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Efficacy of Topical Phenytoin vs Normal Saline Dressing in Management of Diabetic Ulcers

Jawad Azeem, Umer Rathore, Naveed Ahmad, Bilal Nagra, Arslan Hamid, Waleed Umer

ABSTRACT

Objective: To compare the outcomes of topical phenytoin vs normal saline (NS) dressings to treat diabetic foot ulcer (DFU).

Study Design and Setting: Quasi-experimental study conducted in the Department of General Surgery, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from January 2024 to June 2024. The study was carried out under standardized clinical protocols, and all patients were managed in a uniform hospital environment to minimize variability in treatment practices and ensure consistency in outcome assessment.

Methodology: One hundred and ten (110) patients were segregated into two equal groups; (1) Phenytoin dressings group, (2) NS dressings group. Outcomes of these groups were compared. A statistical package for Social Sciences (SPSS) version 23 was utilized to assess the results. Data regarding demographic variables, clinical presentation, and wound characteristics were collected systematically using a structured proforma, and all patients were followed regularly to monitor progress and response to treatment.

Results: One hundred and ten (n=110) patients were equally segregated into two groups. In the Phenytoin group, 50(90.90%) patients had improvement in wound (reduction in Wagner Grade) and in NS group 40(72.72%) patients had wound improvement (p-value 0.01). In the Phenytoin group, 2(3.63%) patients developed local complications and in NS group 7(12.72%) patients had local complications (p-value 0.08). In the Phenytoin group, 46(83.63%) patients had complete healing and in NS group 37(67.27%) patients had complete healing (p-value 0.04). Additionally, patient satisfaction was higher in the Phenytoin group, reflecting better overall acceptance of the treatment modality.

Conclusion: Phenytoin dressings were found to be more effective as compared to NS dressings in promoting healing in DFU, with improved clinical outcomes and higher patient satisfaction.

Key Words: Diabetic foot ulcers, Healing, Normal saline dressings, Outcomes, Phenytoin dressings.

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INTRODUCTION

Diabetes Mellitus (DM) is common chronic metabolic disorder which is characterized by abnormally increased blood sugar levels in human body.[1] It is one of the most common chronic diseases with approximately 10.5% of the global population getting affected with DM as per 2021 global data.[2] A research study conducted in our country (Pakistan) documented the prevalence of DM to be 12.16%.[3] It is a common chronic disease which affects multiple organs and systems in the human body with drastic negative consequences and complications. One of the most fearful complications of DM, which is commonly faced by surgeons all around the world in their routine clinical practice, is diabetic foot ulcer (DFU). The lifetime risk of developing DFU in diabetic patients is 19%–34%.[4] Pathophysiology of DFU is multifactorial and it may occur due to neuropathy, angiopathy, osteoarthropathy and/or reduced immunity against infections.[5] DFU has increased risk of developing wound infection which at times becomes difficult to treat and can lead to the formation of gangrene and ultimately results in amputation if left untreated. Hence, this

complication is significantly associated with increased suffering of patients and also adds to the financial burden on both patients and the healthcare system of the country.

The management of DFU requires combined efforts of a multidisciplinary team and its outcome depends upon the severity and grade of the ulcer. Wegner classification is a common classification system used worldwide to label the severity of a DFU.[6] Superficial and deep foot ulcers (Wegner grade I/II) have traditionally been managed using Normal Saline (NS) soaked serial dressings to keep the ulcer clean and promote the growth of healthy granulation tissue.[7] However, at times this conventional approach does not deliver satisfactory results. Wound healing with this method may be slow or incomplete, and patients may develop local or systemic complications despite good compliance to treatment. Therefore, surgeons have been exploring various modified treatment approaches to achieve better and more favorable outcomes. The goal of these newer modalities is to promote early healing and reduce disease progression and complications. Using phenytoin dressing to treat DFU is a relatively novel method gaining attention. As compared to conventional NS dressings, topical phenytoin is proposed to provide improved outcomes and reduced complication rates.

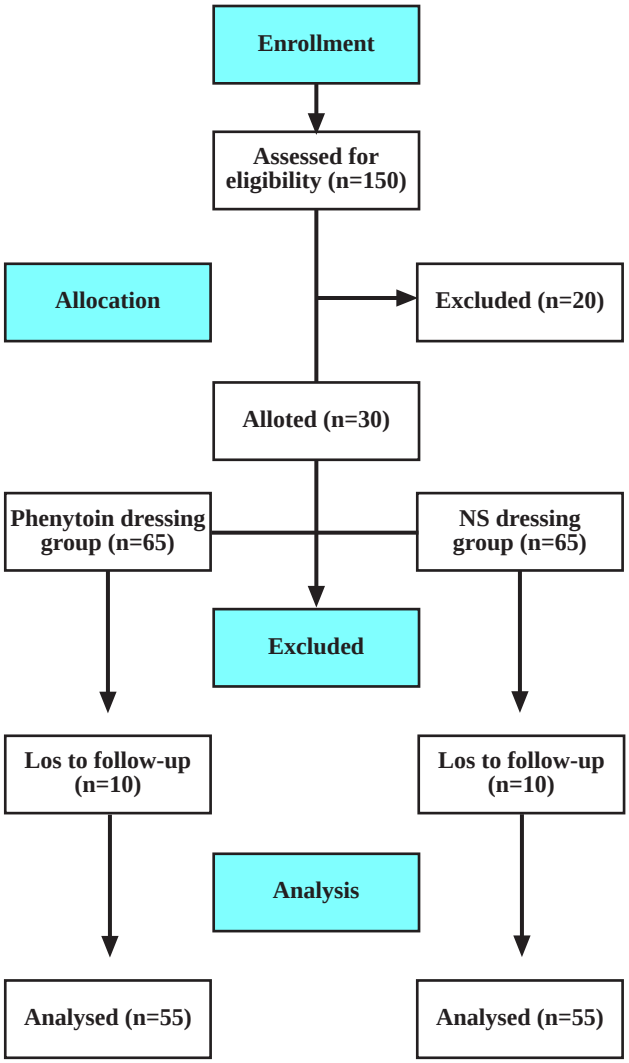
A study conducted in California documented that topical phenytoin dressings significantly enhanced wound healing and provided better results.[8] Another prospective comparative study conducted in India demonstrated superior outcomes with phenytoin dressings compared to NS dressings in terms of earlier and improved healing of DFU.[9] In a systematic review consisting of 23 studies, it was concluded that although topical phenytoin appears to enhance DFU healing, the available evidence is still insufficient to support its routine use, and further large-scale studies are required.[10]

At present, surgeons in various parts of our country are practicing different techniques to achieve early and better healing of DFU and reduce complications. These practices are primarily based on personal preferences and departmental protocols rather than strong evidence-based guidelines. The data on this subject within the local population is still limited. Therefore, a comparative study evaluating conventional NS dressings versus topical phenytoin dressings is essential to establish the superiority of one technique over the other based on solid evidence. Such data will aid surgeons in selecting optimal treatment strategies and improving overall patient outcomes. Additionally, it may contribute towards the development of standardized national guidelines for DFU management and promote cost-effective, evidence-based clinical practice in resource-limited healthcare settings.

METHODOLOGY

A quasi-experimental study was done at the Department of General Surgery, Pak Emirates Military Hospital, Rawalpindi, over a 6-month period (January 2024 to June 2024). The ethical review board's approval (ERC/78/24) was acquired. The WHO Sample Size calculator was used to calculate the sample size, using following parameters: 90% power of the test, 5% level of significance, 63% wound healing after phenytoin dressing and 33% after NS dressing.[11] Based on these, the total sample size of 130 patients was calculated. However, out of these 20 patients, loss to follow-up, resulting in final sample size of 110 patients (55 patients in each group). This information is displayed below in Figure I: -

Figure 1: Patient flow diagram (n = 110)



We included male and female diabetic patients into our study, aged between 20–60 years, who remained compliant with anti-glycemic medications and presented to the Surgical Out Patient Department (OPD) or Emergency Department of our hospital with DFU (Wegner Grade I and II). We ensured that all participants had a clear diagnosis of diabetes mellitus and were on regular follow-up prior to presentation, in order to maintain uniformity in baseline characteristics. In addition, detailed clinical history including duration of

diabetes and prior ulcer episodes was documented for better baseline assessment.

We excluded patients who fulfilled any of the following criteria: Wegner Grade of 3 or more, autoimmune disease, malignancy, significantly malnourished (evaluated by anthropometric assessment), absent lower limb distal pulses, monophasic flow on doppler ultrasound. Patients with acute abscess/sepsis and those who didn't provide consent were also eliminated from the research. This was done to minimize confounding factors that could independently affect wound healing and skew the results of the study. Careful screening ensured inclusion of a relatively homogenous study population.

Participants' selection was from "non-probability consecutive sampling". Objectives of the study were explained to the participants in detail and informed written consent was obtained before inclusion in the study. Age and gender of the patients were recorded in a predesigned proforma. Obesity status (BMI =30) of all patients was also assessed and documented in data proforma. Distal neuro-vascular assessment of lower limbs was also done in all patients. Pedal blood flow was assessed clinically as well as with adjunct investigations. Doppler ultrasound was used to check the flow in lower limb vessels. Ankle-brachial index (ABI) was also checked if there was suspicion of peripheral arterial disease (PAD). Neurological assessment was done by checking proprioception, vibration and fine touch sensations to assess the features of diabetic neuropathy. The presence of foot infection was assessed by checking clinical parameters including erythema, abnormal discharge, crepitus, and foul smell. DFU area was measured in cm^2 using a standardized method and Wegner classification was used to record the grade of the ulcer. For patients with suspicion of osteomyelitis or underlying bone abscess, X-ray was done for confirmation, while MRI was advised for equivocal cases to improve diagnostic accuracy. We also recorded important laboratory parameters including hemoglobin (Hb) and HBA1C levels of all participants from our hospital laboratory. Diabetologist and podiatric teams were also involved in management to optimize glycemic control and provide comprehensive foot care, ensuring a multidisciplinary approach for all patients.

Participants were divided equally into Phenytoin dressing group and NS dressing group by using computer-generated random allocation lists. In Phenytoin dressing group, 100 mg vial of phenytoin was dissolved in 5 mL of sterile 0.9% NaCl and this suspension was used to soak sterile gauze. This soaked gauze was then applied directly over the wound after thorough cleaning and covered with another dry sterile gauze; dressing was changed twice daily. In the NS dressing group, 0.9% NS-soaked sterile gauze was used and changed twice daily. Patients and attendants were trained to continue wound care themselves if professional assistance was not available, and written instructions were also provided to improve compliance and uniformity of technique.

Weekly follow-up visits were planned for 4 weeks, during which outcomes were assessed and compared between groups. During each visit, wound size, granulation tissue formation, and signs of infection were reassessed systematically. Results were evaluated in terms of wound improvement defined as reduction in ulcer grade as per Wegner classification. Appearance of any local complication was also recorded. Patients were further compared in terms of complete ulcer healing and overall satisfaction with the treatment modality, ensuring both clinical and patient-centered outcomes were adequately addressed.

The Statistical Package for Social Sciences (SPSS) version 23 was utilized to evaluate the final results. Categorical variables (gender, obesity, wound improvement, local complication, complete healing and patient satisfaction) were represented as frequency and percentage, and the Chi-Square test was used for comparison. The Shapiro-Wilk test assessed normality of quantitative data (age, Hb, HBA1C). Mann-Whitney U test was applied for non-normally distributed data, while independent sample t-test was used for normally distributed variables. A p-value of <0.05 was considered statistically significant. Additionally, data validation and cleaning procedures were performed prior to analysis to ensure accuracy, and results were interpreted with consideration of potential confounding factors and study limitations.

RESULTS

Our participant's age was 51.04±5.23 years (mean ± SD). 99(90%) of the participants were male and 11(10%) were female. These parameters are shown below: - Quantitative values are expressed as median (interquartile range: IQR). Mann-Whitney U test was applied. Hb(g/dL) of participants was 11.37±1.62 (mean ± SD). HBA1C (%) of patients was 9.70± 1.07. Table II shows this comparison between the participants: In Phenytoin group, 50(90.90%) patients had improvement in wound (reduction in Wagner Grade) and in NS group 40(72.72%) patients had wound improvement (p-value 0.01). In Phenytoin group, 2(3.63%) patients developed local complications and in NS group 7(12.72%) patients had local complications (p-value 0.08). In Phenytoin group, 46(83.63%) patients had complete healing and in NS group 37(67.27%) patients had complete healing (p-value 0.04). 46(83.63%) patients were over-all satisfied with the treatment in Phenytoin group and 37(67.27%) patients were over-all satisfied with the treatment in NS group (p-value 0.04). These results are demonstrated below:

DISCUSSION

In our study, age of the participants was 51.04±5.23 years (mean ± SD). Yao et al, in their study mentioned that DFU was found most commonly in age group 50-59 years, which matches the results of our study.[12] Majority of our participants (90%) were male and only 10% were female. As our research

was done in a military hospital and majority of the entitled patients in military are of male gender, so this fact may have contributed to the gender bias. Iacopi et al, found that male population is affected more commonly with DFU as compared to women (73% male vs 27% female), which matches with the results of our study.[13] 9.09% of our participants were obese with BMI =30. 5.10% of the general population of Pakistan was found to be obese in a research done by Asif et al.[14] This difference may be due to the fact that their research was done on general population of Pakistan, however we added only diabetic patients in our work. Hb(g/dL) of our participants was 11.37±1.62 (mean ± SD). HBA1C of our patients was 9.70±1.07 indicating poorly controlled DM in our patients, which may have contributed to the risk of formation of DFU and development of other complications and may have resulted in the poor heling of the wounds. We found that DFU that was treated with phenytoin dressings showed better improvement in wound as compared to conventional NS dressings. We also noted that Phenytoin dressing resulted in better results as compared to NS dressing in terms of complete healing of the DFU by the end of 4 weeks period. In our study the incidence of local wound complications was reduced with Phenytoin dressing in comparison to conventional NS dressings, however the difference between them was not statistically significant. Shaw et al conducted a similar study and found no difference in DFU healing with phenytoin dressing as compared to NS dressing.[15] These findings don't align with the results that we documented in our study. Ahmad et al conducted a similar study upon our local population in Rawalpindi, Pakistan and found that the topical phenytoin enhances and promotes the healing of DFU as compared to conventional saline soaked dressings which matches the results of our study.[16] Patil et al in a prospective study documented that Phenytoin dressing reduces the formation of slough and discharge from DFU and significantly reduces length of stay in hospital.[17] Bharathi Mohan et al, Adana et al and C. et al conducted similar researches and supported the use of Phenytoin dressings to promote healing in DFU, matching the results of our research. [18,19,20]

DFU is one of the most serious complications of long-standing DM encountered by surgeons in their routine clinical practice. DM results in angiopathy, neuropathy and increased susceptibility of infection which play their part in the development of DFU. If not properly managed, DFU may progress to develop local and systemic complications. Patients

Table1: Comparison of demographic features (n = 110)

Parameters	Study Groups				P-value
	Phenytoin Group (n=55)		NS Group (n=55)		
Age(years), median (interquartile range, IQR)	55 (IQR: 7.0)		48 (IQR:5.0)		<0.001
Gender, (%)	Male	50(90.90%)	Male	49(89.09%)	0.75
	Female	05(9.09%)	Female	6(10.09%)	
Obesity, %	4(7.27%)		5(9.09%)		0.72

Qualitative values are expressed as frequency (percentage), and chi-square test was applied

Table 2: Comparison of laboratory parameters (n = 110)

Parameters	Phenytoin Group (n=55)	NS Group (n=55)	p-value
Hb(g/dL), median (interquartile range, IQR)	11(IQR:2.00)	12(3.10%)	0.12
HBA1C(%), median (interquartile range, IQR)	09(IQR:1.10)	9.80(1.60%)	<0.001

Quantitative values are expressed as median (interquartile range). Mann-Whitney U test was applied

Table 3: Comparison of outcomes (n = 110)

Outcome	Phenytoin Group (n=55)	NS Group (n=55)	p-value
Wound improvement, n(%)	50(90.90%)	40(72.72%)	0.01
Complication, n(%)	2(3.63%)	7(12.72%)	0.08
Complete healing, n(%)	46(83.63%)	37(67.27%)	0.04
Satisfaction, n(%)	46(83.63%)	37(67.27%)	0.04

Qualitative values are expressed as frequency (percentage), and chi-square test was applied.

may develop dry or wet gangrene and can end up in limb amputation or may also develop life threatening sepsis.[21] All these complications drastically affect the health and quality of life of patients and also enhance the financial burden on the patients and health care systems. But with appropriate care and treatment, satisfactory healing of DFU can be achieved and these complications can be prevented. Surgeons have been trying and testing various treatment methods to promote effective healing of DFU. Topical phenytoin dressing is one of these new modified techniques which is a simple, cheap and easily available treatment of DFU. It helps in achieving early and enhanced healing as proven by the results of our study. As compared to the traditional NS dressings, topical phenytoin dressings have provided better wound healing. The phenytoin dressings also deliver better patient satisfaction as compared to the NS dressings. Phenytoin is believed to have enhanced wound healing properties as it increases the proliferation of fibroblasts and enhances the growth of healthy granulation tissue in chronic ulcers. Due to its low cost and easy availability, it is a good choice to effectively treat DFU in underdeveloped and developing nations, where patients may not have easy access to expensive advanced wound care facilities and health care systems, and health insurance may not cover treatment expenses. Moreover, we also found in our study that phenytoin dressings have resulted in reduced incidence of local wound complications as compared to conventional dressings. Although this difference was not statistically significant in our study, we suggest that further large-scale studies need to be conducted with larger sample sizes, longer follow-up, and more diverse populations to support the results of our study.

In addition, incorporation of standardized wound assessment tools and objective healing parameters in future research may provide more robust evidence regarding the efficacy of phenytoin dressings. Patient education regarding glycemic control, foot hygiene, and early reporting of ulcers is equally important to optimize outcomes. Multidisciplinary management involving surgeons, endocrinologists, and wound care specialists can further enhance healing rates and reduce recurrence, thereby improving overall patient prognosis.

Limitations: Single-center and limited follow-up period are the few limitations of our study. Ulcer recurrence and long-term complications were not evaluated. Variations in the demographic features of the participants like age and gender could have impacted the outcomes of the study. Moreover, variation in Hb, HbA1C and control of blood glucose level may have affected the outcomes. The correlation between gender, age, obesity, Hb, HBA1C levels with the treatment outcomes was not established. The research lacks generalizability to the broader community especially to the local non-military civilian female population. Variations in daily wound care could also have affected the outcomes. Additionally, differences in patient compliance, nutritional status, and concurrent comorbidities were not fully accounted for, which may have introduced further bias and influenced healing rates and overall treatment effectiveness across the study population.

CONCLUSION

For treating DFU, topical phenytoin dressings provide better results as compared to NS dressings in terms of enhanced wound healing and overall better patient's satisfaction. Incidence of local wound complications was less with phenytoin dressings; however, this difference was not statistically significant.

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Authors Contribution:
Jawad Azeem: Conception, design, analysis and interpretation of data
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