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Diabetic Ulcer Management: Effect of Papain Urea versus Hydrogen Peroxide

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Abstract

Diabetic foot ulcers (DFUs) represent one of the most feared and costly complications of diabetes mellitus. Globally, an estimated 9.1 to 26.1 million people with diabetes develop foot ulcers annually, with a lifetime risk ranging from 15% to 25%. DFUs contribute significantly to morbidity, mortality, and healthcare expenditure. The five-year mortality rate for patients with a DFU is approximately 42%, which is comparable to several types of cancer.

The presence of slough and necrotic tissue impedes wound healing by serving as a medium for microbial proliferation and inhibiting granulation tissue formation. Therefore, effective and timely debridement—the removal of devitalized tissue—is essential to wound bed preparation and healing. While surgical debridement is often considered the gold standard, it may not be feasible in outpatient or resource-limited settings due to pain, bleeding risk, or patient non-compliance.

Chemical debridement agents, particularly Papain-Urea and Hydrogen Peroxide, are frequently used alternatives. Papain, a proteolytic enzyme derived from papaya, and urea, a denaturant, synergistically act to digest necrotic tissue while sparing healthy granulation. Hydrogen Peroxide, on the other hand, debrides via effervescence and oxidation but is associated with cytotoxicity and delayed epithelialization.

This study aims to compare these two chemical agents in terms of ulcer area reduction, slough removal, granulation, and overall wound healing in diabetic foot ulcers.

Methodology:

This prospective observational comparative study was conducted over a one-year period (2023–2024) in the Department of General Surgery at SIMS, Shivamogga, Karnataka. The objective was to compare the effectiveness of papain-urea ointment with hydrogen peroxide in the debridement and healing of diabetic foot ulcers.

A total of 100 patients diagnosed with diabetic foot ulcers were included in the study. They were randomly divided into two equal groups of 50 patients each. Group 1 received topical papain-urea ointment, while Group 2 received 2% hydrogen peroxide solution. Both groups underwent daily wound dressing, and progress was monitored over a 21-day period.

Results:

A total of 100 patients with diabetic foot ulcers were enrolled in the study and evenly distributed into two groups of 50 each. Group 1 was treated with papain-urea ointment, while Group 2 received 2% hydrogen

peroxide solution. By Day 21, the papain-urea group showed a significantly greater reduction in ulcer size (mean: 10.2 cm^2) compared to the hydrogen peroxide group (mean: 15.3 cm^2), with a p-value of 0.001.The slough percentage was markedly reduced in the papain-urea group (10%) versus the hydrogen peroxide group (27%) ($p < 0.001$).Complete granulation was seen in 100% of papain-urea patients, compared to 78% in the hydrogen peroxide group ($p = 0.006$).Healing was faster in the 41–60 age group, and papain-urea was effective across all ages ($p = 0.005$).No significant difference in outcomes was seen based on sex ($p = 0.344$).No adverse events were reported in either group during the study period.

Conclusion:

This study confirms that Papain-Urea is a safe, cost-effective, and superior alternative to Hydrogen Peroxide in managing diabetic foot ulcers. It significantly improves ulcer area reduction, accelerates slough removal, and enhances granulation tissue formation, all without adverse effects.

Keywords: NIL

Introduction

Diabetes mellitus is a chronic metabolic disorder with widespread global prevalence and significant long-term complications. Among these, diabetic foot ulcers (DFUs) represent one of the most challenging and debilitating complications, affecting up to 25% of diabetic patients during their lifetime[1]. These ulcers result from a combination of peripheral neuropathy, vascular insufficiency, and impaired immune response, making them prone to infection and delayed healing. If not p managed, DFUs may progress to gangrene and eventually lead to lower limb amputation[2,3].

A key component in the successful management of DFUs is wound debridement, which involves the removal of necrotic tissue, debris, and slough from the ulcer bed. This process promotes healthy granulation tissue formation and accelerates the wound healing process[1,4]. While surgical debridement is effective, it may not be suitable for all patients due to pain, bleeding, or comorbid conditions. Hence, chemical debridement has emerged as a non-invasive and convenient alternative, particularly in outpatient settings[5,6].

Two commonly used chemical agents are Papain-Urea and Hydrogen Peroxide. Papain, a proteolytic enzyme derived from the papaya plant, when combined with urea, enhances the breakdown of necrotic tissue while preserving healthy tissue[5,7]. Hydrogen Peroxide, on the other hand, debrides through its oxidizing action and mechanical effervescence but may also damage viable tissue due to its cytotoxic effects[6,8].

This study aims to compare the effectiveness of papain-urea and hydrogen peroxide in terms of ulcer size reduction, slough clearance, and granulation tissue formation in patients with diabetic foot ulcers. The goal is to identify a safer and more efficient debriding agent that can be used effectively in clinical practice.

Methodology

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Inclusion criteria for the study were as follows: patients aged above 18 years, diagnosed with Wagner Grade 1 or 2 diabetic foot ulcers, and with good glycemic control (HbA1c < 8%). Patients with uncontrolled diabetes, clinical evidence of osteomyelitis, peripheral vascular disease, immunocompromised status, or those on systemic

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corticosteroids, chemotherapy, or other immunosuppressive drugs were excluded from the study.

Prior to dressing, each ulcer was cleaned with sterile saline. The appropriate agent— either papain-urea or hydrogen peroxide—was then applied topically, followed by sterile gauze dressing. The wound area, percentage of slough, and presence or absence of granulation tissue were assessed at baseline and then every third day using a transparent tracing method.roperly

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Ulcer area was measured using a sterile transparent acetate sheet placed over the wound, and dimensions were recorded on graph paper to calculate surface area in square centimeters. Slough percentage was recorded based on the proportion of non-viable tissue covering the wound surface, and granulation tissue was scored as present or absent.

All patients received standardized systemic antibiotic therapy guided by culture and sensitivity reports and maintained adequate glycemic control throughout the study. Statistical analysis was performed using SPSS software. Student's t-test and chi- square test were used to analyze quantitative and categorical variables, respectively. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1; Ulcer Size Reduction

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Group	Mean Ulcer Area Difference	Standard Deviation (SD)	p-value
Papain Urea	0.817 cm^2	± 0.2311	
Hydrogen Peroxide	0.695 cm^2	± 0.1529	
			0.001

Patients treated with Papain Urea showed a greater reduction in ulcer area by day 21.

The difference between the two groups is statistically significant (p = 0.001), favoring Papain Urea.

This confirms that Papain Urea is more effective in reducing wound size over the treatment period.

Table 2; Slough Percentage

Group	Mean Slough Area Difference	Standard Deviation (SD)	p-value
Papain Urea	1.5794 cm^2	± 0.5574	
Hydrogen Peroxide	1.0032 cm^2	± 0.2834	
			< 0.001

The Papain Urea group had a greater reduction in slough area than the Hydrogen Peroxide group.

The difference is statistically significant (p < 0.001), favoring Papain Urea for faster and more effective slough removal.

This demonstrates that enzymatic debridement with Papain Urea accelerates wound bed preparation in diabetic ulcers.

Table 3; Granulation Tissue

Group	Epithelization Score (Mean ± SD)	p-value
Papain Urea	1.00 ± 0.00	
Hydrogen Peroxide	0.89 ± 0.317	0.006

All patients in the Papain Urea group achieved full granulation (score = 1) by Day 21.

The Hydrogen Peroxide group showed delayed or incomplete granulation in some patients.

This difference is statistically significant (p = 0.006), indicating that Papain Urea promotes earlier and more complete granulation of diabetic foot ulcers.

Table 4; Age Distribution

Age Group (years)	Papain Urea (n = 50)	Hydrogen Peroxide (n = 50)

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41–50	7 patients (14%)	3 patients (6%)
51–60	16 patients (32%)	7 patients (14%)
61–70	17 patients (34%)	17 patients (34%)
70–80	8 patients (16%)	22 patients (44%)
>80	2 patients (4%)	1 patient (2%)
Total	100%	100%

The Papain Urea group had a greater number of patients in the productive age range (41–60 years), which typically demonstrates faster healing.

The Hydrogen Peroxide group had more patients in the older age brackets (70+ years), which can delay wound healing.

Despite this, Papain Urea showed consistent effectiveness across all age groups, and the difference in slough reduction and healing time by age was statistically significant ($p = 0.005$).

Table 5; Sex Distribution

Sex	**Papain Urea (n = 50)**	**Hydrogen Peroxide (n = 50)**
Male	47 patients (94%)	44 patients (88%)
Female	3 patients (6%)	6 patients (12%)

The study was predominantly male, with over 90% of participants being men.

There was no significant difference in healing outcomes between male and female patients ($p = 0.344$).

This shows that sex did not influence the effectiveness of either Papain Urea or Hydrogen Peroxide in diabetic ulcer healing.

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Discussion

Diabetic foot ulcers (DFUs) are a major contributor to hospitalization, limb loss, and reduced quality of life in individuals with diabetes. Management of DFUs requires a multifactorial approach, including glycemic control, infection prevention, pressure offloading, and wound care, with debridement playing a central role in promoting healing1,4,8. In this study, we compared the effectiveness of two commonly used chemical debriding agents—Papain-Urea and Hydrogen Peroxide—in accelerating healing of DFUs.

Our findings indicate that Papain-Urea was significantly more effective than Hydrogen Peroxide in terms of ulcer size reduction, slough clearance, and granulation tissue formation. These results support the hypothesis that enzymatic debridement offers a more targeted and tissue-friendly approach than chemical oxidation.

Ulcer Size Reduction

One of the primary endpoints of our study was the reduction in ulcer area over 21 days of treatment. Patients in the Papain-Urea group experienced a mean reduction of 57.6%, compared to 35.2% in the Hydrogen Peroxide group ($p = 0.001$). This significant difference suggests that Papain-Urea not only accelerates wound debridement but also enhances epithelial migration and tissue regeneration.

These findings are consistent with Rakesh et al.10, who reported superior outcomes with Papain-Urea over Hydrogen Peroxide in a randomized controlled study on diabetic foot wounds. Similar results were observed by Vijayakumar et al.5, who noted faster healing with Papain-Urea when compared to Collagenase. The current study adds further evidence to the growing preference for enzymatic agents in chronic wound care, especially in diabetic populations where healing is compromised9,12.

Slough Clearance

Slough, the presence of necrotic or fibrinous material on the wound surface, is a significant barrier to healing. In our study, the Papain-Urea group demonstrated a much faster and more complete clearance of slough than the Hydrogen Peroxide group. By Day 21, only 10% of slough remained in the Papain-Urea group compared to 27% in the Hydrogen Peroxide group ($p < 0.001$).

The superior slough removal capacity of Papain-Urea can be attributed to its proteolytic activity, which selectively digests necrotic tissue without damaging viable cells. This selective action is advantageous over Hydrogen Peroxide, whose debriding action is based on the release of reactive oxygen species, which may cause collateral damage to regenerating epithelial cells and fibroblasts8,9. Sarabahi11 emphasized that chemical agents like Hydrogen Peroxide, although useful for mechanical cleansing, may impair healing if used repeatedly or at high concentrations due to cytotoxic effects.

Furthermore, Everett and Mathioudakis8 noted that effective debridement is a prerequisite for initiating granulation and re-epithelialization, supporting our findings that Papain-Urea creates a more favorable environment for subsequent wound healing phases.

Granulation Tissue Formation

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Granulation tissue is a critical indicator of wound bed readiness and healing progression. In our study, all patients (100%) in the Papain-Urea group showed complete granulation by Day 21, whereas only 78% of the Hydrogen Peroxide group achieved similar outcomes ($p = 0.006$). This difference reinforces the concept that enzymatic debridement promotes a biologically active wound bed more effectively than oxidative debridement.

Granulation requires intact fibroblast function, adequate angiogenesis, and minimal cytotoxic interference. By sparing healthy tissue and targeting necrotic debris, Papain-Urea appears to support these processes more robustly. In contrast, the oxidative stress caused by Hydrogen Peroxide may delay fibroblast proliferation and matrix deposition, as demonstrated in studies examining cellular damage from reactive oxygen species6,8,11.

Age And Healing Response

Age is an important factor in wound healing. In our study, patients aged 41 to 60 years showed relatively faster healing than older age groups. However, Papain-Urea showed consistent effectiveness across all age brackets, whereas Hydrogen Peroxide was less effective in older patients ($p = 0.005$). These findings suggest that the tissue- friendly nature of Papain-Urea may overcome some of the age-related impairments in healing, such as reduced cellular turnover and diminished immune response3,4.

This observation is particularly relevant in a country like India, where the diabetic population is aging, and non-invasive, effective outpatient wound care options are urgently needed2,3.

Sex-Based Outcomes

Although our study cohort had a male predominance (>90%), there was no statistically significant difference in outcomes based on sex ($p = 0.344$). This indicates that the efficacy of either debriding agent is not influenced by biological sex. However, the predominance of male patients aligns with epidemiological trends showing higher rates of foot ulcers and amputations in diabetic men, possibly due to greater neuropathy severity and delays in seeking care2,13.

Safety And Tolerability

Neither group experienced any adverse effects or complications during the study period. This suggests that both agents are clinically safe when used under appropriate supervision. However, the painless nature of enzymatic debridement makes Papain-Urea particularly attractive in outpatient settings, especially for elderly or pain-sensitive patients. Previous reports, such as those by Ramundo et al. (2018), have advocated for enzymatic debridement due to its ease of use and minimal discomfort compared to sharp or surgical techniques9,12.

Clinical Relevance And Implications

The findings from this study have practical implications for clinical wound care. In resource-limited settings where surgical debridement is not always feasible, Papain- Urea emerges as a viable, affordable, and effective alternative for chronic wound management. Its faster healing potential could translate to shorter hospital stays, reduced infection rates, and lower amputation risk.

From a public health perspective, integrating Papain-Urea into diabetic wound care protocols could improve outcomes and reduce the economic burden of foot ulcers, which account for a significant share of diabetes-related healthcare costs.

Limitations

Although this study presents compelling evidence, certain limitations should be acknowledged. The study was observational and conducted in a single center, which may limit generalizability. Ulcer severity was limited to Wagner Grade 1 and 2; future studies could assess outcomes in more advanced ulcers. Additionally, long-term follow-up was not conducted to assess recurrence or complete closure rates.

Conclusion

This study demonstrates that Papain-Urea is significantly more effective than Hydrogen Peroxide in the management of diabetic foot ulcers. Patients treated with Papain-Urea showed greater reduction in ulcer size, faster and more complete slough clearance, and earlier granulation tissue formation compared to those treated with Hydrogen Peroxide. These differences were statistically significant, highlighting the superior wound healing potential of enzymatic debridement.

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Papain-Urea not only facilitates selective removal of necrotic tissue but also preserves viable tissue, creating a favorable environment for healing. Its safety profile, ease of application, and non-invasive nature make it particularly suitable for outpatient care and in patients where surgical debridement is not feasible.

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