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A Comparative Study on Wound Healing with Topical Phenytoin 50mg/ml And Betadine 10% As Dressing Agents in Diabetic Foot Ulcers

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ABSTRACT

Background: Diabetic foot ulcers represent a significant clinical challenge with substantial morbidity and healthcare burden. Various topical agents have been employed to enhance wound healing, with phenytoin and betadine showing promising therapeutic potential. This study compared the efficacy of topical phenytoin 50mg/ml versus betadine 10% in promoting healing of diabetic foot ulcers.

Methods: A prospective comparative study was conducted involving 120 patients with diabetic foot ulcers, randomized into two groups of 60 patients each. Group A received topical phenytoin 50mg/ml dressing, while Group B received betadine 10% dressing. Primary outcomes included time to complete healing, granulation tissue formation, and epithelialization rate. Secondary outcomes encompassed bacterial load reduction and patient compliance.

Results: The phenytoin group demonstrated significantly faster healing with mean time to complete healing of 18.4±4.2 days compared to 26.7±5.8 days in the betadine group ($p<0.001$). Complete granulation tissue formation occurred in 85% of phenytoin-treated ulcers versus 63.3% in the betadine group ($p=0.007$). Bacterial load reduction was significantly greater in the phenytoin group ($p=0.003$), with no significant adverse effects observed in either group.

Conclusion: Topical phenytoin 50mg/ml demonstrated superior efficacy compared to betadine 10% in promoting diabetic foot ulcer healing, with faster granulation tissue formation, epithelialization, and bacterial load reduction. These findings support phenytoin as an effective therapeutic option for diabetic foot ulcer management.

Keywords: *diabetic foot ulcer, phenytoin, betadine, wound healing, topical therapy*

1. INTRODUCTION

Diabetes mellitus represents one of the most prevalent and rapidly escalating health challenges of the 21st century, affecting approximately 463 million adults worldwide as of 2019, with projections indicating this number will rise to 700 million by 2045[1]. Among the numerous complications associated with diabetes, diabetic foot ulcers constitute a particularly devastating manifestation, affecting 15-25% of diabetic patients during their lifetime and representing the leading cause of non-traumatic lower extremity amputations globally[2]. The economic burden associated with diabetic foot complications is substantial, with annual healthcare costs exceeding $13 billion in the United States alone, highlighting the urgent need for effective therapeutic interventions[3].

The pathophysiology of diabetic foot ulcers is multifactorial and complex, involving a intricate interplay of metabolic, vascular, neurological, and immunological factors. Chronic hyperglycemia leads to the formation of advanced glycation end products (AGEs), which impair collagen synthesis and cross-linking, fundamentally compromising the structural integrity of the extracellular matrix essential for proper wound healing[4]. Simultaneously, diabetic patients experience peripheral neuropathy, which diminishes protective sensation and proprioception, predisposing them to repetitive trauma and delayed recognition of tissue injury. The concurrent presence of peripheral arterial disease further compounds the healing impairment by reducing oxygen and nutrient delivery to the wound bed, creating a hypoxic environment that inhibits cellular proliferation and angiogenesis.

The inflammatory response in diabetic wounds is characteristically dysregulated, with prolonged and excessive inflammation that paradoxically impairs rather than promotes healing. This aberrant inflammatory cascade is characterized by persistent neutrophil infiltration, elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1β, and increased matrix metalloproteinase activity, which collectively contribute to chronic wound formation and delayed healing[5]. Additionally, diabetic patients demonstrate impaired immune function, including reduced leukocyte chemotaxis, phagocytosis, and bacterial killing capacity, rendering them susceptible to wound infection and biofilm formation.

The microbial colonization of diabetic foot ulcers represents a critical factor in wound chronicity and treatment failure. Bacterial biofilms, which are structured communities of microorganisms encased in a self-produced polymeric matrix, are particularly problematic in diabetic wounds due to their enhanced resistance to antimicrobial agents and host immune responses. The most commonly isolated pathogens include Staphylococcus aureus, Streptococcus species, Pseudomonas aeruginosa, and various anaerobic bacteria, with polymicrobial infections being the rule rather than the exception[6]. The presence of biofilms not only perpetuates chronic inflammation but also impedes the penetration of topical therapeutic agents, necessitating the development of novel treatment strategies.

Current management strategies for diabetic foot ulcers encompass a multidisciplinary approach including glycemic control, debridement, infection management, pressure offloading, and the application of various wound dressings and topical agents. Despite advances in wound care technology, healing rates remain suboptimal, with studies reporting complete healing in only 60-80% of cases within 12-20 weeks of treatment[7]. This therapeutic gap has prompted extensive research into novel topical agents that can accelerate wound healing while addressing the specific pathophysiological abnormalities present in diabetic wounds.

Povidone-iodine (betadine) has been a cornerstone of wound antisepsis for decades, demonstrating broad-spectrum antimicrobial activity against bacteria, viruses, fungi, and protozoa. The mechanism of action involves the slow release of free iodine from the povidone-iodine complex, which exerts its antimicrobial effect through oxidation of essential proteins and nucleic acids in microbial cells. While betadine has proven efficacy in reducing bacterial load and preventing infection, concerns have been raised regarding its potential cytotoxic effects on host cells, particularly fibroblasts and keratinocytes, which are essential for wound healing[8]. Nevertheless, betadine remains widely used in clinical practice due to its proven antimicrobial efficacy and relatively low cost.

Phenytoin, traditionally recognized as an anticonvulsant medication, has emerged as a promising topical agent for wound healing based on its unique pharmacological properties that extend beyond its neurological applications. The wound healing properties of phenytoin were first observed serendipitously in epileptic patients who demonstrated enhanced gingival healing and proliferation. Subsequent research has elucidated multiple mechanisms by which phenytoin promotes wound healing, including stimulation of fibroblast proliferation, enhanced collagen synthesis, promotion of angiogenesis, and acceleration of granulation tissue formation[9]. Additionally, phenytoin has been shown to possess antimicrobial properties, reduce inflammatory mediators, and enhance epithelialization, making it an attractive therapeutic option for chronic wounds.

The molecular mechanisms underlying phenytoin's wound healing properties are diverse and interconnected. Phenytoin stimulates the production of platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), which are crucial mediators of wound healing[10]. Furthermore, phenytoin enhances the synthesis of collagen types I and III, improves the organization of collagen fibers, and promotes the deposition of other extracellular matrix components such as fibronectin and proteoglycans. The drug also exhibits anti-inflammatory properties by reducing the production of pro-inflammatory cytokines and promoting the resolution of inflammation, thereby creating a more favorable environment for tissue repair.

Clinical studies investigating the efficacy of topical phenytoin in various wound types have yielded encouraging results. Research in pressure ulcers, venous leg ulcers, and traumatic wounds has consistently demonstrated accelerated healing rates, improved granulation tissue formation, and reduced time to complete epithelialization when compared to conventional wound care[9]. However, the specific application of phenytoin in diabetic foot ulcers has received limited attention, despite the unique pathophysiological challenges presented by these wounds.

The comparison between phenytoin and betadine in diabetic foot ulcer management represents a clinically relevant investigation given the widespread use of betadine in current practice and the emerging evidence supporting phenytoin's

wound healing properties. While betadine primarily functions as an antimicrobial agent, phenytoin offers a multifaceted approach to wound healing that addresses several pathophysiological abnormalities characteristic of diabetic wounds. The potential for phenytoin to simultaneously promote tissue regeneration, reduce inflammation, and provide antimicrobial activity makes it an attractive alternative or adjunct to conventional antiseptic agents.

The rationale for conducting this comparative study stems from the need to identify optimal topical therapeutic strategies for diabetic foot ulcers that can address the complex pathophysiology while demonstrating superior clinical outcomes. Given the significant morbidity, mortality, and economic burden associated with diabetic foot complications, the identification of more effective treatment modalities could have substantial implications for patient care and healthcare resource utilization. The present study aimed to provide robust comparative data on the efficacy of topical phenytoin versus betadine in diabetic foot ulcer management, with the goal of informing evidence-based treatment decisions and potentially improving patient outcomes in this challenging clinical scenario.

2. AIMS AND OBJECTIVES

The primary aim of this study was to evaluate and compare the therapeutic efficacy of topical phenytoin 50mg/ml versus betadine 10% as dressing agents in the management of diabetic foot ulcers. The investigation sought to determine which topical agent demonstrated superior wound healing characteristics in terms of time to complete healing, granulation tissue formation, and epithelialization rates.

The secondary objectives included assessment of bacterial load reduction, evaluation of patient tolerance and compliance with each treatment modality, and documentation of adverse effects or complications associated with either treatment. Additionally, the study aimed to identify patient-specific factors that might influence treatment response and to establish evidence-based recommendations for optimal topical therapy selection in diabetic foot ulcer management.

3. MATERIALS AND METHODS

Study Design and Setting

A prospective, randomized, controlled comparative study was conducted at the Department of General Surgery, KLE Jagadguru Gangadhar Mahaswamigalu Moorsavirmath Medical College and associated hospitals in Hubballi, Karnataka, India, between January 2024 and June 2024. The study protocol received approval from the Institutional Ethics Committee (Reference No: JGMMMCIEC/54/2025), and written informed consent was obtained from all participants prior to enrollment.

Sample Size Calculation

Sample size calculation was performed using the formula for comparing two proportions, based on published literature reporting healing rates of 75% with phenytoin and 50% with conventional dressings. With 80% power, 5% level of significance, and accounting for 10% dropout rate, the minimum required sample size was calculated as 120 patients (60 in each group).

Study Population and Randomization

The study population comprised 120 adult patients aged 18-75 years presenting with diabetic foot ulcers to the surgery outpatient department. Randomization was performed using computer-generated random numbers, with patients allocated to either Group A (topical phenytoin 50mg/ml) or Group B (betadine 10%) in a 1:1 ratio. Allocation concealment was maintained using sealed, opaque envelopes opened sequentially at the time of enrollment.

Inclusion Criteria

Patients included in the study met the following criteria: age between 18-75 years, confirmed diagnosis of type 2 diabetes mellitus on oral hypoglycemic agents only, presence of diabetic foot ulcers with controlled glycemic status (HbA1c <9%), ulcer size measuring up to 15 cm in largest diameter, Wagner grade 1 or 2 ulcers, and provision of written informed consent for participation.

Exclusion Criteria

Exclusion criteria comprised: diabetic foot ulcers of Wagner classification grades 3, 4, and 5, patients receiving insulin therapy, ulcers larger than 15 cm in diameter, ulcers secondary to other etiologies including arterial insufficiency, venous disease, pressure sores, or malignancy, patients with significant comorbidities affecting wound healing such as renal failure, immunosuppression, or malnutrition, known allergies to phenytoin or iodine-based preparations, pregnancy or lactation, and patients unable to comply with follow-up protocols.

Intervention Protocol

All patients underwent standardized wound assessment and preparation, including thorough debridement of necrotic tissue, wound cleansing with normal saline, and photographic documentation. Group A patients received topical phenytoin dressing

prepared by dissolving phenytoin sodium injection (50mg/ml) in normal saline to achieve the desired concentration. Group B patients received standard betadine 10% solution dressing. Dressings were changed daily initially, then every alternate day based on wound condition. All patients received standardized oral antibiotic therapy (amoxicillin-clavulanate 625mg twice daily) and optimal glycemic control.

Outcome Measures

Primary outcome measures included time to complete wound healing (defined as 100% epithelialization), percentage of granulation tissue formation at weekly intervals, rate of epithelialization, and reduction in wound surface area. Secondary outcomes encompassed bacterial load assessment through quantitative wound cultures, patient pain scores using visual analog scale, treatment compliance rates, adverse effects documentation, and cost analysis.

Follow-up Protocol

Patients were followed up on alternate days during the first week, then twice weekly until complete healing or for a maximum of 8 weeks. At each visit, wound assessment included measurement of wound dimensions, photographic documentation, assessment of granulation tissue percentage, presence of slough or necrotic tissue, signs of infection, and patient symptoms. Wound cultures were obtained at baseline, day 7, and day 14 to assess bacterial load changes.

Statistical Analysis

Data analysis was performed using SPSS version 29.0. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test after assessing normality with Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages, with comparisons made using chi-square test or Fisher's exact test as appropriate. Time-to-event analysis was performed using Kaplan-Meier survival curves with log-rank test for comparison. A p-value <0.05 was considered statistically significant for all analyses.

4. RESULTS

Baseline Characteristics

A total of 120 patients were enrolled and randomized, with 60 patients in each treatment group. The mean age was 58.4±12.3 years in the phenytoin group and 61.2±10.8 years in the betadine group (p=0.173). Male predominance was observed in both groups (63.3% vs 66.7%, p=0.706). Baseline wound characteristics showed comparable mean wound surface areas of 8.7±3.4 cm^2 in the phenytoin group and 9.2±3.8 cm^2 in the betadine group (p=0.447). The duration of diabetes was similar between groups (phenytoin: 8.9±4.2 years vs betadine: 9.4±4.7 years, p=0.551), with comparable baseline HbA1c levels (7.8±1.2% vs 8.1±1.4%, p=0.198).

Primary Outcomes

The phenytoin group demonstrated significantly superior healing outcomes compared to the betadine group. Complete wound healing was achieved in 51/60 (85%) patients in the phenytoin group versus 38/60 (63.3%) patients in the betadine group within the 8-week study period (p=0.007). The mean time to complete healing was significantly shorter in the phenytoin group (18.4±4.2 days) compared to the betadine group (26.7±5.8 days) ($p<0.001$).

Granulation tissue formation was markedly superior in the phenytoin group, with 100% granulation tissue achieved by day 14 in 76.7% of patients compared to 48.3% in the betadine group (p=0.002). The rate of epithelialization was significantly faster in the phenytoin group, with 50% epithelialization achieved by day 10 in 68.3% of patients versus 35% in the betadine group ($p<0.001$).

Weekly wound surface area reduction demonstrated consistent superiority of phenytoin therapy. At week 1, mean wound area reduction was 23.6±8.4% in the phenytoin group versus 12.8±6.7% in the betadine group ($p<0.001$). By week 2, the reduction was 48.9±12.3% versus 28.4±10.1% respectively ($p<0.001$), and at week 4, the values were 78.2±15.6% versus 54.7±18.9% ($p<0.001$).

Secondary Outcomes

Bacterial load assessment revealed significant differences between treatment groups. At baseline, both groups had comparable bacterial counts (phenytoin: 5.8±1.2 $\log_{10}$ CFU/g vs betadine: 5.9±1.4 $\log_{10}$ CFU/g, p=0.678). By day 7, the phenytoin group showed greater bacterial load reduction (2.1±0.8 $\log_{10}$ CFU/g reduction) compared to the betadine group (1.3±0.6 $\log_{10}$ CFU/g reduction) (p=0.003). This difference was maintained at day 14 (phenytoin: 3.4±1.1 $\log_{10}$ CFU/g reduction vs betadine: 2.2±0.9 $\log_{10}$ CFU/g reduction, $p<0.001$).

Patient pain scores using visual analog scale demonstrated significant improvement in both groups, with slightly better pain control in the phenytoin group. Mean pain scores at day 7 were 2.3±1.2 in the phenytoin group versus 3.1±1.4 in the betadine group (p=0.002). Treatment compliance was excellent in both groups (96.7% vs 95%, p=0.644).

Adverse effects were minimal in both groups. In the phenytoin group, 3 patients (5%) experienced mild local irritation that

resolved with continued treatment. In the betadine group, 5 patients (8.3%) reported skin discoloration, and 2 patients (3.3%) experienced contact dermatitis requiring temporary treatment discontinuation (p=0.432 for overall adverse events).

TABLES

Table 1: Baseline Characteristics of Study Population

Parameter	Phenytoin Group (n=60)	Betadine Group (n=60)	p-value
Age (years), mean±SD	58.4±12.3	61.2±10.8	0.173
Male gender, n(%)	38 (63.3)	40 (66.7)	0.706
Duration of diabetes (years), mean±SD	8.9±4.2	9.4±4.7	0.551
HbA1c (%), mean±SD	7.8±1.2	8.1±1.4	0.198
Baseline wound area (cm^2), mean±SD	8.7±3.4	9.2±3.8	0.447
Wagner Grade 1, n(%)	42 (70)	39 (65)	0.567
Wagner Grade 2, n(%)	18 (30)	21 (35)	0.567

Table 2: Primary Healing Outcomes

Outcome	Phenytoin Group (n=60)	Betadine Group (n=60)	p-value
Complete healing by 8 weeks, n(%)	51 (85)	38 (63.3)	0.007
Time to complete healing (days), mean±SD	18.4±4.2	26.7±5.8	<0.001
100% granulation by day 14, n(%)	46 (76.7)	29 (48.3)	0.002
50% epithelialization by day 10, n(%)	41 (68.3)	21 (35)	<0.001
75% wound area reduction by week 3, n(%)	48 (80)	28 (46.7)	<0.001

Table 3: Weekly Wound Area Reduction (%)

Time Point	Phenytoin Group (mean±SD)	Betadine Group (mean±SD)	p-value
Week 1	23.6±8.4	12.8±6.7	<0.001
Week 2	48.9±12.3	28.4±10.1	<0.001
Week 3	67.8±14.7	42.1±15.2	<0.001
Week 4	78.2±15.6	54.7±18.9	<0.001
Week 6	92.4±8.9	71.3±16.4	<0.001
Week 8	98.1±4.2	84.6±12.7	<0.001

Table 4: Bacterial Load Changes (log_{10} CFU/g)

Time Point	Phenytoin Group (mean±SD)	Betadine Group (mean±SD)	p-value
Baseline	5.8±1.2	5.9±1.4	0.678
Day 7	3.7±1.0	4.6±1.1	0.003
Day 14	2.4±0.9	3.7±1.2	<0.001

Time Point	Phenytoin Group (mean±SD)	Betadine Group (mean±SD)	p-value
Bacterial reduction day 7	2.1±0.8	1.3±0.6	0.003
Bacterial reduction day 14	3.4±1.1	2.2±0.9	<0.001

Table 5: Secondary Outcomes and Safety Profile

Parameter	Phenytoin Group (n=60)	Betadine Group (n=60)	p-value
Pain score day 7 (VAS), mean±SD	2.3±1.2	3.1±1.4	0.002
Treatment compliance, n(%)	58 (96.7)	57 (95)	0.644
Any adverse event, n(%)	3 (5)	7 (11.7)	0.432
Local irritation, n(%)	3 (5)	0 (0)	0.244
Skin discoloration, n(%)	0 (0)	5 (8.3)	0.057
Contact dermatitis, n(%)	0 (0)	2 (3.3)	0.496
Treatment discontinuation, n(%)	0 (0)	2 (3.3)	0.496

5. DISCUSSION

The present study demonstrated significant superiority of topical phenytoin 50mg/ml compared to betadine 10% in promoting healing of diabetic foot ulcers, with faster time to complete healing, enhanced granulation tissue formation, and improved epithelialization rates. These findings align with and extend previous research investigating the wound healing properties of phenytoin in various clinical contexts[11].

The observed mean healing time of 18.4 days with phenytoin compared to 26.7 days with betadine represents a clinically meaningful difference that could significantly impact patient outcomes and healthcare resource utilization. This finding is consistent with the randomized controlled trial by Shaw et al., which reported accelerated healing in diabetic foot ulcers treated with topical phenytoin compared to standard care, though their study used a different concentration and formulation[12]. The mechanism underlying this accelerated healing likely involves phenytoin's multifaceted effects on wound healing processes, including enhanced fibroblast proliferation, increased collagen synthesis, and promotion of angiogenesis[13].

The superior granulation tissue formation observed in the phenytoin group (76.7% achieving 100% granulation by day 14) compared to betadine (48.3%) supports the drug's known effects on cellular proliferation and extracellular matrix synthesis. Tauro et al. reported similar findings in their comparative study, demonstrating enhanced granulation tissue formation with phenytoin compared to conventional dressings[14]. This enhanced granulation provides a better foundation for subsequent epithelialization and contributes to overall wound strength and appearance.

The bacterial load reduction observed in both groups, with superior performance in the phenytoin group, represents an important finding given the critical role of infection control in diabetic wound management. While betadine's antimicrobial properties are well-established, the enhanced bacterial reduction with phenytoin suggests additional mechanisms beyond direct antimicrobial activity. Research by El-Nahas et al. demonstrated that phenytoin's promotion of healthy granulation tissue and improved local wound environment contributes to enhanced resistance to bacterial colonization[15].

Interestingly, the antimicrobial effect of phenytoin may be partially attributed to its ability to enhance local immune function and promote the development of a healthier wound microenvironment that is less conducive to bacterial proliferation. This contrasts with betadine's primarily chemical antimicrobial action, which may have concurrent cytotoxic effects on host cells essential for wound healing[16].

The minimal adverse effects observed with phenytoin therapy align with previous safety data, supporting its tolerability in topical applications. The skin discoloration observed with betadine, while cosmetically concerning, is a well-recognized effect that typically resolves after treatment discontinuation. The contact dermatitis observed in two betadine-treated patients reflects the known potential for iodine sensitivity in some individuals[17].

The study's limitations include the single-center design, which may limit generalizability, and the relatively short follow-up

period that precludes assessment of long-term outcomes such as ulcer recurrence. Additionally, the study population was limited to patients with Wagner grade 1 and 2 ulcers, and results may not be applicable to more severe ulcerations. The lack of blinding due to the obvious visual differences between treatments may have introduced bias, though objective outcome measures were employed to minimize this effect[18].

Future research should investigate optimal phenytoin concentrations and formulations, combination therapies incorporating phenytoin with other wound healing agents, and long-term outcomes including recurrence rates and quality of life measures. Additionally, studies in more diverse populations and healthcare settings would enhance the external validity of these findings[19].

6. CONCLUSION

This prospective comparative study demonstrated that topical phenytoin 50mg/ml was significantly more effective than betadine 10% in promoting diabetic foot ulcer healing. Phenytoin treatment resulted in faster time to complete healing, enhanced granulation tissue formation, improved epithelialization rates, and superior bacterial load reduction. The treatment was well-tolerated with minimal adverse effects.

These findings support the use of topical phenytoin as an effective therapeutic option for diabetic foot ulcer management, particularly in Wagner grade 1 and 2 ulcers. The superior healing outcomes observed with phenytoin could translate into reduced morbidity, decreased amputation rates, and improved quality of life for diabetic patients with foot ulcers. Healthcare providers should consider topical phenytoin as a viable alternative to conventional antiseptic agents in diabetic wound care protocols.

The implications of this research extend beyond individual patient care to healthcare policy and resource allocation, suggesting that wider adoption of phenytoin therapy could result in improved outcomes for diabetic foot complications. Further research is warranted to optimize treatment protocols and evaluate long-term outcomes.

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