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Efficacy of Topical Phenytoin Dressing in Diabetic Ulcer Healing

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ABSTRACT

The study focuses on the efficacy of topical phenytoin dressings in treating diabetic foot ulcers (DFUs). DFUs are a common and severe complication of diabetes, affecting about 15% of diabetic patients in their lifetime. In India, they account for 85% of diabetes-related amputations. These ulcers are challenging to treat due to the complexity of diabetes and its effects on various bodily systems. Standard treatments for DFUs often yield unsatisfactory results, leading to the exploration of alternative therapies, such as phenytoin, an anticonvulsant discovered in 1908. Despite its primary use in managing seizures, phenytoin has demonstrated potential in promoting wound healing by stimulating fibroblast proliferation, collagen deposition, and reducing infection risk. This study, conducted over two years in the Department of Surgery at Dr. B.R.A.M Hospital, Raipur, aimed to evaluate the effectiveness of phenytoin compared to traditional treatments like betadine. Forty patients with diabetic ulcers participated, divided equally between the phenytoin and betadine treatment groups. Results showed that patients treated with phenytoin experienced greater ulcer size reduction and a significant decrease in infection rates compared to those treated with betadine. The study used various statistical analyses, including t-tests and chi-square tests, to compare ulcer healing, infection rates, and hospital stay duration between the two groups. The findings suggest that phenytoin dressings are more effective in promoting wound healing in diabetic ulcers than betadine. This is supported by significant reductions in ulcer size, improved microbial clearance, and shorter hospital stays in the phenytoin group. However, the study acknowledges the need for larger-scale, multi-center trials to confirm these results and optimize treatment protocols for diabetic foot ulcers.

INTRODUCTION

Diabetic foot ulcers (DFUs) pose a significant challenge in the management of diabetes mellitus, affecting around 15% of individuals with diabetes throughout their lives. In India, DFUs account for approximately 85% of amputations related to diabetes, underscoring the serious health implications associated with this condition. The management of DFUs is complex and multifaceted, requiring a comprehensive approach that involves various body systems, including neurological, circulatory, skeletal, immunological, and integumentary systems, to effectively combat the metabolic dysregulation contributing to their development [1,2,3].

The burden of DFUs extends beyond individual patients, placing considerable strain on healthcare Systems due to prolonged morbidity and potential disability. Traditional treatments for chronic leg ulcers, including DFUs, often fail to produce satisfactory healing outcomes, leading to increased interest in alternative therapeutic options. One promising approach is the use of phenytoin, an anticonvulsant medication developed in 1908. While primarily recognized for its anticonvulsant properties, phenytoin has shown unexpected benefits in promoting wound healing, particularly for DFUs [4,5,6].

The discovery of gingival hyperplasia as a side effect of phenytoin in 1939 led researchers to investigate its wound healing potential. Studies suggest that phenytoin promotes ulcer healing by stimulating fibroblast proliferation, collagen deposition, neovascularization, and granulation tissue formation, along with antibacterial properties that reduce infection risk. However, its use in managing diabetic foot ulcers (DFUs) remains limited due to inconsistent research results and methodological issues. Despite this, encouraging outcomes in smaller studies indicate a need for

further investigation into phenytoin's efficacy [7,8].

Diabetic foot ulcers (DFUs) develop due to a combination of intrinsic and extrinsic factors, including growth factor deficiencies and reduced cellular activity. While external factors are easily recognizable, intrinsic deficiencies significantly hinder wound healing, necessitating targeted therapies when standard treatments are ineffective. Managing DFUs typically includes offloading pressure with specialized footwear, maintaining a moist environment with suitable dressings, performing debridement when necessary, and ensuring optimal blood glucose control. Various topical agents have been studied, with effectiveness dependent on their pharmacological properties and formulation. Topical phenytoin, available as a spray, shows promise for enhancing wound healing, although high solvent concentrations may cause side effects like skin dryness. Understanding DFUs requires knowledge of the normal healing process and skin anatomy, which consists of the epidermis, dermis, and subcutaneous tissue, each serving vital protective and functional roles in maintaining skin integrity and facilitating healing [9,10,11].

DFUs typically develop on the feet, particularly on the plantar surface, heels, and other areas prone to pressure. These ulcers often present as chronic, deep, circular lesions with well-defined edges, sometimes penetrating through the epidermis and dermis to involve muscles and bones, leading to complications such as osteomyelitis. Peripheral neuropathy, a common complication in diabetes, reduces pain sensitivity, delaying injury detection and contributing to ulcer formation. Additionally, peripheral vascular dysfunction restricts blood flow, limiting the delivery of oxygen and nutrients essential for effective healing. Ulcers may also exhibit thickened skin, known as callus, around the wound site [12,13,14].

Diabetes negatively impacts the skin and peripheral tissues through several mechanisms. Chronic hyperglycemia leads to the accumulation of advanced glycation end-products (AGEs), which impair the structural integrity of skin proteins, reducing flexibility and strength. Microvascular complications disrupt blood flow, resulting in ischemia and insufficient oxygen and nutrient delivery to tissues. Neuropathy diminishes sensory perception, increasing the likelihood of unnoticed injuries and ulceration. Furthermore, diabetes can weaken the immune system, making the skin more susceptible to infections and hindering the healing process. Collectively, these factors contribute to the prevalence and chronicity of diabetic ulcers, complicating their management [15,16,17].

Wound healing is a complex process that occurs in four stages: hemostasis, inflammation, proliferation, and remodeling. Immediately following an injury, hemostasis involves blood vessel constriction and clot formation to prevent bleeding. The inflammatory phase recruits immune cells like neutrophils and macrophages to clear debris and fight infection. During the proliferation phase, new tissue forms through angiogenesis and fibroblast activity, resulting in granulation tissue. The final remodeling phase reorganizes and strengthens collagen fibers, restoring tissue integrity over weeks to months. Effective wound healing relies on a sufficient blood supply for delivering nutrients and oxygen; ischemia, commonly seen in diabetes, impedes this process and increases infection risk. Nutritional status also plays a vital role, as adequate protein and vitamins are necessary for healing. Impaired immune function due to diabetes complicates infection management and prolongs inflammation, contributing to delayed healing. Phenytoin, originally developed as an anti-epileptic drug, has shown promise in enhancing wound healing by promoting fibroblast proliferation and collagen synthesis while improving blood flow. Topical phenytoin formulations have demonstrated effectiveness in diabetic ulcers, but challenges like skin irritation from high solvent concentrations remain. Further research is essential to optimize its application and improve patient outcomes in managing diabetic foot ulcers [18,19,20,21].

The study aims to assess the efficacy of topical phenytoin dressings in promoting the healing of diabetic ulcers. Specifically, it will measure the rate of ulcer size reduction, analyze culture and sensitivity patterns in ulcers treated with phenytoin, and evaluate the impact of this treatment on the duration of hospitalization for diabetic ulcer patients.

MATERIAL AND METHODS

This observational analytical study was conducted at the Department of Surgery, Dr. B.R.A.M Hospital, Raipur (C.G.). for 2 years with 1 year of data collection. Ethical approval has been obtained from the Ethical Approval Committee of Dr. B.R.A.M Hospital, Raipur (C.G.) with a diagnosis of diabetic ulcer.

Study Population:

This observational study included patients aged over 18 years, of both sexes, admitted to the Surgery Department at Dr. B.R.A.M Hospital, Raipur (C.G.), with a diagnosis of diabetic foot ulcers. Excluded were patients unwilling to participate, those with chronic ulcers of other etiology, comorbidities affecting healing, osteomyelitis, and allergies to phenytoin.

Data Analysis:

Statistical analysis was performed to compare the efficacy of topical phenytoin dressings against traditional wound treatments for diabetic ulcers. Continuous variables, including ulcer size reduction and hospital stay duration, were assessed using the Student's t-test. Categorical variables, such as granulation tissue presence and infection rates, were analyzed with the chi-square test. A p-value of less than 0.05 indicated statistical significance, and statistical software was utilized to ensure robust and reliable results.

RESULT

The study compares the age and gender distribution of 40 diabetic ulcer patients treated with either phenytoin or betadine, with 20 patients in each group. In terms of age, both groups have similar distributions: the phenytoin group has patients across the 19-79 age range, while the betadine group has no patients in the youngest (19-29) or oldest (60-79) age groups. The majority of patients in both groups are aged 40-59 years. A p-value of 0.998 indicates no significant difference in age distribution between the groups. Similarly, gender distribution is nearly identical, with the phenytoin group having 15 males and 5 females, and the betadine group having 14 males and 6 females. The p-value of 0.979 shows no significant gender differences between the two groups. Both age and gender demographics are comparable across the treatments.

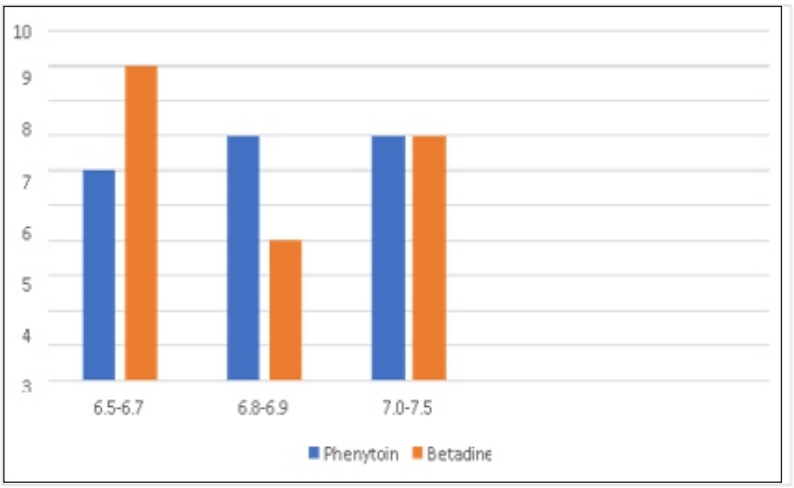

Figure 1: Patient Distribution as Per HBA1c Levels

The figure illustrates the distribution of patients across various HbA1c levels, categorized by their treatment with either Phenytoin (n = 20) or Betadine (n = 20). It shows how patients are distributed within each HbA1c range for both treatment groups, highlighting differences in allocation. Despite these variations, the p-value of 0.899 indicates no statistically significant difference between the two groups, suggesting that the choice of Phenytoin or Betadine does not significantly affect HbA1c levels in this study.

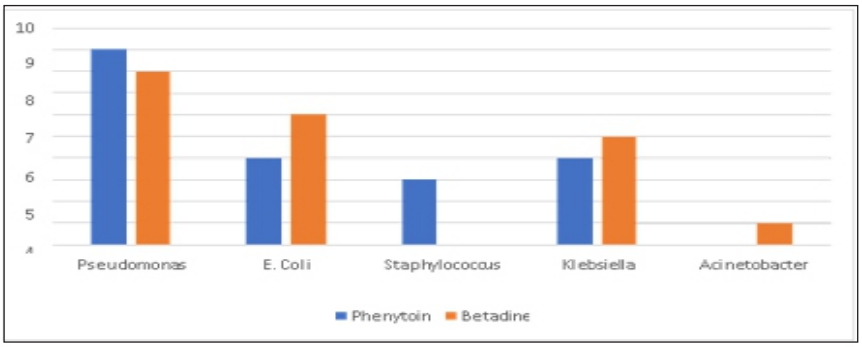

Figure 2: Patient Distribution as Per Culture Sensitivity Before Treatment

The figure presents culture sensitivity data for patients prior to treatment with either Phenytoin or Betadine, focusing on bacterial strains such as Pseudomonas, E. Coli, Staphylococcus Aureus, Klebsiella, and Acinetobacter. Both treatment groups include 20 patients each, with the prevalen-nce of each bacterial strain outlined for both groups. The p-values consistently exceed the threshold for statistical significance, indicating no significant difference in the distribution of these bacterial cultures between patients treated with Phenytoin or Betadine.

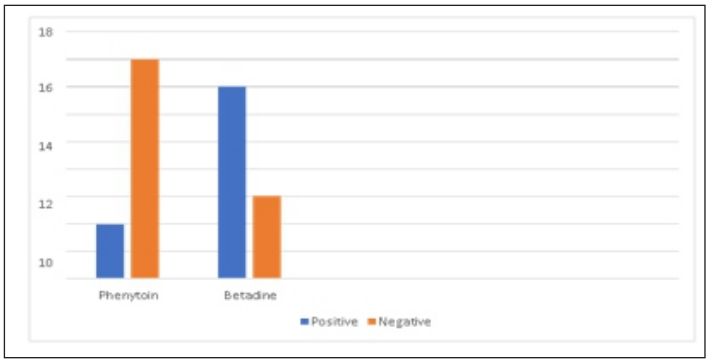

Figure 3: Patient Distribution as Per Culture Sensitivity After Treatment

The figure illustrates patient distribution based on culture sensitivity data after treatment with Phenytoin or Betadine. A significant difference is observed, with 14 patients testing positive for bacterial cultures in the Betadine group compared to only 4 in the Phenytoin group. This difference is statistically significant, as reflected by a p-value of 0.002. Additionally, 16 patients in the Phenytoin group tested negative for culture sensitivity post-treatment, while only 6 patients in the Betadine group showed negative results. This suggests Phenytoin may be more effective in reducing positive bacterial cultures than Betadine.

Table 1: Patient Distribution as Per the Number of Days Hospitalized

No. of Days Hospitalized	Phenytoin (N = 20)	Betadine (N =20)	P Value
20-29 days	14	14	0.125
30-39 days	5	6	
>40 days	1	0	

The table displays patient distribution based on hospitalization duration, divided into three intervals: 20-29 days, 30-39 days, and over 40 days. There is no significant difference between the Phenytoin and Betadine groups, with most patients (14 in each group) hospitalized for 20-29 days. Additionally, 5 patients in the Phenytoin group and 6 in the Betadine group stayed 30-39 days. Notably, one patient in the Phenytoin group had an extended hospital stay of 66 days.

Table 2: Patient Distribution as Per Initial Surface Area of Diabetic Ulcer Before Treatment

Surface Area (cm^2)	Phenytoin(N=20)	Betadine(N=20)	P Value
0-49	8	11	0.911
50-99	5	3	
100-149	2	3	
> 150 cm^2	5	3	

The table shows the initial surface area of diabetic ulcers before treatment, divided into four ranges. In the Phenytoin group, most patients had ulcers under 100 cm^2, while in the Betadine group, 11 patients had ulcers in the 0-49 cm^2 range.

Table 3: Patient Distribution as Per Final Surface Area of Diabetic Ulcer After Treatment

Surface Area (cm^2)	Phenytoin (N=20)	Betadine (N=20)	P Value
0-49 cm^2	15	14	0.001
50-99 cm^2	3	3	
100-149 cm^2	2	0	
> 150 cm^2	0	3	

The table highlights the distribution of diabetic ulcers by final surface area after therapy, showing significant differences between the Phenytoin and Betadine groups. Notably, 15 patients in the Phenytoin group and 14 in the Betadine group had ulcers in the 0-49 cm^2 range. However, three patients in the Betadine group had ulcers larger than 150 cm^2, while none in the Phenytoin group did. This suggests that Phenytoin may be more effective in reducing the size of larger diabetic ulcers compared to Betadine.

Table 4: Patient Distribution as Per Controlled Area mm²

Controlled Area (mm^2)	Phenytoin (N=20)	Betadine (N=20)	P Value
0-499 mm^2	15	4	0.001
500-999 mm^2	3	11	
1000-1500 mm^2	2	5	

The table shows patient distribution by controlled ulcer area in the Phenytoin and Betadine groups. In the Phenytoin group, 75% of patients had ulcers in the 0-499 mm² twin. range, compared to 20% in the Betadine group. A p-value of 0.001 indicates a significant difference, suggesting Phenytoin is more effective in reducing ulcer size, particularly in smaller ulcers.

Table 5: Patient Distribution as Per Area of Reduction in %

Area of Reduction (%)	Phenytoin (N=20)	Betadine (N= 20)	P Value
0-25%	2	14	0.001
26-50%	12	4	
>50%	6	2	

The table highlights a notable difference in ulcer reduction between the Phenytoin and Betadine groups. In the 0-25% reduction range, 70% of Betadine patients experienced minimal improvement, compared to just 10% of Phenytoin patients. Conversely, 60% of Phenytoin patients achieved a 26-50% reduction, compared to 20% in the Betadine group. Additionally, 30% of Phenytoin patients saw more than 50% improvement, while only 10% in the Betadine group did. This suggests Phenytoin may be more effective in promoting greater ulcer reduction.

DISCUSSION

This prospective study was conducted on patients diagnosed with diabetic ulcers and admitted to the Department of Surgery at Dr. B.R.A.M Hospital in Raipur, Chhattisgarh. The objective was to compare the efficacy of phenytoin versus betadine in treating diabetic ulcers, ultimately noting that phenytoin is more effective than betadine in managing these conditions [22].

In terms of age and gender distribution, the phenytoin group (n = 20) consisted of 50% of patients aged between 50 and 59 years, while 25% were in the 40 to 49 age range. In the betadine group (n = 20), 65% of patients fell within the 50-59 age group, and 35% were in the 40-49 age range. This demographic trend indicates a predominance of middle-aged patients in both treatment groups [23].

In terms of gender distribution, 75% of patients treated with phenytoin were male, while 25% were female. In the betadine group, 70% were male and 30% were female. This indicates a higher prevalence of male patients in both treatment groups, with the current study's findings reflecting similar trends observed in previous research. In the phenytoin group, a majority of 64% were male, further supporting the gender distribution results in this study [24].

The study also measured HbA1c levels among the patients. In the phenytoin group, the HbA1c levels were primarily in the ranges of 6.8-6.9 and 7.0-7.5, each accounting for 35% of the patients. In contrast, 45% of patients in the betadine group had HbA1c levels ranging from 6.5-6.7. These findings suggest a notable difference in glycemic control between the two groups.

Regarding culture sensitivity, 45% of patients treated with phenytoin had positive cultures for Pseudomonas, while 20% tested positive for Staphylococcus aureus. Conversely, 40% of patients in the betadine group showed positive cultures for Pseudomonas, and 30% had positive cultures for E. coli before treatment. After treatment, all patients in the phenytoin group showed negative culture results, while 80% in the betadine group remained positive [25].

These findings indicate that a significant proportion of patients treated with phenytoin showed negative culture results, suggesting its effectiveness in reducing microbial burden. In this study, 84% of patients treated with phenytoin had negative cultures, while 92% of those treated with betadine achieved similar outcomes. However, contrasting results were noted in another study, where 52% of patients still had positive cultures after phenytoin treatment. Overall, these results imply that phenytoin may be more effective in facilitating wound healing, particularly for diabetic ulcers [26].

The study observed positive outcomes with phenytoin treatment, including shorter hospital stays of fewer than 30 days. During their hospital stays, 75% of the phenytoin group and 70% of the betadine group experienced excellent ulcer healing, achieving wound area reductions to less than 50 cm^2. Additionally, phenytoin dressings were shown to significantly reduce wound size, promoting granulation tissue production more effectively than traditional dressings [27].

The mean percentage reduction in ulcer surface area was significantly greater in the phenytoin group, with a mean reduction of 61.46% compared to 57.59% in the betadine group. This difference highlights phenytoin's potential as an effective treatment option for diabetic foot ulcers. Moreover, other research has indicated similar findings, with phenytoin-treated patients showing significant reductions in wound area compared to those treated with betadine, further validating the results of this study.

This study highlights the superiority of phenytoin over betadine in treating diabetic ulcers, evidenced by better outcomes in various metrics, including age distribution, gender, HbA1c levels, microbial cultures, hospital stays, and wound healing percentages. Continued exploration and clinical application of phenytoin may improve management strategies for patients suffering from diabetic foot ulcers [28].

CONCLUSION

This study evaluates the effectiveness of phenytoin versus betadine in treating diabetic foot ulcers, indicating that phenytoin may be superior in reducing ulcer size and enhancing wound healing. Patients treated with phenytoin experienced significant reductions in ulcer area, reduced microbial load, and fewer post-operative complications. However, the study's limitations-such as small sample size, short follow-up, and single-center design-necessitate larger, multi-center trials for further validation. Overall, the findings support phenytoin as a promising therapeutic option, warranting additional research.

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