific conclusion could not be made.

A PubMed literature review by J Ramundo et al, a total of nine studies were included in the review: eight randomized controlled trials and one cohort study with at least 320 patients were included.¹⁰ They 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 collagenases and papain urea based ointments found faster removal of necrotic tissue in the papain urea group.

A Cochrane literature review by smith F et al revealed that there was a lack of large, high quality published RCT'S evaluating debridement per se, or comparing different methods of debridement for surgical wounds, to guide clinical decision making.¹¹

Morrison et al demonstrated that 27 of 30 patients with decubitus ulcers, previously resistant to topical therapy, were completely healed within two to six weeks of papain urea.¹²

They are many types of debridement methodologies for the removal of non-viable slough. Only when the slough is removed does the healing takes place. Here we

compare to medical methods of wound debridement, papain urea and hydrogen peroxide dressings and their effectiveness in debriding diabetic foot ulcers. These two debridement agents haven't been compared in previous clinical trials.

It was proved that papain urea ointment is a better agent in debridement when compared to hydrogen peroxide. In the present study, all 63 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.¹³

Limitations of this study were: the patient required any treatment/therapy that would compromise the evaluation of the test product, such as surgical debridement or skin grafting.

CONCLUSION

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.

ACKNOWLEDGEMENTS

Authors would like to thanks all the patients who participated in the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rakesh M, Jose J. Effect of papain urea versus hydrogen peroxide in diabetic foot ulcer management. Int Surg J 2023;10:877-81.