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A PROSPECTIVE AND COMPARITIVE STUDY ON "IMPACT OF PHENYTOIN DRESSING ON DIABETIC FOOT WOUND HEALING RATE"

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ABSTRACT

Background: Diabetic foot ulcers [DFUs] are a major complication of diabetes mellitus, contributing to significant morbidity and increased risk of lower limb amputation. Poor wound healing in diabetic patients necessitates alternative therapeutic strategies. Phenytoin sodium, originally an anti-epileptic drug, has demonstrated potential in enhancing wound healing. This study evaluates the efficacy of 2% phenytoin sodium solution as a topical dressing for DFUs. **Methods:** A prospective, comparative, cross-sectional study was conducted in a tertiary care hospital with 52 patients randomized into two groups. The test group received 2% phenytoin sodium dressing, while the control group received conventional dressings. Wound healing was monitored through granulation tissue formation, healing rate, and overall wound progression. Safety and adverse effects were documented. Statistical analysis was performed using the chi-square test in SPSS. **Results:** The test group exhibited significantly faster granulation tissue formation compared to the control group [$p < 0.01$]. Phenytoin dressing demonstrated superior wound healing efficacy, with a lower incidence of wound infections and better tissue regeneration. **Conclusion:** Topical application of 2% phenytoin sodium solution enhances wound healing in DFUs by promoting granulation tissue formation and reducing bacterial load. Phenytoin is a cost-

effective and safe alternative for DFU management. Further large-scale studies are required to validate these findings and optimize its clinical application.

KEYWORDS: Phenytoin sodium, Diabetic foot ulcers, Wound healing, Granulation tissue, Topical dressing, Diabetes mellitus.

INTRODUCTION

Diabetes mellitus [DM] is a chronic metabolic disorder characterized by persistent hyperglycemia, leading to various complications, including diabetic foot ulcers [DFUs]. DFUs are among the most serious and frequent complications of diabetes, contributing to substantial morbidity and an increased risk of lower limb amputation. The global prevalence of DFUs is rising due to an increase in diabetes incidence, and it is estimated that every 20 seconds, an amputation occurs globally due to diabetes-related complications.[1] The International Diabetes Federation emphasizes the need for improved strategies to prevent and manage DFUs, given their significant social, medical, and economic burden.[2]

DFUs result from a combination of peripheral neuropathy, microvascular dysfunction, ischemia, and impaired immune response, leading to poor wound healing.[3] Hyperglycemia exacerbates these conditions by inducing oxidative and nitrosative stress, leading to endothelial dysfunction and impaired fibroblast activity.[4] Standard treatment approaches include infection control, debridement, offloading, and advanced wound care therapies. However, there is a need for alternative therapeutic approaches that enhance wound healing and reduce the risk of complications.

Phenytoin, originally an anti-epileptic drug, has gained attention for its wound healing properties. It promotes fibroblast proliferation, collagen deposition, and granulation tissue formation, which are crucial for wound healing.[5] Previous studies have demonstrated that topical phenytoin application accelerates ulcer healing by reducing bacterial load and enhancing tissue regeneration.[6] Despite its promising benefits, further investigation is required to establish its clinical efficacy in DFU treatment.

DIABETIC FOOT ULCERS

Diabetes Mellitus [DM] is a prevalent condition causing diabetic foot ulcers [DFUs], leading to limb amputations for over 1 million people worldwide. DFUs cause significant social, medical, and financial costs, and the International Diabetics Foundation is working to raise awareness. Foot ulcers account for 85% of all amputations in diabetic patients before the condition worsens. Evaluating and updating the global epidemiology of DFUs is crucial to reduce financial burden, improve patient quality of life, and develop prevention and treatment strategies.[2,3]

CAUSES OF DIABETIC FOOT ULCERS:

Diabetes can cause tissue necrosis, ulceration, and gangrene due to neuropathy, microvascular dysfunction, poor glycaemic control, and ischemia. Diabetes can lead to macroangiopathy, which affects coronary and peripheral circulation, and microvascular dysfunction, which increases artery permeability. Hyperglycemia can cause diabetic retinopathy and neuropathy.[4,5]

POOR WOUND HEALING IN DIABETIC PATIENTS

Hyperglycaemia

Hyperglycemia leads to overproduction of superoxide by the mitochondrial electron-transport chain, causing nitrosative stress and the creation of metabolic derivatives like nitro tyrosine and peroxynitrite. These compounds can cause microvascular and macrovascular problems and endothelial damage. Hyperglycemia is associated with blood artery stiffness, decreased tissue oxygenation, and altered blood vessels, making wounds more susceptible to infection. The thickening of the basement membrane in diabetic foot ulcers may also contribute to poor healing.[5,6,7,8]

Diabetes wounds are characterized by increased inflammatory cells, fibroblasts, and apoptosis, which degrade extracellular matrix components, impairing healing. Hypoxic wounds, caused by inadequate oxygen delivery and tissue perfusion, also hinder healing due to the increase in free oxygen radicals, leading to prolonged damage.[8]

Treatment

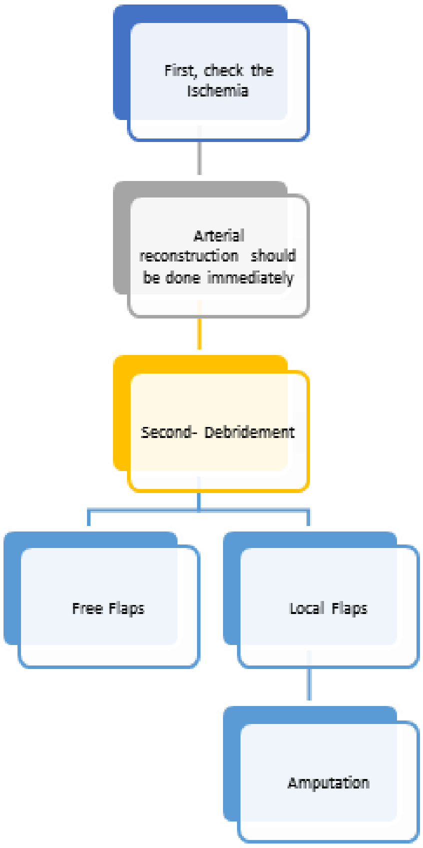


Fig. 1.4: Treatment Protocol.[4]

Debridement is the process of removing foreign bodies and necrotic tissue from a wound to accelerate healing and encourage recovery. It is a crucial part of wound bed preparation for managing chronic wounds. There are various wound debridement procedures, including mechanical, conservative sharp, enzymatic, autolytic, and surgical methods. Enzymatic debridement, such as collagenase-based dressings, has been proposed as a viable option when conventional treatments are impractical. The application of maggots for biodebridement has grown in popularity within the past decade.[9-10]

Offloading is the gold standard treatment for active diabetic foot ulcers [DFU] and avoiding future ulcers on pressure points. Offloading devices can achieve over a 90% decrease in forefoot peak pressure compared to barefoot walking. Shear-reducing insoles can be used to optimize offloading devices. Phenytoin is effective in healing wounds by stimulating fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism, and antibacterial activity. Studies have shown that phenytoin reduces bacterial load, improves granulation tissue formation, and accelerates wound healing.[11,12]

Phenytoin is considered safe, efficient, and cost-effective in treating ulcers of various etiologies due to its ability to speed wound healing, improve granulation tissue, reduce bacterial population at the ulcer surface area, and cause fast and full healing. A 2% Phenytoin sodium suspension is useful for topical application instead of powder or injectable form.[13,14]

Phenytoin, a vulnerable drug, has been reported to have systemic adverse effects, including ataxia, dizziness, difficulty falling or staying asleep, jerky eye movements, loss of coordination, disorientation, slurred speech, headache, taste changes, constipation, growth of unwanted hair, enlarged lips, overgrown gums, pain, severe rash, and skin blisters. There is no evidence of severe systemic effects on topical use of Phenytoin, as it functions locally and does not experience typical systemic metabolic changes. This post examines Phenytoin's potential role in wound pharmacology, suggesting it could be used to stimulate chronic wounds and change wound healing dynamics.[15]

Infections are linked to diabetic sores and ulcers, affecting a growing portion of the senior population. Biofilm, a resistance to standard antimicrobial therapies, is the main obstacle to recovery. Silver nanotechnology has gained attention in therapeutically enhanced healthcare due to its medicinal qualities and broad-spectrum antibacterial effectiveness. This has opened new opportunities for cutting-edge infection management and wound healing methods.[16]

Table 1: Wagner's classification of Diabetic foot ulcer.[17]

Grade	Description
Grade0	Skin intact but bony deformities lead to "foot at risk"
Grade1	Super ficial ulcer
Grade2	Deeper, full thickness extension
Grade3	Deep abscess formation or osteomyelitis
Grade4	Partial Gangrene of forefoot
Grade5	Extensive Gangrene

This study aims to evaluate the efficacy of 2% phenytoin sodium solution as a topical dressing for DFUs compared to standard wound care, assessing its impact on granulation tissue formation and overall wound healing.

METHODOLOGY

This prospective, comparative, cross-sectional study was conducted in a tertiary care hospital, with a total of 52 subjects enrolled based on the Krejcie and Morgan formula. Patients aged 18 years or older with a diagnosis of DFU and Wagner Grade I–III ulcers were included.

Exclusion criteria encompassed patients with non-healing or neuropathic ulcers without diabetes, pregnant or lactating women, and patients with Wagner Grade IV–V ulcers or gangrene. Participants were randomized into two groups: the control group, receiving standard wound care with Megaheal or other conventional dressings, and the test group, receiving wound care with a 2% phenytoin sodium solution. The wound was cleaned using normal saline and betadine before applying the 2% phenytoin sodium solution, prepared by mixing 4 mL of phenytoin sodium in 10 mL of normal saline. A sterile gauze soaked in this solution was applied to the wound before dressing. Dressings were changed regularly, and healing progression was monitored. The primary outcome measures included granulation tissue formation assessed using the Wagner grading system, healing rate comparisons between groups, documentation of safety and adverse reactions, and statistical analysis using SPSS and the chi-square test for significance.

Fig- i

Fig-ii

Fig – iii

Fig - iv

Fig. i, iii, iv: Diabetic Foot ulcer healing progress in Subjects having treated with 2%Phenytoin dressing.

Fig. ii: Diabetic Foot ulcer healing progress in subjects having treated with conventional drssings.

RESULTS

Thought out the course of study 28 subjects met inclusion and exclusion criteria. The enrolled subjects informed consent was taken and randomized into control and standard groups. The control group subject's wounds are dressed with conventional treatment options like megaheal, urea etc. The standard group subjects wound were dressed with 2% phenytoin sodium.

Age group of 40-50 years are more predominant in the study population with 35.7%.

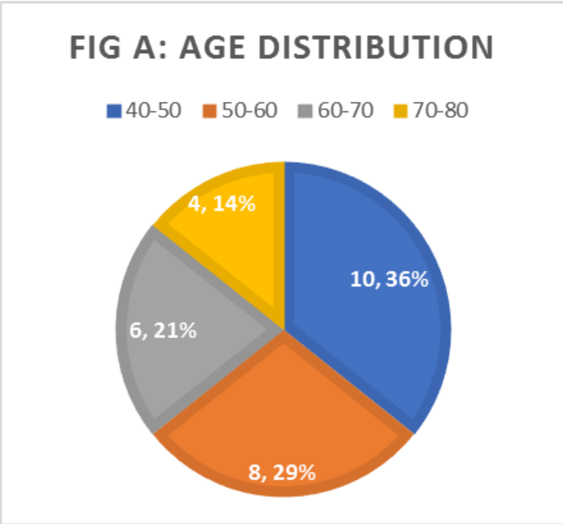


FIG A: AGE DISTRIBUTION
40-50
50-60
60-70
70-80
10, 36%
8, 29%
6, 21%
4, 14%

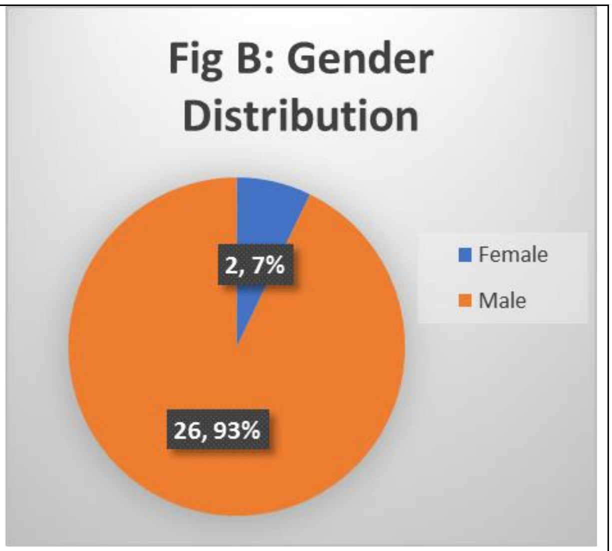


Fig B: Gender Distribution
Female
Male
2, 7%
26, 93%

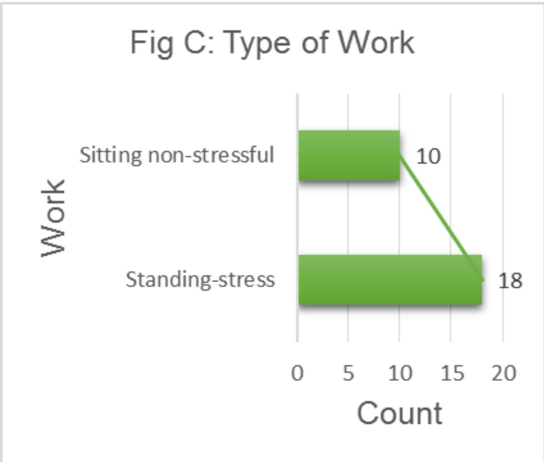


Fig C: Type of Work
Work
Sitting non-stressful
Standing-stress
10
18
0
5
10
15
20
Count

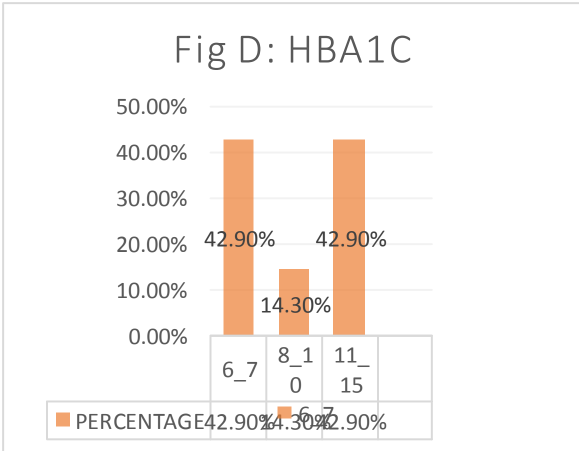


Fig D: HBA1C
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
42.90%
14.30%
42.90%
6_7
8_10
11_15
PERCENTAGE42.90%14.30%42.90%

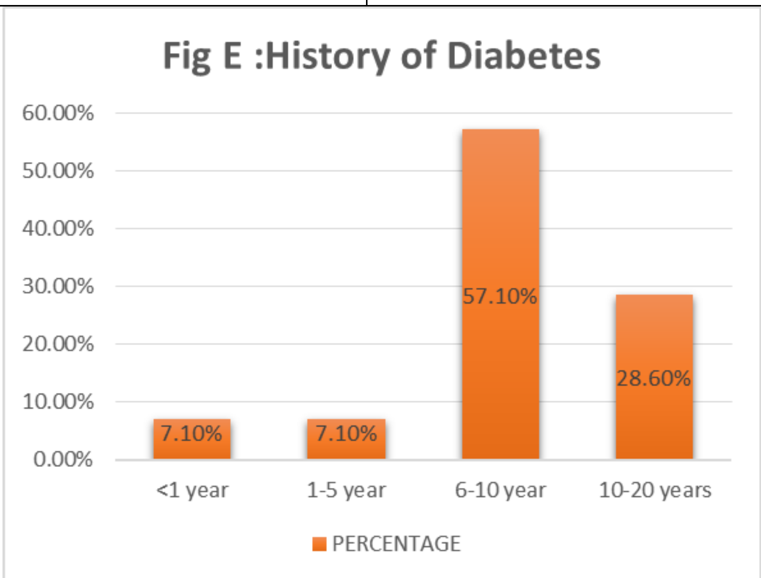


Fig E :History of Diabetes
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
7.10%
7.10%
57.10%
28.60%
<1 year
1-5 year
6-10 year
10-20 years
PERCENTAGE

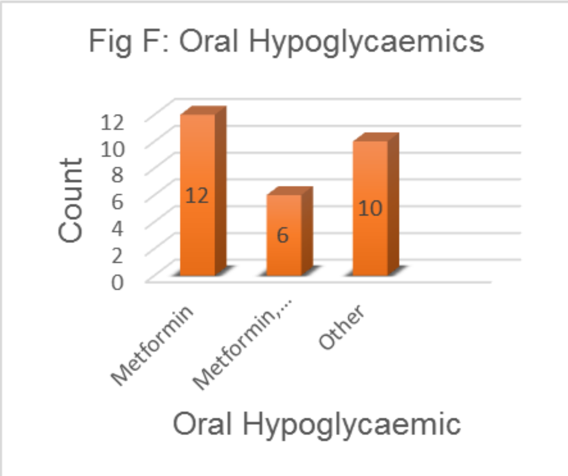


Fig F: Oral Hypoglycaemics

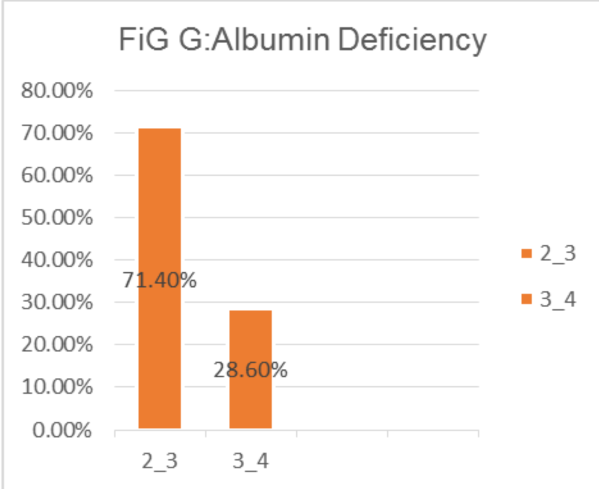


FiG G:Albumin Deficiency

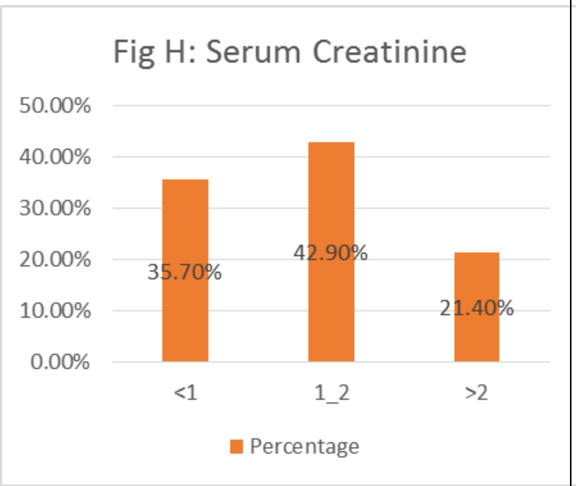
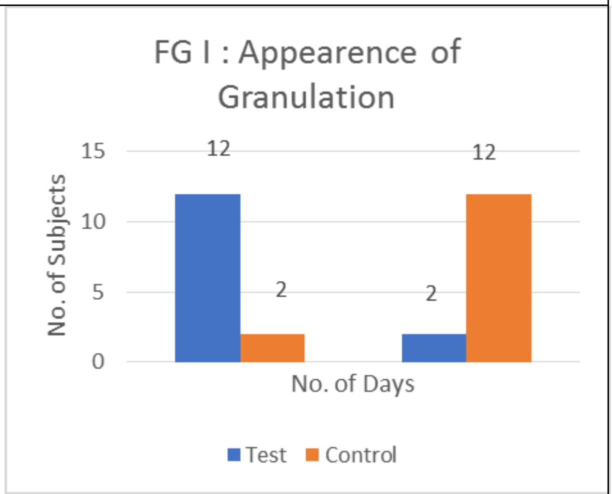
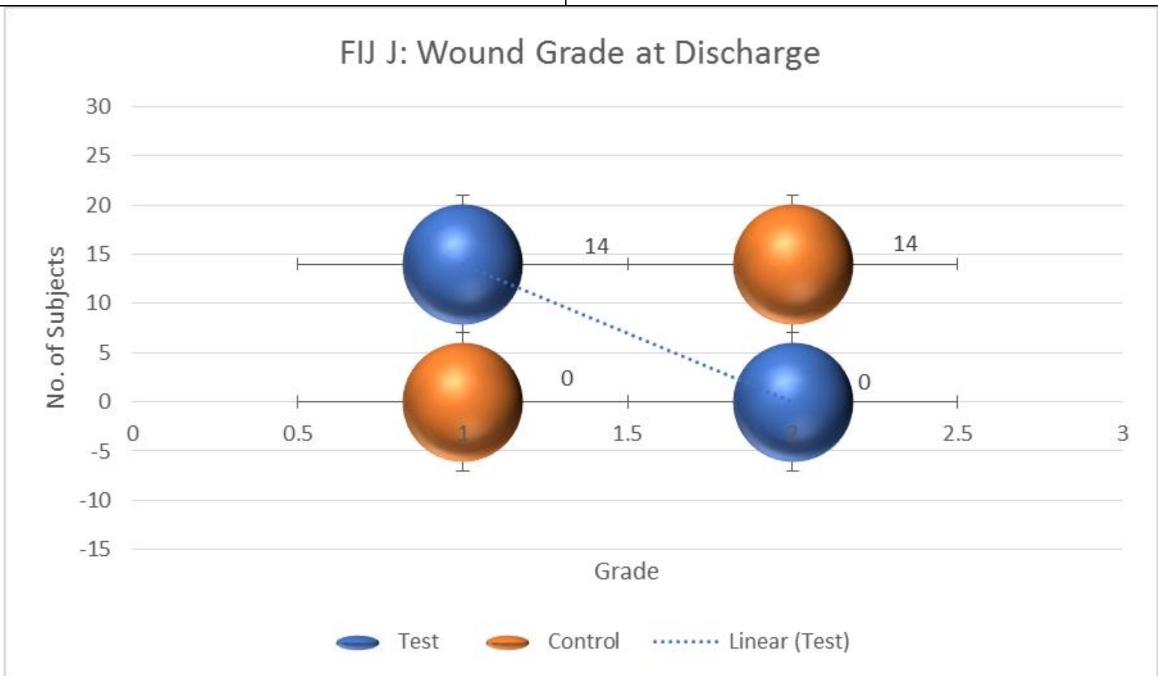


Fig H: Serum Creatinine



FG I : Appearence of Granulation



FIJ J: Wound Grade at Discharge

The age distribution [Fig. A] indicates that most individuals fall within the 40-60 years category, which suggests that middle-aged adults are at a higher risk of complications such as diabetic foot ulcers [DFUs]. This could be attributed to prolonged exposure to hyperglycemia, increasing the likelihood of vascular and neuropathic complications. The lower proportion of elderly individuals [70-80 years: 14%] may reflect a survival bias, as long-standing diabetes with complications might lead to increased morbidity and mortality before reaching this age.

The gender distribution [Fig. B] shows a 93% male predominance, highlighting a potential gender-based predisposition or differences in healthcare-seeking behavior. This could be linked to occupational exposures, lifestyle choices, and delayed medical intervention in men. Studies suggest that men with diabetes often have poorer glycemic control and higher risks of foot complications due to delayed wound healing and neuropathy.

Regarding HbA1C levels [Fig. D], the findings indicate that a large proportion [42.9%] of patients have poorly controlled diabetes [HbA1C ≥ 11%], which significantly increases the risk of DFUs, infections, and amputations. Another 42.9% of patients have HbA1C in the 6-7% range, which is considered well-controlled, yet still predisposes individuals to complications if additional risk factors like smoking, obesity, or hypertension are present. The intermediate group [14.3% with HbA1C between 8-10%] suggests that a subset of patients has moderate control but still faces potential microvascular complications.

The history of diabetes [Fig. E] provides insight into disease progression, with 57.1% of patients having had diabetes for 6-10 years, a period often associated with increased risk of neuropathy, retinopathy, and vascular complications. Patients in the 10-20 years category [28.6%] are even more likely to develop chronic complications. The smaller percentages of those with less than 1 year [7.1%] and 1-5 years [7.1%] indicate that early-stage diabetes patients are a minority in the dataset, possibly due to the lower likelihood of severe complications at this stage.

The type of work [Fig. C] is another crucial factor, revealing that standing [stressful] occupations [18 individuals] are more prevalent than sitting [non-stressful] jobs [10 individuals]. This suggests that prolonged standing and physical stress may contribute to foot complications, pressure ulcers, and delayed wound healing in diabetic patients. Work-related strain may also be linked to poor glycemic control due to irregular eating patterns and stress-induced hyperglycemia.

Figure F presents the relationship between smoking habits and diabetes complications. The data categorizes patients into smokers and non-smokers, highlighting the impact of smoking on diabetes-related conditions. Smoking is a major risk factor for diabetic foot ulcers [DFUs] due to its detrimental effects on microvascular circulation, which impairs oxygen delivery and delays wound healing. Additionally, smoking accelerates neuropathy and peripheral arterial disease [PAD], both of which significantly contribute to foot complications. The figure emphasizes the higher prevalence of DFUs among smokers, reinforcing the necessity of smoking cessation programs as a critical component of diabetes management.

Figure G illustrates the prevalence of hypertension among diabetic patients, demonstrating its strong association with diabetes complications. Hypertension is a common comorbidity in diabetes, significantly increasing the risk of macrovascular complications, including peripheral arterial disease, stroke, and cardiovascular disease. The presence of hypertension exacerbates foot-related complications by impairing blood circulation, leading to delayed wound healing and an increased risk of infection and gangrene. The figure highlights the necessity of rigorous blood pressure control through antihypertensive therapy, dietary modifications, and regular monitoring to prevent diabetes-associated complications.

Figure H presents the Body Mass Index [BMI] distribution among diabetic patients, illustrating the direct correlation between obesity and the risk of DFUs. Higher BMI levels are associated with poor glycemic control, increased systemic inflammation, and excessive mechanical pressure on the feet, all of which contribute to ulcer formation and progression. The figure categorizes patients into normal weight, overweight, obese, and severely obese groups, showing a higher proportion of DFU cases among individuals with elevated BMI. The findings highlight the necessity of weight management strategies, including caloric restriction, structured exercise programs, and pharmacological interventions, to mitigate DFU risk and improve overall diabetes outcomes.

Figure I A 3D Bubble Chart is an advanced data visualization technique used to display relationships between three variables simultaneously. In the context of diabetes-related complications:

1. Axes Representation – The X-axis could represent HbA1C levels, the Y-axis could indicate diabetes duration, and the Z-axis [bubble size] could reflect the incidence or severity of complications like DFUs, infections, or amputations.

2. Bubble Size and Position – Larger bubbles in a specific region suggest a higher concentration of patients experiencing severe complications. For instance, a large bubble at HbA1C >10% and diabetes duration >10 years would indicate that long-standing poorly controlled diabetes strongly correlates with foot ulcers and other vascular issues.

3. Color Coding – Different colors may be used to categorize low, moderate, and high-risk groups. For instance, patients with HbA1C ≤7% and diabetes duration <5 years might be in green [low risk], while those with HbA1C ≥10% and >10 years of diabetes might be in red [high risk].

The visual data representation highlights key risk factors influencing diabetes complications, particularly DFUs. The age and gender distribution suggest that middle-aged men are at higher risk. Poor glycemic control [HbA1C levels] significantly contributes to complications, and diabetes duration plays a crucial role in disease progression. Furthermore, occupational stress due to prolonged standing could be an additional risk factor in foot-related complications. Lastly, an advanced visualization like a 3D Bubble Chart provides a clearer understanding of multi-dimensional relationships in the dataset, allowing for targeted interventions in high-risk diabetic patients.

Table 2: Frequencies of Appearance of Fresh granulation tissue in subjects.

Group	2-3 days	4-5 days	Total
Test	12	2	14
Control	2	12	14
Total	14	14	28

Table 3: Chi-Square Tests- Association of Initiation of granulation tissue formation with choice of Treatment.

<table>
<tr><th>Chi-Square Tests</th><th>Value</th><th>df</th><th>Asymptotic Significance [2-sided]</th><th>Exact Significance [2-sided]</th><th>Exact Significance [1-sided]</th></tr>
<tr><td>Pearson Chi-Square</td><td>7.143[a]</td><td>1</td><td>0.008</td><td rowspan="4">0.029</td><td rowspan="4">0.015</td></tr>
<tr><td>Continuity Correction□</td><td>4.571</td><td>1</td><td>0.033</td></tr>
<tr><td>Likelihood</td><td>7.925</td><td>1</td><td>0.05</td></tr>
<tr><td colspan="4">Fisher’s Exact Test</td></tr>
</table>

Table 4: Chi-square test of Association between wound grade at discharge in subjects of standard and control group.

<table>
<tr><th>Chi-Square Tests</th><th>Value</th><th>df</th><th>Asymptotic Significance [2-sided]</th><th>Exact Significance [2-sided]</th><th>Exact Significance [1-sided]</th></tr>
<tr><td>Pearson Chi-Square</td><td>14.000[a]</td><td>1</td><td><0.001</td><td rowspan="4"><0.001</td><td rowspan="4"><0.001</td></tr>
<tr><td>Continuity Correction□</td><td>10.286</td><td>1</td><td>0.001</td></tr>
<tr><td>Likelihood Ratio</td><td>19.408</td><td>1</td><td><0.001</td></tr>
<tr><td colspan="4">Fisher's Exact Test</td></tr>
</table>

Table 5: Chi-square test for Association between choice of treatment and NLR ratio at discharge.

Chi-Square Tests	Value	df	Asymptotic Significance [2-Sided]
Pearson Chi-Square	7.778[a]	3	0.051
Likelihood Ratio	9.873	3	0.02
Linear-by-Linear Association	5.2	1	0.023
N of Valid Cases	28		

Table 4: NLR ratio at discharge in patients receiving Test and control treatment.

DRUG	1-1.9	2-2.9	3-3.9	>4	Total
Standard	14	0	0	0	14
Control	4	6	2	2	14
Total	18	6	2	2	28

Table 2 shows the frequencies of fresh granulation tissue appearance in subjects from the test and control groups. In the test group, 12 subjects (85.7%) exhibited granulation tissue formation within 2-3 days, while 2 subjects (14.3%) showed it in 4-5 days. In contrast, the control group had only 2 subjects (14.3%) with granulation tissue formation in 2-3 days, whereas 12 subjects (85.7%) showed it in 4-5 days. This indicates a faster initiation of granulation tissue formation in the test group compared to the control group.

Table 3 presents the results of the chi-square test assessing the association between the initiation of granulation tissue formation and treatment choice. The Pearson Chi-Square value of 7.143 ($p = 0.008$) indicates a statistically significant association, suggesting that the test treatment promotes faster granulation tissue formation. The Fisher's exact test ($p = 0.015$) and continuity correction ($p = 0.033$) further confirm this association.

Table 4 evaluates the association between wound grade at discharge and treatment group using a chi-square test. The Pearson Chi-Square value of 14.000 ($p < 0.001$) indicates a highly significant association. The continuity correction ($p = 0.001$) and likelihood ratio ($p < 0.001$) further reinforce the statistical significance. This suggests that the test treatment led to significantly better wound healing outcomes compared to the control group.

Table 5 (previously Table 13) examines the association between treatment choice and NLR (Neutrophil-to-Lymphocyte Ratio) at discharge. The Pearson Chi-Square value of 7.778 ($p = 0.051$) suggests a marginally significant association, while the likelihood ratio ($p = 0.02$) and linear-by-linear association ($p = 0.023$) indicate a trend where the test treatment may contribute to a more favorable NLR ratio at discharge.

Table 6 outlines the distribution of NLR ratios at discharge among patients receiving test and control treatments. In the test group, all 14 subjects (100%) had an NLR ratio between 1-1.9, indicating minimal systemic inflammation and better recovery. Conversely, in the control group, only 4 subjects (28.6%) had an NLR ratio of 1-1.9, while 6 subjects (42.9%) had a ratio between 2-2.9, 2 subjects (14.3%) between 3-3.9, and 2 subjects (14.3%) above 4, reflecting a higher degree of systemic inflammation and possibly delayed wound healing. This supports the efficacy of the test treatment in reducing inflammatory markers and improving healing outcomes.

DISCUSSION

The study found a significant association between the choice of dressing material used and the formation of granulation tissue. The wound grade at discharge was also associated with the choice of dressing material. However, the association between NLR ration and wound healing caused by control or test treatment was insignificant. Diabetic foot ulcers are the most common cause of limb amputations due to numerous micro and macrovascular problems arising from diabetes mellitus. These ulcers often go unreported or unrecognised due to lack of timely foot screening. Diabetic foot ulcers require a multidisciplinary approach to therapy, including surgical treatments, systemic treatment with antidiabetic medications, and addressing low albumin levels. To expedite the creation of granulation tissue during wound healing, it is crucial to address slough formation and infection control.

Wound care is still crucial as soft tissue wound healing takes longer than four weeks. Phenytoin sodium stimulates connective tissue and aids in the early production of granulation tissue, acting effectively on wounds. After receiving phenytoin [Test] dressing for two to three days, 92% of participants in the standard group noticed the beginning of granulation tissue.

People with diabetes for six to ten years are more likely to develop diabetic foot ulcers, and an increased risk of amputation may result from long-term hyperglycaemia or other macrovascular problems. Diet and lifestyle choices are also important factors in managing diabetes, with insulin treatment and oral hypoglycaemic medications used during hospital stays.

Diabetic foot ulceration remains a major cause of lower limb amputations, emphasizing the need for effective wound care strategies. The findings from this study indicate that topical phenytoin sodium significantly accelerates wound healing by promoting early granulation tissue formation. This is consistent with previous research demonstrating the wound-healing properties of phenytoin through fibroblast proliferation, collagen synthesis, and antibacterial effects.[7]

Among the study participants, a statistically significant association was observed between the type of dressing and granulation tissue formation, with the test group [phenytoin] exhibiting faster wound healing than the control group [$p < 0.01$]. These findings align with previous studies where topical phenytoin resulted in improved healing outcomes compared to conventional treatments.[8]

The impact of albumin levels on wound healing was also observed, with many participants presenting hypoalbuminemia, a factor known to delay wound healing. Addressing nutritional deficiencies alongside wound care may further optimize healing outcomes.[9]

Another critical factor in DFU management is blood glucose control. In this study, insulin and oral hypoglycemic agents were used to manage blood glucose levels, reducing the impact of hyperglycemia-induced endothelial dysfunction.[10] The combination of systemic glycemic control and effective wound dressing significantly influences healing outcomes.

While phenytoin dressing was found to be effective in promoting wound healing, there were no significant adverse effects reported. Previous literature suggests that systemic side effects of phenytoin are minimal when used topically, making it a safe option for wound management.[11] Further research on phenytoin formulations, such as hydrogel-based applications, may enhance patient compliance and efficacy in DFU treatment.[12]

This study contributes to the growing evidence supporting the use of phenytoin as a cost-effective, readily available dressing for DFUs. However, larger, multicenter trials are needed to validate these findings and optimize clinical guidelines for its application.

The systematic review by Geice et al. [2021] aimed to assess the effectiveness of various topical interventions, including phenytoin, in promoting the healing of diabetic foot ulcers [DFUs]. The study systematically reviewed randomized clinical trials [RCTs] published between 2009 and 2020 using databases such as PubMed, Scopus, Web of Science, and Cochrane. Out of 5,651 articles screened, 58 met the inclusion criteria. The review identified phenytoin as a particularly effective treatment, achieving a healing rate of approximately 95.82% ± 2.22%. The study highlighted phenytoin's ability to stimulate fibroblast proliferation, enhance granulation tissue formation, and reduce infection risks, making it a cost-effective option for DFU management. Additionally, the systematic review emphasized the growing use of biomaterials alongside pharmaceutical agents for DFU treatment, underscoring the need for further comparative trials to establish optimal treatment protocols.[19]

In contrast, Tabana et al. [2024] conducted a retrospective observational study to compare the effectiveness of topical phenytoin with conventional dressings in treating neuropathic diabetic foot ulcers with mild infections. The study analyzed medical records of 120 patients treated between 2015 and 2020 at a tertiary care center, with 60 patients receiving phenytoin and 60 undergoing conventional dressing. The results demonstrated that ulcer size reduction was significantly greater in the phenytoin group [45% by week four] compared to the conventional group [25%]. The median time to complete healing was also significantly shorter for the phenytoin group [8 weeks vs. 12 weeks, $p < 0.05$]. Furthermore, granulation tissue appeared earlier in the phenytoin-treated group, with an average onset of 10 days compared to 18 days in the conventional group [$p < 0.01$]. Importantly, the recurrence rate of ulcers was lower in the phenytoin group [10% vs. 30%, $p < 0.05$], reinforcing its potential as a superior wound care intervention.[20]

Similar trends were observed regarding the efficacy of 2% phenytoin sodium solution in enhancing wound healing in DFUs in the current study. Like the study by Tabana et al.

[2024], the present manuscript reports faster wound size reduction and earlier granulation tissue formation in the phenytoin group compared to the control. The statistical significance of these results [$p < 0.01$] aligns with prior evidence that phenytoin accelerates wound healing through its ability to promote fibroblast proliferation, collagen deposition, and angiogenesis. However, while Tabana et al. [2024] reported lower ulcer recurrence rates, the current study does not specifically address recurrence, highlighting an area for further investigation. Meanwhile, the findings from Geice et al. [2021] support the broader clinical applicability of phenytoin by synthesizing multiple RCTs, reinforcing that phenytoin is a viable and cost-effective alternative to conventional wound care.

Overall, the results from these studies and the current manuscript collectively demonstrate that topical phenytoin significantly enhances DFU healing rates compared to conventional treatments. The growing body of evidence supports its inclusion in DFU treatment protocols, and further large-scale multi-center trials are needed to establish optimal dosage, administration frequency, and long-term outcomes.

CONCLUSION

Phenytoin, a debridement agent, was found to be efficient on topical application as a 2% solution, preventing white residue formation due to poor miscibility. It was found cost-effective and a good choice for dressing diabetic foot ulcers due to its activity of stimulating granulation tissue formation, reducing bacterial load, and preventing slough and wound discharge. The NLR ratio had no association with wound healing caused by standard or control treatments, as both were topical treatments. Phenytoin dressings accelerated wound healing rates by inducing early granulation tissue development, making them a promising alternative to conventional methods.

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