

Original Research Article

A study to compare the effect of topical phenytoin dressing and conventional saline dressing in chronic non-healing ulcers

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ABSTRACT

Background: Chronic non-healing ulcers; particularly diabetic and venous ulcers impose a major healthcare burden and affect quality of living. Efficacy of conventional strategies used for treatment of chronic non-healing ulcers is limited due to factors like microbial infection, necrotic tissues, tissue hypoxia, and other prevailing co-morbidities. The aim of the study was to compare efficiency of topical phenytoin-based dressings to conventional saline-based dressings for treatment of chronic non-healing wound ulcers.

Methods: A prospective observational study was conducted on 60 patients who were divided in two groups. First group received conventional saline dressing-based treatment and second received topical phenytoin dressing based treatment for chronic non-healing ulcers. Efficiency of the treatment strategy was determined by statistically comparing parameters like duration of hospital stay, nature of discharge, appearance of healthy granulation tissue, and pus culture evaluation upon admission and post one and two weeks of treatment.

Results: Diabetes and trauma were observed to be two major causes of chronic non-healing ulcers. No cases of venous impairment and osteomyelitis were observed in participating patients. Topical phenytoin dressing based treatment significantly reduced the duration of hospital stay and number of patients with serous discharge and aided in rapid formation of healthy granulation tissue in comparison to conventional saline based dressings. Topical phenytoin dressings also prevented microbial infection and colonization on chronic non-healing ulcers.

Conclusions: Topical phenytoin-based dressing was concluded to efficiently and rapidly heal chronic ulcers while preventing microbial infection in comparison to conventional saline-based dressings.

Keywords: Topical phenytoin dressing, Conventional saline dressing, Chronic ulcers, Non-healing ulcers, Diabetic ulcers, Venous ulcers

INTRODUCTION

Chronic non-healing ulcers are lesions that are either spontaneous or traumatic, and do not heal in 6 to 9 weeks or in defined time duration because of interruption in normal healing process due to lack of growth factors and cytokines which are responsible tissue regeneration and tissue remodelling.^{1,2} Non-healing ulcers are non-responsive to initial therapy and due its chronic persistence they can be colonized by parasites, fungi, bacteria and viruses.³ Global prevalence rate of chronic non-healing ulcers ranges from 1.9% to 13% and is the major cause of admissions in the surgical ward.⁴ The incidence of chronic

non healing ulcers is more prevalent in people older than 65 years or aging population due to lifestyle diseases like obesity, diabetes and atherosclerotic occlusion.⁵ Chronic non-healing ulcers debilitates the sufferers as it drastically affects quality of life due to financial burden imposed because of treatment expenses and reduction in productivity.³⁻⁶

Chronic non-healing ulcers may be venous, diabetic, arterial, traumatic, neurotrophic or lymphatic.⁷ Diabetes and venous diseases like venous hypertension are considered to be major causative factors for chronic non healing ulcers.⁸ Majority of the diabetic patients develop

lower extremity chronic ulcers which cannot be healed easily due to diabetic neuropathy; these non-healing diabetic ulcers are susceptible to infection by microorganisms due to their chronic nature.⁹

Majority of venous ulceration also occur in lower extremities and are caused due to venous diseases that damage the venous walls leading to development of chronic non healing ulcers.¹⁰ It is reported and observed that around 12% cases of chronic non healing ulcers of lower extremity require amputation.¹¹ Chronic non healing diabetic ulcers is reported as one of the major cause of non-traumatic foot and ankle type of lower extremity amputations.⁹⁻¹² After amputation there are very high chances of ulcer reoccurrence in the opposite extremity.^{11,12} Even if the limb is saved, prolonged hospital stay, repeated wound debridement and regular intake of antibiotics to prevent microbial infection leads to physical, mental and financial trauma in sufferers of chronic non healing ulcers.¹⁻⁵

Strategies employed for the management and treatment of chronic non healing wound ulcers are aimed towards obtaining rapid wound closure.¹³ Conventional treatment strategies include repeated wound cleansing with saline, necrotic tissue debridement and application of dry or moist gauze dressing.¹³ However; the efficacy of the conventional strategy used for treatment or management of chronic non healing ulcers is limited due to several factors like microbial infection in ulcer, presence of debris and necrotic tissues, tissue hypoxia, immunodeficiency, malnutrition, systemic diseases like diabetes mellitus and use of corticosteroids.¹⁴ The treatment modalities or chronic non healing ulcers thus involves debridement of necrotic tissue, use of topical antibacterial, antiseptics or antibiotics to manage or prevent microbial infection in ulcers, ischemia, diabetes and management of other comorbidities.¹⁵

Phenytoin is an anticonvulsant therapeutic agent used in prophylaxis and management of different types of seizures.¹⁶ Additionally topical application of phenytoin increase the proliferation of fibroblasts and deposition of collagen, it enhances the granulation tissue formation and decrease the activity of collagenase, phenytoin also leads to neovascular-ization.^{16,17} Phenytoin exhibits anti-microbial activity and helps in prevention or management of microbial infection caused by *S. aureus*, *Escherichia coli*, *Klebsiella* species and *Pseudomonas* when applied topically on ulcers thus phenytoin is observed and reported to exhibit positive effects in chronic ulcer healing.¹⁶⁻¹⁸

Aim and objectives

Efficacy and safety of any therapeutic substance or treatment strategy should be supported by clinical evidences and justification. The aim of the study was towards investigating and comparing the efficacy of topically applied phenytoin dressings against conventional strategies used in management and treatment of chronic

non-healing ulcers. The specific objectives of this study were to investigate the efficiency of topical phenytoin dressing against conventional saline dressing on the basis of parameters like pus culture and sensitivity used to assess presence of microorganisms, nature of discharge to assess whether the discharge is purulent or serous, appearance of healthy granulation tissue, rate of healing and duration of hospital stay.

METHODS

Study design, location and duration

Current investigation was a prospective observational study conducted on patients admitted to general surgical wards of Government T. D. Medical college hospital; a tertiary care centre located in Alappuzha. The study was conducted for duration of six months.

Study population and sample size

Current study was conducted on total 60 patients fulfilling the inclusion criteria, who were admitted at general surgery wards of Government T. D. Medical college hospital for treatment of chronic non-healing ulcers. Conventional saline dressing treatment was given to patients (50%) admitted during the first three months of the study and topical phenytoin dressing treatment was given to patients (50%) admitted for the next three months of study.

Inclusion criteria

Inclusion criteria for current study were- all patients between the age group 13-70 years exhibiting any grade of traumatic or diabetic chronic ulcers except grade 0 and 5 as per Wagner classification.

Exclusion criteria

Exclusion criteria for current study were patients with fistulas of organs or cavities, discharging sinus from bone, gangrene foot and malignancy.

Procedure

The patients were divided in two groups with each group consisting of 30 patients. Pus culture and sensitivity tests were done for both the groups of patients upon admission and after one week and two weeks post treatment. Arterial Doppler studies were performed on both the groups of patients upon admission to assess the vascularity of the limb. X-ray of the affected regions were taken to rule out the presence of osteomyelitis. In case of abundant slough debridement of wound was done on patients of both the groups. After cleaning or debriding the ulcer, the ulcer dimensions and the surface area were assessed and recorded using dry gauze mapping. The surface area of the ulcer was reassessed after one and two-weeks post treatment. First group of patients was given conventional

saline dressing-based treatment were ulcer was cleaned with saline, and debridement was done if abundant slough was present. The wound was then covered with sterile surgical pads after cleaning the surrounding skin with povidone iodine.

Daily cleaning and dressing were done and oral or parenteral antibiotics were given as per indication. Second group was given topical phenytoin dressing based treatment. Wound was first cleaned with saline and debridement was done if abundant slough was present. 100 mg phenytoin sodium tablet was suspended in 5 ml of sterile saline solution under aseptic conditions. Sterile gauze was then soaked in the above suspension and was placed over the ulcer at about 20 mg/cm² of TBSA. Finally, a dry sterile surgical pad was applied after cleaning the surrounding area with povidone iodine.

Daily cleaning and dressing were done and oral or parenteral antibiotics were given as per indication. Outcome of treatment was assessed after one week and two weeks post treatment on the basis of parameters like whether a patient is discharged or skin graft was observed with healthy granulation tissue and on the basis of reduction in serous discharge and raw area of ulcer remaining. Those patients whose wound culture was observed to be sterile but not fit for grafting were discharged for dressing in a local hospital and were asked to come for follow up. Amputation was done in patients who exhibited spreading of infection with a nonviable limb.

Statistical analysis

Clinical data obtained from the study was analysed using SPSS software. The data was represented as distribution of patients in terms of percentage according to initial indications or treatment outcomes. Observed data was compared using Student t test and Chi square tests depending on the variables and $p < 0.05$ was considered as level of significance.

RESULTS

It was observed from the results of current investigation that out of total 60 patients, 41 patients were males (68.33%) and 19 were females (31.66%) number of males were significantly higher than number of females (Figure 1).

All the patients of the study belonged to the age group of 30-70 years. It was observed that 37 patients (61.66%) exhibited ulcer of grade 3 and 23 patients (38.33%) exhibited grade 2 ulcer according to Wagner classification (Figure 2). The duration of hospital stays among patients of both the groups ranged between 10-29 days. It was observed that duration of hospital was significantly higher in patients of conventional saline dressing-based treatment group as compared to topical phenytoin dressing based

treatment group. In conventional saline dressing-based treatment group 4 out of 30 patients stayed in hospital for ≤ 15 days whereas; 26 patients stayed in hospital for more than 15 days. In topical phenytoin dressing based treatment group out of total 30 patients; 15 (50%) patients stayed in the hospital for ≤ 15 days whereas, remaining 15 (50%) stayed in hospital for more than 15 days (Figure 3). Results of Doppler studies revealed that majority of the patients 51 (85%) showed no vascular impairment whereas, only 09 (15%) out of 60 patients exhibited vascular impairment (Figure 4).

X-ray investigation studies revealed that none of the patients exhibited osteomyelitis. It was observed that in total 40 (66.66%) of patients out of 60 diabetes was the cause of ulcer and in 20 (33.33%) patients trauma was the main causative factor for ulceration.

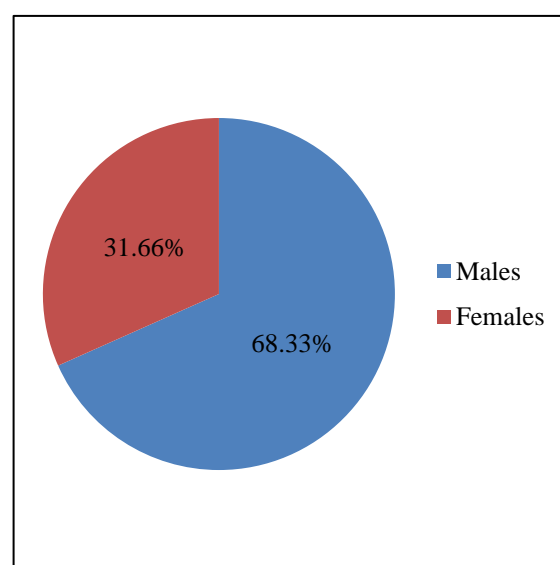


Figure 1: Gender based distribution of patients.

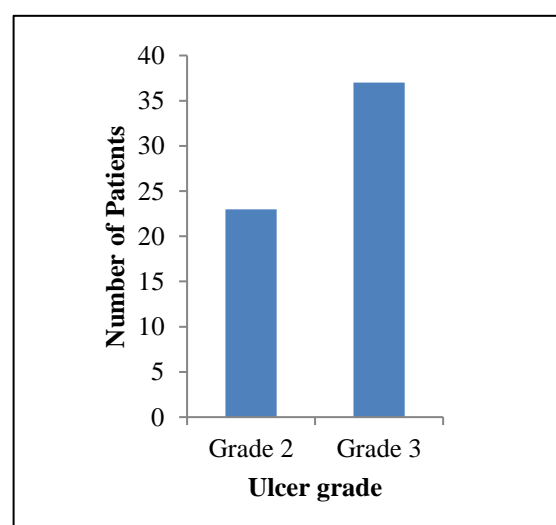


Figure 2: Distribution of patients on the basis of ulcer grade.

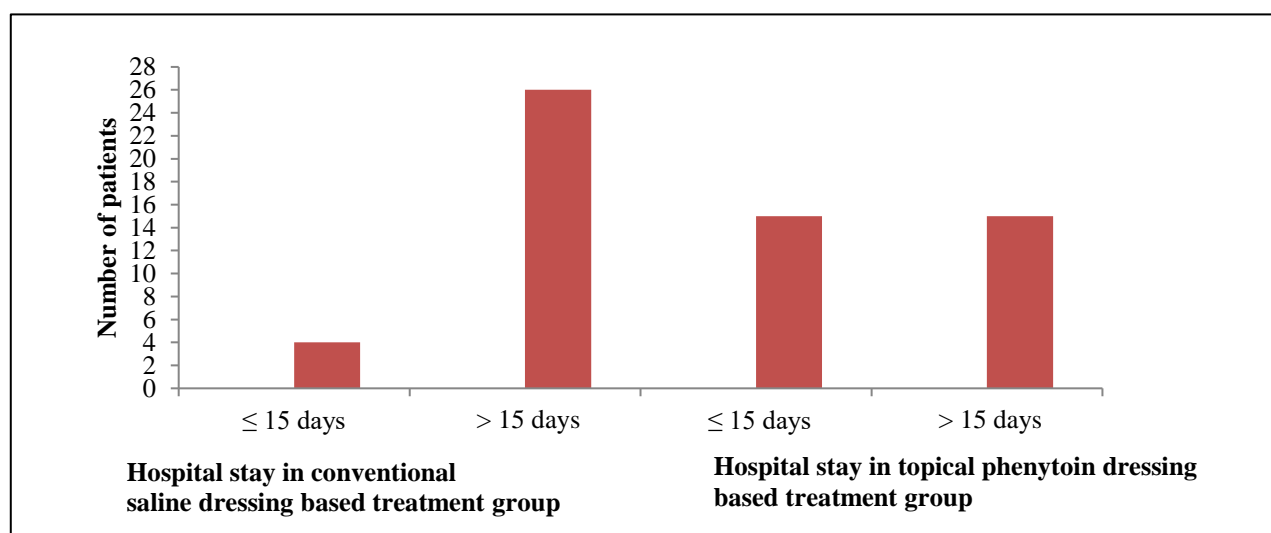


Figure 3: Distribution of patients on the basis of hospital stay in days.

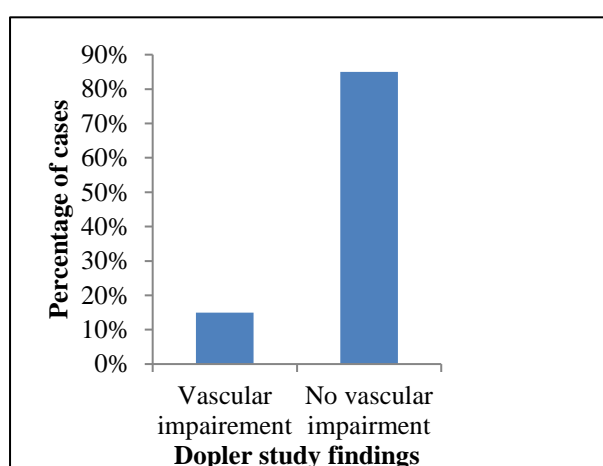


Figure 4: Distribution of patients on the basis of Doppler study.

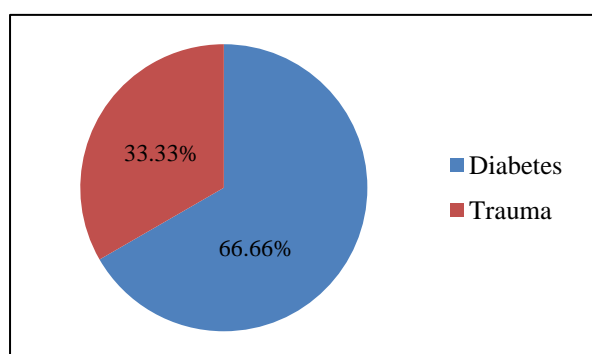


Figure 5: Distribution of patients on the basis of causes of ulcer.

Comparing the results of investigation on the basis of nature of discharge in conventional saline dressing-based treatment group and topical phenytoin dressing based treatment group it was observed that upon admission there was no significant difference in the nature of discharge

among the patients of both conventional saline dressing-based treatment group and topical phenytoin dressing based treatment groups. Investigation results comparison in terms of nature of discharge after first and second weeks post treatment among the patients of conventional saline dressing-based treatment group and topical phenytoin dressing based treatment groups revealed that there was either significant reduction in discharge or all together no discharge in the patients of topical phenytoin dressing based treatment group when compared to patients of the conventional saline dressing-based treatment group. It was observed that after second week of treatment, significant number of patients in the topical phenytoin dressing based treatment group (56.66%) exhibited no discharge as compared to conventional saline dressing-based treatment group (23.33%). Only 7 out of 30 patients in the topical phenytoin dressing based treatment group showed discharge against 20 out of 30 patients in conventional saline dressing-based treatment group (Table 1).

Comparison of investigational studies on the basis of appearance of healthy granulation tissue revealed that none of the patients either in conventional saline dressing-based treatment group or in topical phenytoin dressing based treatment group exhibited healthy granulation tissue on admission. The appearance of healthy granulation tissue among the patients of topical phenytoin dressing based treatment group post one week and two weeks of treatments was observed to be more than that in conventional saline dressing-based treatment group however; it was observed that difference in number of patients with healthy granulation tissue amongst conventional saline dressing-based treatment group and topical phenytoin dressing based treatment groups was not significant (Table 2).

Statistical comparison between the patients of conventional saline based treatment group and topical phenytoin dressing based treatment group on the basis of pus culture investigation studies revealed that pus culture

of all the patients (100%) upon admission in both the groups were unsterile. One-week post treatment, it was observed that numbers of patients in topical phenytoin dressing based treatment group (51.85%) with sterile pus culture were more in comparison to the conventional saline dressing-based treatment group (36.66%), however, the difference in number of patients with sterile pus culture in both topical phenytoin dressing based treatment group and

conventional saline dressing-based treatment group were insignificant ($p=0.248664$). Pus culture investigation studies two weeks post treatment revealed that number of patients (79.16%) with sterile pus culture in topical phenytoin dressing based treatment group were significantly more than the number of patients (50%) with sterile pus culture in conventional saline dressing-based treatment group ($p=0.027423$) (Table 3).

Table 1: Distribution of patients on the basis of nature of discharge.

Nature of discharge	Conventional saline dressing-based treatment group N (%)	Topical phenytoin dressing based treatment group N (%)	Chi square value	P value	Significance
Upon admission					
No discharge	0 (0)	0 (0)	0.7387	0.390073	Not significant
Serous	7 (23.33)	10 (33.33)			
Purulent	23 (76.66)	20 (66.66)			
After first week of treatment					
No discharge	3 (10)	12 (40)	18.6267	0.00009	Significant
Serous	10 (33.33)	16 (53.33)			
Purulent	17 (56.66)	2 (6.66)			
After second week of treatment					
No discharge	7 (23.33)	17 (56.66)	10.2925	0.005821	Significant
Serous	11 (36.66)	4 (13.33)			
Purulent	9 (30)	3 (10)			

Table 2: Distribution of patients on the basis of appearance of healthy granulation tissue.

Appearance of healthy granulation tissue	Conventional saline dressing-based treatment group N (%)	Topical phenytoin dressing-based treatment group N (%)	Chi square value	P value	Significance
Upon admission					
Present	0 (0)	0 (0)	0	1	Not significant
Absent	30 (100)	30 (100)			
After first week of treatment					
Present	12 (40)	16 (57.14)	1.7045	0.191702	Not significant
Absent	18 (60)	12 (42.85)			
After second week of treatment					
Present	14 (51.85)	15 (62.5)	0.5873	0.443458	Not significant
Absent	13 (48.14)	9 (37.5)			

Table 3: Distribution of patients on the basis of pus culture.

Pus culture	Conventional saline dressing-based treatment group N (%)	Topical phenytoin dressing-based treatment group N (%)	Chi square value	P value	Significance
Upon admission					
Sterile	0 (0)	0 (0)	0	1	Not significant
Unsterile	60 (100)	60 (100)			
After first week of treatment					
Sterile	11 (36.66)	14 (51.85)	1.3308	0.248664	Not significant
Unsterile	19 (63.33)	13 (48.14)			
After second week of treatment					
Sterile	15 (50)	19 (79.16)	4.864	0.027423	Significant
Unsterile	15 (50)	05 (20.83)			

DISCUSSION

Results of current study which was carried to assess and compare the efficiency of topical phenytoin dressing based treatment for chronic non-healing ulcers in comparison to conventional saline dressing-based treatment method indicated that out of total 60 patients participating in current study male patients outnumbered the female patients. It was observed that all the patients participating in current study belonged to the age group between 30 to 70 years, these was in accordance to study conducted by Suthar et al where they reported the mean age of patients with chronic non healing ulcers to be 62 ± 13 years.¹⁹ Current study findings revealed that participating patients exhibited either grade 2 or grade 3 ulcers according to Wagner classification which was in accordance to the study reported by Wadatalla et al.²⁰

It was observed that diabetes followed by trauma were the main causes of chronic non healing ulcers in the participating patients of present study, this findings were in accordance to the report published by Sen where he stated diabetic and traumatic wounds to be most prevalent types of chronic non healing wounds.²¹ X-ray study findings in current study revealed that out of 60 participating patients none of the patients exhibited osteomyelitis, these results were deviating from study reports published by Giurato et al which stated that there is a close association of chronic non healing wound ulcers with osteomyelitis.²² In current study it was observed that there was no vascular impairment in majority of study participants as revealed by Doppler studies this observation deviated from the study report of Kerstein who stated that usually venous chronic non healing ulcers are associated with venous impairment.²³

It was observed through the current study findings that duration of hospital stays among the patients who received topical phenytoin-based dressing treatment was lesser (10 to 23 days) as compared to the patients who received conventional saline based dressing treatment (12-29 days). It was also observed that majority of patients who received topical phenytoin-based dressing treatment were discharged from hospital in less than 15 days whereas, majority of patients who received conventional saline based dressing treatment exhibited the hospital stay for more than 15 days. It was observed through current study findings that significant number of patients who received topical phenytoin dressing based treatment showed no serious discharge post two weeks of treatment in comparison to patients who received conventional saline dressing-based treatment for chronic non-healing ulcers.

It was observed through results of present investigation that greater number of patients who received topical phenytoin dressing based treatment exhibited the appearance of healthy granulation tissue in comparison to patients who received conventional saline dressing-based treatment for chronic non-healing ulcers. Results of current investigation revealed that pus culture of

significant number of patients post two weeks of treatment with topical phenytoin based dressing for chronic non healing ulcers was sterile indicating that there was no microbial colonization observed in chronic ulcers of topical phenytoin based treatment group; conversely it was observed that pus culture of 50% patients who received conventional saline dressing based treatment was unsterile indicating microbial infection in chronic non healing ulcers.

Thus from current study findings it was observed that topical phenytoin dressing based treatment of chronic non healing ulcers is not only more efficient in comparison to conventional saline based dressing treatment but topical phenytoin application also prevents microbial infection and colonization in chronic non healing ulcers the results of current investigation were in accordance to studies reported by Hokkam et al, Patil et al, Hao et al and Bharathi et al that claimed phenytoin dressings as more efficient treatment strategy for chronic non healing ulcers.²⁴⁻²⁷

Limitations

Limitations of present investigation were the small sample size of study participants and shorter duration of follow-up. Larger sample size and longer follow up duration would be recommended to establish a more significant correlation between the study parameters for both the treatment strategies.

CONCLUSION

Investigated parameters like nature of discharge, appearance of healthy granulation tissue, rate of healing and duration of hospital stay in the current study revealed that topical phenytoin-based dressing is more efficient strategy for management and treatment of chronic non-healing ulcers as compared to conventional saline dressing-based treatment. It was concluded from the study findings that topical phenytoin dressing based treatment not only significantly reduces the hospital stay duration of patients by aiding rapid healing of chronic ulcers but additionally topical application of phenytoin also prevented microbial infection or colonization in chronic non-healing ulcers.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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