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A STUDY ON EFFICACY OF PHENYTOIN ON CHRONIC NON-HEALING DIABETIC ULCER

General Surgery

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ABSTRACT

Background: Chronic non-healing ulcer is one of the commonly faced surgical conditions by surgeons. It is one of the major causes for morbidity in diabetic patients. Inspite of various types of dressing agents available, choosing an appropriate dressing is a challenging aspect in the management of diabetic ulcer. Topical phenytoin causes rapid wound remodeling in non-healing ulcers and its application in wound healing needs further study. **Objective:** To assess the efficacy of topical phenytoin compared to conventional wound care in improving the healing process and to prove it as a relatively low cost and easy to use option in the management of diabetic ulcers. **Methodology:** Our study is a randomized prospective study conducted in the Department of Surgery, KR Hospital attached to Mysore Medical College and Research Institute, Mysuru on 50 patients with non-healing chronic diabetic ulcer during the period of November 2018 to May 2020. The patients were randomly divided into two groups study and control group (Study - phenytoin; Control - 5% povidone iodine). Wound measurement and culture growth was taken on day one and end of 14th day. Mean reduction in ulcer area and culture growth at the end of 14 days was noted. **Results:** In our study, we have observed that mean reduction in ulcer size in phenytoin group (8643.68±2348.95 mm^2) is statistically significant compared to povidone iodine group (2067.45±464.88 mm^2) and there is 56.8 ± 2.3% reduction in size in phenytoin group compared to 17.7±1.4% in the povidone group which is statistically significant. **Conclusion:** Phenytoin has a fibroblast proliferating and anti bacterial property which can be used in faster healing for chronic diabetic ulcers as topical agent thereby reducing its systemic side effects.

KEYWORDS

Diabetic ulcers; Povidone iodine; Topical phenytoin; Wound area

INTRODUCTION

Diabetic foot disease poses a growing global public health challenge and a major financial burden on healthcare systems worldwide. The prevalence of diabetes is exploding worldwide and is expected to involve more than 500 million people in next 10 to 15 years.

Diabetes is the leading cause of foot pathology, causing foot ulcerations from neuropathy, infection, and ischemia. Indeed, most non traumatic amputations in the United States and Canada are secondary to diabetic foot ulcers. Among people within the United States, up to 15% have active ulcers and 1 in 4 have a lifetime risk of developing a diabetic foot ulcer. Infection occurs in approximately half of diabetic foot ulcers, and many of these require amputation. Diabetic foot ulcers are one of the leading cause for hospital admissions and costlier aspects of diabetic care. This has led to a growing risk of amputation among diabetic patients, because 85% of patients presenting with a foot ulcer are at risk for a subsequent amputation. Various methods have been proposed by many authors over a period of time for healing and prevention of diabetic ulcer.[1]

The optimal topical therapy for diabetic foot ulcer remains ill defined. Standard method of dressings includes betadine and saline dressings but their disadvantage is maintaining the moist environment over longer duration. To overcome this newer dressings with various mechanism have been introduced. It includes hydrocolloid wound gels, growth factors, enzymatic debridement compounds, hyperbaric oxygen therapy, cultured skin substitutes, and other wound therapies have been advocated. All of these therapies are associated with significant expense and are being utilized in some situations without sufficient scientific evidence in favor of their efficacy.[2,3]

Phenytoin (diphenylhydantoin) was introduced into therapy in 1937 as an anticonvulsant. During course of the treatment the common side effect observed was gingival hyperplasia and this stimulatory effect may help in wound healing.

Since wound healing is a complicated process involving multiple steps. The mechanism by which phenytoin promotes wound healing is not understood completely. Several theories have been proposed on the phenytoin mechanism of action which include:[9,10]

1) Stimulation of fibroblast proliferation.
2) Enhancing the formation of granulation tissue.
3) Decreasing collagenase activity.
4) Inhibition of glucocorticoid activity.
5) Direct or Indirect antibacterial activity by affecting inflammatory cells.
6) Phenytoin increases gene expression of the platelet derived growth factor b chain in macrophage and monocytes and hence increases granulation tissue formation.

Diabetic ulcers are the indication for 50% of non traumatic amputations. There is a need for evaluation of new method for treating these ulcers which is economical and more effective in increasing healing rate and decreasing the amputation rate. Some studies on topical phenytoin have shown increased healing rate in chronic foot ulcers than other conventional dressings.[4,5,6] Systemic absorption of phenytoin on topical use in diabetic ulcer was not significant. Other side effects noticed on use of topical phenytoin in diabetic ulcer were transient burning sensation initially and hypergranulation.[4,5,6]

Though many studies are conducted on using topical phenytoin in chronic leg ulcers only few studies are conducted on diabetic ulcers and such studies have not been conducted in our institute.

OBJECTIVES OF THE STUDY

To assess the efficacy of topical phenytoin compared to conventional wound care in improving the healing process and to prove it as a relatively low cost and easy to use option in the management of diabetic ulcers.

METHODS

This prospective randomized comparative study included 50 patients with diabetic ulcers admitted In KR Hospital attached to Mysore Medical College and Research Institute, Mysuru from November 2018 to May 2020 satisfying all the inclusion criteria mentioned below after obtaining consent and clearance from the ethical committee

INCLUSION CRITERIA-

- Patients with chronic ulcers (ulcers of 4 weeks duration) with diabetes mellitus and wound size <5% TBSA

EXCLUSION CRITERIA-

- Chronic non-healing wounds of other etiology .
- Diabetes mellitus with gangrenous changes.
- Wounds with osteomyelitis.
- Other co-morbid conditions like generalized debility and other factors, which adversely affect wound healing.

The data were collected from 50 patients who were having diabetic ulcers satisfying the inclusion criteria mentioned above. The whole

sample population was equally divided into group A and group B randomly.

All patients underwent detailed clinical examination and relevant investigations and the wounds were thoroughly debrided and the ulcer dimensions as well as the surface area assessed using measuring tape, before both types of dressings were applied. The control group and study group were subjected to daily dressing. Discharge was sent for culture and sensitivity. Empirical antibiotics were started with ciprofloxacin and metronidazole changed to sensitive antibiotics after sensitivity report and also measures were taken for adequate glycemic control with Inj. plain insulin, oral hypoglycemic drugs and diabetic diet. The patients were followed up for 2 weeks in both study and control groups.

Application of Dressing:
Patients in group A were dressed with topical phenytoin (study group) and group B with povidone iodine (control group)

Topical Phenytoin:
Phenytoin sodium tablet was crushed and dissolved in 5ml of normal saline to form a suspension. Sterile gauze was soaked in the suspension and spread evenly over the ulcer and left for 24 hours till the next dressing.

Dosage of phenytoin depend on the surface area of ulcer
0 to 5 cm2-100mg
5.1 to 9cm2-150mg
9.1 to 15cm2-200mg
>15cm2- 300mg.

Control group dressing was done with 5% povidone iodine (betadine) once a day.

Before applying both dressing daily, wound was cleaned with normal saline and debridement was done if necessary. Ulcer size was measured initially and at the end of 14 days, size was recorded. Size was measured twice and mean of two was taken. Wound was also observed for granulation tissue, discharge at the end of 14 days was recorded, wound discharge was sent for culture and sensitivity on 14th day of treatment.

Statistical analysis
Analysis was done by using Cramer's V test, Independent-Samples T Test, Repeated measure ANOVA and level of significance chosen at $p<0.05$.

Investigations done were:
Routine blood investigations
-HbA1c
-Fasting Blood Sugar, Post prandial Blood Sugar
-Pus culture and sensitivity
-X-ray
-Arterial Doppler study

Ethical clearance was obtained from Mysore Medical College and Research Institute's ethics committee on human subject.

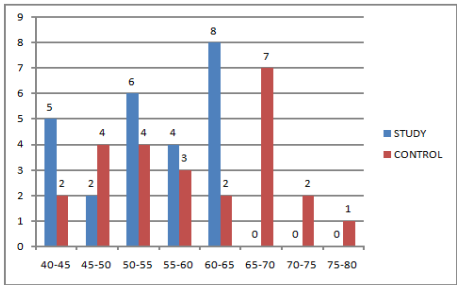
RESULTS

The present study was conducted in KR Hospital attached to Mysore Medical College and Research Institute, Mysuru and the findings are tabulated as below.

During the study year from November 2018 to May 2020, 50 patients with Diabetic foot ulcers were randomized into study (topical phenytoin dressings) and control (Povidine iodine) group. These groups were studied for the effect of conventional normal povidone iodine dressings versus topical phenytoin dressings on wound healing. A total of 50 patients who satisfied the selection criteria were involved in the study and analysis was done by using Cramer's V test, Independent-Samples t-test, Repeated measure ANOVA.

Table 1: Age wise distribution

Age group distribution (years)	Groups	
	Study	Control
40-45	5	2
45-50	2	4
50-55	6	4
55-60	4	3
60-65	8	2
65-70	0	7
70-75	0	2
75-80	0	1

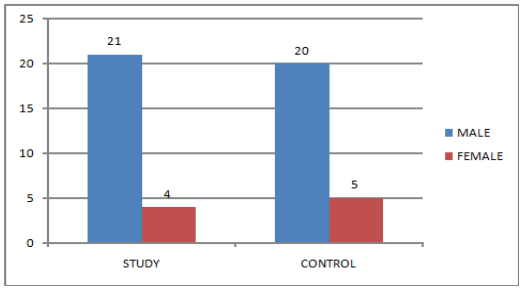


Graph 1: Age-wise distribution

In this study, the age distribution between the groups had no statistically significant difference.

Table 2: Gender distribution

Gender		Groups		Total	Signifi cance
		Study	Control		
Male	Number	21	20	41	0.713
	Percentage	84.0%	80.0%	82.0%	
Female	Number	4	5	9	
	Percentage	16.0%	20.0%	18.0%	
Total	Number	25	25	50	
	Percentage	100.0%	100.0%	100.0%	

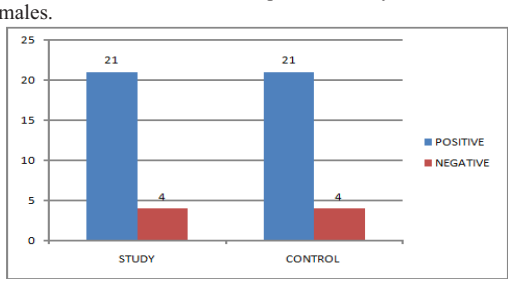


Graph 2: Gender distribution

Table 3: Culture conversion on day 1

Culture		Groups		Total	Significance
		Study	Control		
Positive	Number	21	21	42	1.000
	Percentage	84.0%	84.0%	84.0%	
Negative	Number	4	4	8	
	Percentage	16.0%	16.0%	16.0%	
Total	Number	25	25	50	
	Percentage	100.0%	100.0%	100.0%	

In the study group total number of males and females were 21(84%) and 4(16%) respectively. In the control group total number of males and females were 20 (80%) and 5(20%) respectively. Statistically in this study, there was no significant difference in sex distribution between interventional and control group. The table depicts that incidence of diabetic foot ulcer was predominantly more in male than in females.

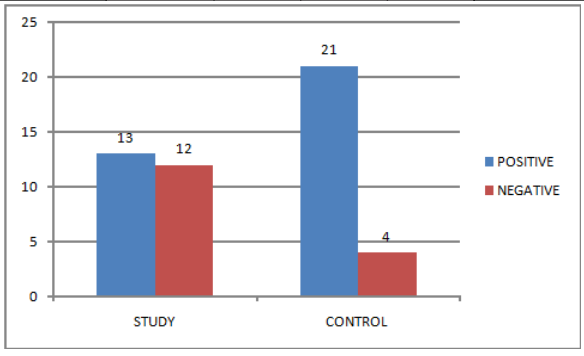


Graph 3: Culture conversion on day 1

In our study on day one, 21 (84%) patients in study group showed growth on culture and 4 (16%) patients showed no bacterial growth. In control group 21(84%) patients showed growth on culture media and remaining 4 (16%) showed no growth. There was no significant difference between two groups in positive culture growth on day one.

Table 4: Culture conversion on day 14

Culture		Groups		Total	Significance
		Study	Control		
Positive	Number	13	21	34	0.015
	Percentage	52.0%	84.0%	68.0%	
Negative	Number	12	4	16	
	Percentage	48.0%	16.0%	32.0%	
Total	Number	25	25	50	
	Percentage	100.0%	100.0%	100.0%	

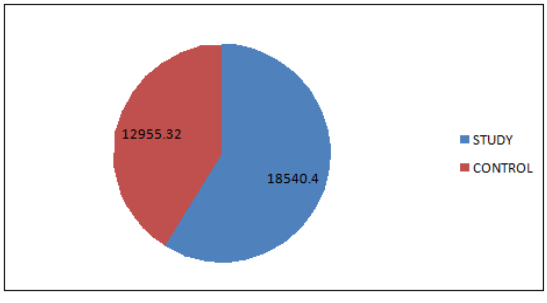


Graph 4: Culture conversion on day 14

Table 5: Comparison of culture conversion between day 1 and day 14

Comparison of culture conversion between day 1 and day 14

			Session		Total	Significance
			Day 1	Day 14		
Study	Positive	Number	21	13	34	0.015
		Percentage	84%	52.0%	68%	
	Negative	Number	4	12	16	
		Percentage	16%	48%	32%	
	Total	Number	25	25	50	
		Percentage	100%	100%	100%	
Control	Positive	Number	21	21	42	1.000
		Percentage	84%	84%	84%	
	Negative	Number	4	4	8	
		Percentage	16%	16%	16%	
	Total	Number	25	25	50	
		Percentage	100%	100%	100%	



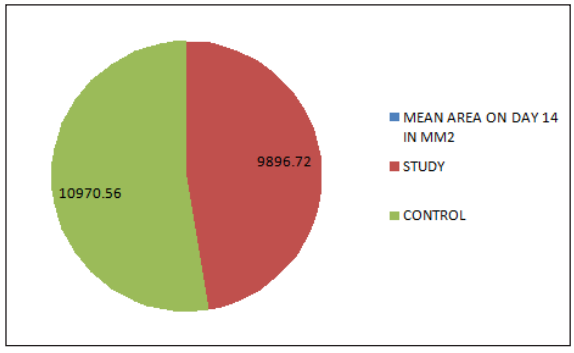
Graph 5: Wound area (mm2) on day 1

In our study, culture conversion from positive to negative was statistically significant ($p<0.05$) in phenytoin group when compared to povidone iodine group. In study group, 21 patients out of 25 were culture positive on day one which reduced to 13 patients (84% to 52%) on day 14 and no conversion of bacterial growth was noted in control group.

El-Zayat[7] in his study reported reduction of wound contamination with topical phenytoin and postulated it is not a direct anti bacterial effect, but rather a change in the pH and improvement in local circulation. However Lodha8 et al suggested that phenytoin may have a direct antibacterial effect. Further in vivo and in vitro studies are required to establish the anti-infective effect of topical phenytoin dressing and its mechanism of action.

Table 6: Wound area (mm2) on day 1 and day 14

Wound area	Groups	N	Mean SD	t-value	df	Significance
Day 1	Study	25	18540.4030714.32	.772	48	.444
	Control	25	12955.3219124.38			
Day 14	Study	25	9896.7219494.016	-.207	48	.837
	Control	25	10970.5617158.33			

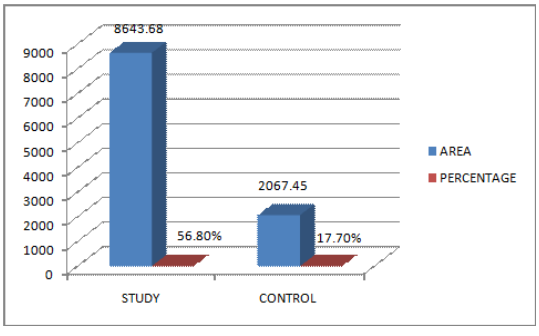


Graph 6: Wound area (mm2) on day 14

In our study, there was no statistically significant difference between the study (18540.40 mm2) and control (12955.32 mm2) in the initial wound area on day 1.

Table 7: Mean reduction in wound area (mm2)

Reduction in	Groups	N	Mean SD	t-value	df	Significance
Size	Study	25	8643.6811744.75	2.694	47	0.010
	Control	24	2067.462277.47			
Percentage	Study	25	56.8011.98	13.671	47	0.000
	Control	24	17.797.34			



Graph 7: Course of reduction in wound area (mm2)

In our study, we observed that mean reduction in ulcer size in phenytoin group (8643.68±2348.95 mm2) was statistically significant compared to povidone iodine group (2067.45±464.88 mm2) and there was 56.8 ± 2.3% reduction in ulcer size in phenytoin group compared to 17.7± 1.4% in control group which is statistically significant.

DISCUSSION

An ideal dressing is every surgeon's desire, a dressing that promotes chronic ulcer healing without any complications. Successful wound dressing should keep the wound moist and be devoid of any adverse reactions such as infection, maceration and allergy.

Diabetic ulcers are chronic wounds, stuck in inflammation phase and shows cessation of epidermal growth. The present study was conducted at Mysore Medical College and Research Institute, Mysuru to study the effect of topical phenytoin on diabetic ulcer healing dynamics.

Our study compares the efficacy of topical phenytoin with conventional povidone iodine dressing on chronic non-healing

diabetic ulcers. In both the groups the base line characteristics were similar. In our study non-healing ulcers of more than 4 weeks were chosen and in this study the treatment period was 2 weeks. In patients treated with topical phenytoin dressings the mean wound area in mm2 reduced from 18540.400 to 9896.72. The percentage of reduction in wound size was 56.82.3% compared to the 17.71.4% in control group. This study demonstrated that topical phenytoin dressings results in rapid wound area reduction and reduces wound infection in diabetic foot ulcers as culture conversion from positive to negative was statistically significant ($p<0.05$) in phenytoin group when compared to povidone iodine group. In study group, 21 patients out of 25 were culture positive on day one which reduced to 13 patients (84% to 52%) on day 14 and no conversion of bacterial growth was noted in control group.

The study is similar to the study conducted by Muthukumarswamy MG et al. The difference between the present study and the one done by Muthu was he used a thin layer of phenytoin powder over the wound. The study's sample size was 100, fifty in each group, mean age in study group was 56.4 yrs and 58.7 yrs in control. Graft take up was 72.4% and 58.43% respectively. Hospital stay was 21 days in study group and 45 days in control group. His study was done as a prospective randomized controlled comparative study to compare the efficacy of topical phenytoin moist dressing to conventional most wound dressing in management of diabetic ulcer.

In the present study it was seen that the incidence of diabetic ulcers were more in males (84%) compared to females (16%). The second national data source, NHDS documented higher hospital rates in males suffering from diabetic ulcers.

In our study, there was very significant faster reduction in wound size in phenytoin group compared to povidone iodine group. On day 14, the wound area in study group was 9896.72 mm2 when compared to control group 10970.56 mm2 which is statistically significant (p-value 0.207). Overall this study showed that phenytoin dressing is safe and effective in treating chronic foot ulcers. This study was conducted only for 2 weeks and complete epithelialisation and wound reduction was not awaited for.

CONCLUSION

With the use of topical phenytoin dressing in comparison with the povidone iodine dressing for the treatment of diabetic foot ulcers, the following conclusions were derived;

- Compared to study group, topical phenytoin dressing showed faster and better healing rates.
- Topical phenytoin group had better wound area and percentage reduction
- There were no adverse reactions on topical application.
- Compared to povidone iodine group the appearance of granulation tissue was earlier in topical phenytoin group.
- Topical phenytoin may also have an anti infective effect.

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