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Original Article

Surgery Section

Phenytoin versus Normal Saline Dressings in the Healing of Chronic Diabetic Foot Ulcers: A Longitudinal Study

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ABSTRACT

Introduction: Chronic wounds, especially the non healing type, are among the foremost common conditions encountered by a surgeon. Currently, steady research is being pursued on the creation of fancy and indulgent topical growth factors for wound healing. One such agent is phenytoin which has a stimulatory effect on connective tissue. Several studies were conducted worldwide to study the effect of phenytoin on chronic ulcers. However, such studies are lacking in our geographical area.

Aim: To compare the efficacy of topical phenytoin dressings with conventional saline dressings in the healing of chronic Diabetic Foot Ulcers (DFUs), in terms of the surface area of ulcer, granulation tissue formation as a percentage of the surface area of ulcer, duration of hospital stay, and side effects.

Materials and Methods: This was a longitudinal study that included 100 patients with chronic DFUs admitted to a tertiary care hospital, in North Andhra Pradesh for a period of 1 year. The study population was divided into two groups based on the patient's willingness for undergoing topical phenytoin therapy. Patients willing to undergo the topical phenytoin dressing therapy formed the study group (n=50) and those who were not willing were subjected to traditional saline dressings, which formed the control group (n=50). The variables of the surface area of the ulcer, granulation tissue formation as a percentage of the surface area of the ulcer, duration of hospital stay, and side effects of topical phenytoin dressings were compared using Paired, and Unpaired Student's t-test, and the p-value of <0.05 was considered significant.

Results: The mean age in the study group was 53.94 years and in the control group was 55.92 years. The male:female ratio in the study group was 5:1 and in the control group was 3:1. The mean ulcer surface area in the control group was 37.6 cm^2 and in the study group was 40.4 cm^2 (p-value=0.012). The mean area of granulation tissue formation in the control group was 36.07 cm^2±5.7, and in the study group was 39.63 cm^2±2.6 of the total ulcer surface area (p-value=0.001). The granulation tissue formation in the control group was 95.93% of the total ulcer surface area, and in the study group was 98.09% of the total ulcer surface area (p-value=0.001). The mean hospital stay in the control group was 31.3±4.2 days and in the study group was 27.8±2.4 days (p-value=0.001).

Conclusion: Phenytoin is better alternative dressing agent with lesser side effects for diabetic foot ulcer care.

Keywords: Dressing agent, Granulation tissue, Hospital stay, Surface area

INTRODUCTION

Chronic wounds, especially the non healing type, are among the foremost common conditions encountered by a surgeon. The peculiarity of chronic wounds is that, despite daily dressings with expensive local applications, the wound doesn't heal. The problem is especially seen in DFU, [1-4], venous ulcers, and pressure ulcers [5]. It is estimated that 19-34% of patients with diabetes are likely to be affected by DFUs in their life time [6]. DFUs are the most common cause of hospitalisation in patients with Diabetes Mellitus. The aetiology of DFUs is multifactorial. The major underlying causes are peripheral neuropathy and ischemia from peripheral vascular disease. Other factors include trauma, deformity, callus formation, and oedema [7]. Treating these wounds is a continuous task for the surgeon. Currently, steady research is being pursuedon the creation of fancy and indulgent topical growth factors for wound healing. Thus, there remains a pursuit for better wound healing agents. One such agent is phenytoin, which is competitive and economical, convenient to use, and effortlessly available. Phenytoin was initially introduced for the treatment of convulsive disorders. In 1938, Meritt and Putnam published their note-worthy data using phenytoin to treat major, absence and psychic equivalent seizures [8]. One of the frequent side effects of systemic phenytoin treatment is the development of gingival hyperplasia [9,10]. This evident stimulatory effect of phenytoin on connective tissue promises a hopeful possibility for its use in wound healing [11]. Normal saline is a non irritant, physiological and isotonic solution. It acts by clearing away the cellular debris, reducing tissue edema, and thus preparing the wound bed for further management. The phenytoin wound healing mechanisms may include: stimulation of fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity, inhibition of glucocorticoid activity, stimulating neovascularisation, and increasing the gene expression of platelet-derived growth factor β-chain within macrophages and monocytes [12-18]. Several studies were conducted worldwide to study the effect of phenytoin on chronic ulcers. Many of them have proven the substantial benefit of phenytoin in wound care [19-26]. However, such studies are lacking in our geographical area. Hence, the present study was conducted to demonstrate the efficacy of topical phenytoin dressings and compare them with traditional saline dressings in the healing of chronic diabetic foot ulcers, in terms of extent (surface area) of ulcer, granulation tissue formation as a percentage of the surface area of ulcer, duration of hospital stays and side effects of phenytoin dressings.

MATERIALS AND METHODS

A longitudinal study was conducted in King George Hospital affiliated with Andhra Medical College of North Andhra Pradesh from August 2020 to July 2021. Institutional Ethics Committee approval was

obtained (08/IECAMC/FEB/2020). Informed consent was obtained. The study included 100 patients with chronic diabetic foot ulcers.

Inclusion criteria: Patients with diabetic foot ulcers of chronic duration (≥3 months). Diabetic patients between the cohort of 25 and 70 years. Patients who have ulcers measuring over one cm^2 over the lower leg and foot. Patients with glucose levels between 110 and 130 gm/dL. Patients with grade I and II ulcers of Wagner's classification [17] and patients who gave a legit consent for participation.

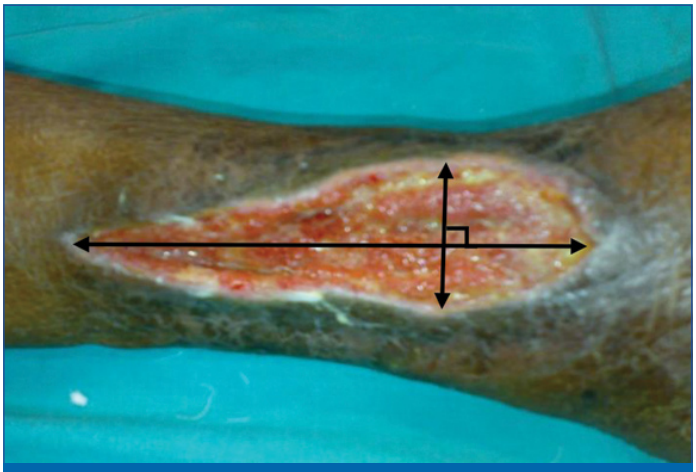
Exclusion criteria: Patients who were unwilling to participate in the study. Patients who were below the age of 25 years. Ulcers related to osteomyelitis, tuberculosis, and malignancy. Patients who were seropositive and had other co-morbid conditions like renal failure, and generalised debility which adversely affects wound healing, and patients known to be allergic to phenytoin were excluded.

Procedure

The study population was divided into two groups based on the patient's willingness for undergoing topical phenytoin therapy for the wound.

- **Control group** (n=50)- Patients who were not willing to take up the phenytoin dressings and hence were subjected to traditional saline dressings
- **Study group** (n=50)- Patients who were willing to undergo the topical phenytoin dressing therapy.

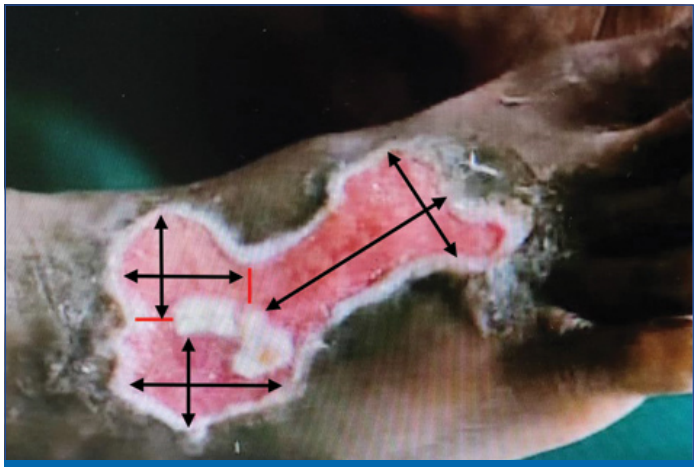
The wounds were thoroughly debrided wherever necessary. Pus culture and sensitivity studies were done for both study and control group patients and antibiotic therapy was advocated accordingly. The patients were subjected to X-rays to rule out the presence of osteomyelitis. After slough removal, the ulcer surface area was determined through mechanical planimetry by multiplying the two maximal perpendicular diameters of the ulcer, and it was expressed in square centimeters (cm^2) [Table/Fig-1].



[Table/Fig-1]: Measuring ulcer surface area.

For phenytoin dressing, one 100 mg phenytoin sodium tablet was placed in 5 mL of sterile normal saline to make a suspension. Sterile gauze was soaked in the suspension of phenytoin and placed over the wound at 20 mg/cm^2. The traditional dressing was done with a sterile surgical pad soaked with saline solutionat 5 mL/cm^2. Both the group patients were followed-up daily for 14 days.

At the end of 14 days, the extent of the ulcer area in both the control and study groups were inspected and compared based on the following parameters: Granulation tissue formation as a percentage of ulcer's extent (surface area) and duration of hospital stay. The granulation tissue formed at the end of 14 days was measured through mechanical planimetry by multiplying the two maximal perpendicular diameters of the granulation tissue formed, and it was expressed in square centimeters (cm^2). If in case the granulation tissue formed was patchy or if there was a non healing part of ulcer in between the granulation tissue formed, the ulcer was divided into multiple parts and the area of each part was calculated separately and added excluding the non healed area. This measurement was done twice and if both the values were identical then it was taken into consideration and if not, the mean of two values was taken into account. Then the percentage of ulcer area at the beginning of the study that is covered with granulation tissue at the end of the study was calculated [Table/Fig-2].



[Table/Fig-2]: Wound healing showing granulation tissue measurement.

STATISTICAL ANALYSIS

The data obtained were evaluated statistically, and the results were analysed using Microsoft excel 2016 version. The variables in both the groups were compared using Paired and Unpaired Student's t-test. A p-value <0.05 was considered significant.

RESULTS

It was observed that there were 42 males and 8 females in the study group and 37 males and 13 females in the control group. The mean age in the study group was 53.94±9.26 years and the mean age in the control group was 55.92±7.98 years. The number of cases with grade-1 ulcer was 14 in the study group and 17 in the control group whereas the number of cases with grade-2 ulcer was 36 in the study group and 33 in the control group.

The mean ulcer surface area in the control group was 37.6 cm^2 and in the study group was 40.4 cm^2 [Table/Fig-3]. The mean area of granulation tissue formation in the control group was 36.07 cm^2±5.7 and in the study group was 39.63 cm^2±2.6 of the total ulcer surface area. The mean of percentages of area of granulation tissue formation in the control group was 95.91% of total ulcer surface area and in the study group was 98.09% of total ulcer surface area.The p-value is 0.001, which is significant [Table/Fig-4].

Group	Surface area		t-value	p-value
	Mean±SD (cm^2)	Median (cm^2)		
Saline	37.60±7.22	38.6100	2.548	0.012
Phenytoin	40.40±2.84	40.2200		

[Table/Fig-3]: Ulcer Surface area.
A p-value of <0.05 was considered significant

Group	Granulation tissue area		t-value	p-value
	Mean±SD (cm^2)	Median (cm^2)		
Saline	36.071±5.7160	37.060	3.996	0.001
Phenytoin	39.63±2.6753	39.650		

[Table/Fig-4]: Area of Granulation tissue formation.
A p-value of <0.05 was considered significant

The mean hospital stay in the control group was 31.3±4.2 days and that in the study group was 27.8±2.4 days (p-value=0.001) [Table/Fig-5].

The most common organisms isolated in our study group were *E.Coli* (n=13), *Pseudomonas* (n=13), followed by *Klebsiella* (n=10),

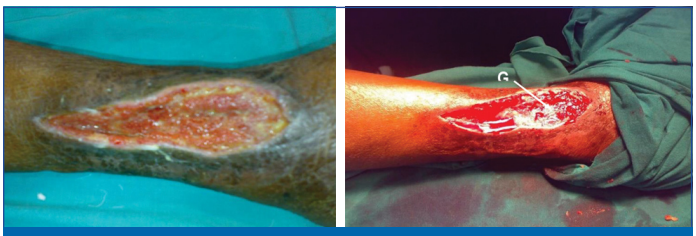
Group	Duration of hospital stay		t-value	p-value
	Mean±SD (days)	Median (days)		
Saline	31.30±4.200	30.00	4.992	0.001
Phenytoin	27.88±2.413	28.00		

[Table/Fig-5]: Duration of Hospital Stay.
A p-value of <0.05 was considered significant

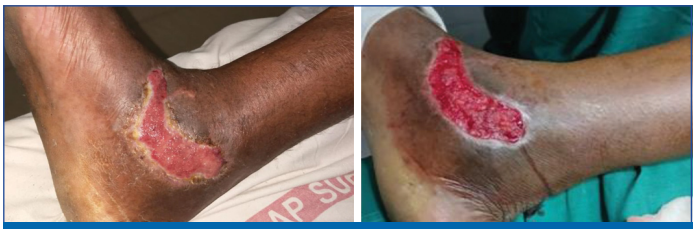
and *Staphylococcus* (n=4). The culture was sterile in 10 patients whereas in control group the most common organisms isolated were *E.Coli* (n=14), *Pseudomonas* (n=14), *Klebsiella* (n=13), *Staphylococcus* (n=4), *and Streptococcus* (n=1).

The culture was sterile in 4 patients in the control group. The treatment with antibiotics was based on the pus culture and sensitivity reports.

In both groups, no side effects or complications occurred during the hospital stay. The patients were followed-up after one month of discharge for any complications. No further complications were noted at the follow-up. The representative figures of predressing and postdressing for both study and control group is shown in [Table/Fig-6-9].



[Table/Fig-6]: Ulcer before phenytoin dressing. **[Table/Fig-7]:** Ulcer after phenytoin dressing. (Images from left to right)



[Table/Fig-8]: Ulcer before saline dressing. **[Table/Fig-9]:** Ulcer after saline dressing. (Images from left to right)

DISCUSSION

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates, and controlling local infections by local medications to the level of providing an adequate environment and promoting wound healing. This has been achieved by modern wound dressing agents which promote granulation tissue formation [18]. Phenytoin is one such promising agent which still requires extensive research for its application in chronic DFUs.

Phenytoin dressings in chronic DFUs which is an area of interest because of their low tendency for healing which poses a challenge for researchers worldwide.

In the present study, the mean age in the study group was 53.94 years and in the control group was 55.92 years. The results were similar to a study by Singh KS et al., in which the mean age was 53.50±7.52 years in the phenytoin group, while 53.35±7.29 years in the conventional group [19]. Our results were similar to another study conducted by Tauro LF et al., who identified the mean age in the study group to be 50.11±14.0 years and in the control group to be 51.41±13.4 years [20]. Patil V. et al., observed that the mean age of the study group was 48.5±12.49 years and that of the control group was 49.74±10.9 years. Their observations were slightly lower than the mean age of our study in both study and control groups [21].

In our study population, males outnumbered females which were similar to the findings of KS Sandhu et al., and Bharadva PB et al., [19,22]. This is in contrast to the studies conducted by Hokkam E et al., and Korber A et al., where females outnumbered males [23,24].

The amount of good granulation tissue is a major indicator of healthy healing. The mean granulation tissue formation as a percentage of surface area of ulcer in the saline dressing control group was 95.93% of the total ulcer surface area and in the phenytoin dressing study group was 98.09% of total ulcer surface area. These results were similar to a study by KS Singh et al., Tauro LF et al., and Yadwadkar S et al., revealed similar observations [19,20,25] [Table/Fig-10]. But their observations were slightly lower than that observed in the present study. However, Vijaya Patil et al., and Bharadva PB et al., observed a mean granulation area formation of only 62% and 67% respectively in their study groups [21,22].

Studies	Place of the study and Sample population (n)	Mean Granulation Area (in %)	
		Study	Control
Present study (2023)	Visakhapatnam, Andhra Pradesh, India (n=100)	98.09	95.93
Singh KS et al., [19] (2018)	Patiala, Punjab, India (n=40)	84.36	74.93
Yadwadkar S et al., [25] (2015)	Ahmednagar, Maharashtra, India (n=50)	97.93	97.07
Azeez A et al., [26] (2017)	Tumkur, Karnataka, India (n=90)	92	83
Tauro LF et al., [20] (2013)	Mangalore, Karnataka, India (n=200)	87.94	74.64
Patil V et al., [21] (2013)	Bijapur Karnataka, India (n=100)	62	12
Bharadva PB et al., [22] (2017)	Baroda, India (n=56)	67	10

[Table/Fig-10]: Comparison of granulation tissue area among various studies.

The mean hospital stay in the phenytoin dressings study group was 27.8±2.4 days and in the saline dressings control group was 31.3±4.2 days. The mean hospital stay of the total patient-population is 29.6±3.8 days. Our results were comparable to the results of studies conducted by Bharadva PB et al., and Yadwadkar S et al., whose hospital stay in their study groups were 26.48±3.2 days and 23.96±10.61 days respectively [22,25]. The hospital stay of the study groups in the studies conducted by Tauro LF et al., (36.26±2.64 days) and Azeez A et al., [26] (35.68±3.42 days) was higher than the observations made in the present study [20,26]. This was in contrast to a lower hospital stay observed by Singh KS et al., (21.35±4.17 days) and Vijaya Patil et al., (20.04±9.14 days) [19,21] in their study groups [Table/Fig-11].

Studies	Place of the study and sample population n	Average length of hospital stay (in days)	
		Study	Control
Present study (2023)	Visakhapatnam, Andhra Pradesh, India (n=100)	27.8±2.4	31.3±4.2
Yadwadkar S et al., [25] (2015)	Ahmednagar, Maharashtra, India (n=50)	26.48±3.2	33.2±3.2
BharadvaPB et al., [22] (2017)	Baroda, India (n=56)	23.96±10.61	35.10±14.23
Tauro LF et al., [20] (2013)	Mangalore, Karnataka, India (n=200)	36.26±2.64	40.97±3.31
Vijaya Patil et al., [21] (2013)	Bijapur Karnataka, India (n=100)	20.04±9.14	26.10±5.70
Azeez A et al., [26] (2017)	Tumkur, Karnataka, India (n=90)	35.68±3.42	47.31±7.3
SinghKS et al., [19] (2018)	Patiala, Punjab,India (n=40)	21.35±4.17	27.30±6.48

[Table/Fig-11]: Comparison of the length of hospital stay among various studies.

There were no adverse effects observed to topical phenytoin dressings in our study. These findings were in correlation with those observed by Shaw et al., who did not report any reactions [27].

Limitation(s)

The most important limitation of this study is its sample size and that it is not a randomised control study. The follow-up period was short. A randomised controlled study with a larger sample and longer follow-up period may help to further substantiate the findings or reveal variations that were not observed in the present study.

CONCLUSION(S)

Topical phenytoin dressings were superior to traditional saline dressings in the management of chronic diabetic foot ulcers. There were no side effects either to topical phenytoin dressings or conventional saline dressings during the hospital stay or during the follow-up period. Phenytoin may be a better alternative dressing agent for DFU care.

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