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Effect of topical phenytoin with normal saline dressing in patients of diabetic foot ulcers

Manohar Srinivas Reddy¹, Chandrashekar Reddy Jagadish Madinur²*

¹Department of Surgery, Sri Devraj Urs Medical College and Research Institute, Kollar, India

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*Correspondence:

Dr. Chandrashekar Reddy Jagadish Madinur,

E-mail: chandujams@gmail.com

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ABSTRACT

Background: The management of wound and wound dressing is an important aspect of chronic ulcer management. Choosing an appropriate dressing can be a complex process. Topical phenytoin helps in faster wound remodelling. The objective of the study was to assess the effect of topical phenytoin dressing with normal saline dressing in healing of diabetic foot ulcer in terms of mean decrease in size of the ulcer.

Methods: The present study was conducted on 60 patients with diabetic foot ulcer. The patients were divided into two different groups (group 1 topical phenytoin and group 2 normal saline dressing). Wound measurement was taken on day one and end of every week for four weeks. Mean reduction in ulcer area at the end of four weeks was calculated.

Results: There was no statistical difference in the baseline characteristics like age, sex and initial wound area of the ulcer between the two groups. The mean reduction in wound area was 1856.9 ± 724.9 mm² in patients treated with topical phenytoin dressings and 1066.8 ± 565.3 mm² in patients treated with normal saline dressings, which is statically significant (p<0.001).

Conclusions: The study concluded that the topical phenytoin dressing can be used for the healing of diabetic foot

Keywords: Diabetic ulcers, Topical phenytoin, Normal saline dressing, Wound area

INTRODUCTION

Chronic wounds, especially non healing types are one of the most common surgical conditions a surgeon comes across. One of the most feared complication of long term diabetes is loss of leg or foot. It has been estimated that one in five of all diabetic admissions to hospitals are for foot ulcers. From time immemorial doctors have been trying many methods to treat these types of wounds.

The diabetic foot ulcers arrest in inflammatory stage of healing due to neuropathy, angiopathy and infections. Risk of lower extremity amputation is 15 fold higher in

diabetics than non-diabetics. 15% of all the diabetics develop diabetic ulcer and the commonest site being the foot.² Treatment of these diabetic feet is a major problem. The quest for better wound healing is one of the oldest challenge for the medical practice.

The management of wound and wound dressing is an important aspect of diabetic ulcer management, which is neglected many a times. Care of the wound involves management of the ulcer, care of exudates and knowledge and rational use of myriad dressing materials.

Basic requirements of the ideal ulcer dressing are to maintain high humidity between wound and dressing;

²Department of General Surgery, Navodaya Medical College, Raichur, India

absorbent, which removes excess exudates; non-adherent, allowing easy removal without trauma at dressing change; safe and acceptable to patient (non-allergic); permits gaseous exchange but impermeable to microorganism; cost-effective.³

During the last decades, a wide variety of innovative dressings have been introduced.

Cost-effective treatment plan for diabetic foot includes surgical debridement of wound, improvement of circulation through surgery or therapy, special dressing and antibiotics. Numerous topical medication and gels are promoted for ulcer and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings. Topical antiseptic such as povidine-iodine are usually considered to be toxic to healing wounds

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 are 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.⁴⁻⁹

Patients with diabetic ulcers most of the time suffers which is defective wound healing and wound infections, which eventually leads to amputation of the lower limbs. 10

Few studies stated that topical phenytoin increased the healing rate of diabetic foot ulcers between 3rd and 4th week, but there was no difference in complete healing of the ulcers compared to other conventional dressings.^{4,5}

Phenytoin acts by stimulating fibroblasts enhancing granulation tissue formation, decreasing collagenase activity. 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. 5-8

Managing of diabetic foot ulcer is a challenge for surgeons. Different treatments have been studied and a traditional dressing with normal saline is used for treating the diabetic foot ulcer. It is not very effective and efficient. Insulin has been shown to promote proliferation and tissue healing by stimulating the growth of endothelial cells, keratinocytes and fibroblasts.

Though many studies are conducted on using topical phenytoin in chronic leg ulcers only few studies are conducted on diabetic ulcers, hence the present study undertaken to evaluate the effect of topical dressing with normal saline dressing in healing of diabetic foot ulcers.

METHODS

The present prospective study was conducted on patients with diabetic ulcers admitted in department of surgery, KLES hospital and medical research centre, Belgaum during January 2010 to December 2010 period of study satisfying all the inclusion criteria mentioned below after obtaining consent and clearance from the ethical committee.

Inclusion criteria

Patients with age between 35-70 years, patients with blood glucose level between 110 and 130 gm/dl, patients with grade one and grade two of Wagener's classification were included in the study.

Exclusion criteria

Patients with grade 3, grade 4 and grade 5 ulcers of Wagener's classification, patients with a bent peripheral pulses-dorsalis pedis, anterioral tibial, posterior tibial artery, patients who are not on regular follow up and not willing to enroll in the study, other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing were excluded from the study.

The data was collected form 60 patients who are having diabetic ulcers satisfying all the inclusion criteria mentioned. All the patients were randomly allocated in two groups. The whole sample population was divided into group A and group B based on computerized random number. Group A contained 30 patients and Group B contained 30 patients.

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. Empherical antibiotics were started with ciprofloxacin and metronidazole changed to sensitive antibiotics after asensitivity report. The patients were followed up for 4 weeks in both study and control groups.

Application of dress

Group A was dressed with topical phenytoin and group B with normal saline.

Topical phenytoin

Phenytoin sodium tablet was crushed and dissolved in 5 ml 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 depended on the surface area of ulcer: 0 to 5 cm 2 -100 mg, 5.1 to 9 cm 2 -150 mg, 9.1 to 15 cm 2 -200 mg, >15 cm 2 -300 mg.

Control group dressing was done with normal saline 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 every week for 4 weeks and 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 each week and recorded, wound discharge was sent for culture and sensitivity on 10th day of treatment.

Statistical analysis

Descriptive statistics such as mean, SD and percentage was used to present the data. Comparison between groups was done by using t-test. A p value less than 0.05 were considered as significant. Data analysis was performed by using software SPSS vs16.0.

RESULTS

In the interventional group, total number of males and females were 25 (83.33%) and 5 (16.66%) respectively. The male:female ratio was 5:1. In control group, total number of male and females were 26 (86.66%) and 4

(13.33%) respectively. The male:female ratio was 6.5:1. Statistically in this study there was no significant difference in sex distribution between interventional and control group.

In this study, the mean age in interventional group and control group were 54.8±9.96 and 56.9±10.77, respectively. Statistically there was no significant difference in mean age between interventional and control groups.

In our study on day zero, 20 (66.7%) of 30 patients in study group showed growth on culture and 10 patients showed no organism growth. In control group 16 of 30 patients showed growth on culture media and remaining 14 showed no growth. There was no significant difference between two group in positive culture growth on day zero (p=0.292).

On day 10 of the study 11 (36.7%) of 30 patients showed positive for culture in study group and 13 (43.3%) of 30 patients were positive for culture in control group. There was no significant difference between two groups for positive culture on day 10 (p=0.59).

In this study out of 20 patients in study group who positive for the culture growth on day zero, 9 had no growth on culture on day 10. the conversion of positive culture on day zero to negative culture on day 10 is statistically significant (p=0.004) in study group.

Interventional group **Control group** Characteristics % N Sex Male 25 83.3 26 86.7 5 4 13.3 Female 16.7 56.9±10.77 54.8±9.96 Age in years (mean±SD)

Table 1: Basic characteristics.

Table 2: Comparison of culture growth between groups at day 0 and 10.

	Interventional group		Control group				
	Positive (%)	Negative (%)	Positive (%)	Negative (%)	χ² value	P value	Remarks
At 0 day	20 (66.7)	10 (33.3)	16 (53.3)	14 (46.7)	1.11	0.29	Not significant
At 10 days	11 (36.7)	19 (63.3)	13 (43.3)	17 (56.7)	0.28	0.59	Not significant

Table 3: Culture conversation on day 10.

Basal cultures	Culture on da	y 10	P value	Remarks
Dasai cuitures	Positive	Negative	P value	Kemarks
Interventional group				
Positive	11	9	0.004	Cionificant
Negative	0	10	0.004	Significant
Control group				
Positive	13	3	0.25	Not significant
Negative	0	14	0.25	Not significant

Table 4: Comparison of wound area (mm²) between groups at initial and final.

	Interventional group		Control group		Tuelma	Dwolno	Remarks
	Mean	SD	Mean	SD	T value	P value	Remarks
Initial wound area (mm²)	2827.1	1149.1	3227.8	1791.8	1.03	0.31	Not significant
Final wound area (mm²)	973.2	453.3	2161	1293.2	4.75	< 0.0001	Highly significant

Table 5: Comparison of wound area reduction (mm²) between groups.

	Interventional group		Control group		T value	Danahas	Damaulia
	Mean	SD	Mean	SD	1 value	P value	Remarks
Reduction							
wound area	1856.9	724.9	1066.6	565.3	4.71	< 0.0001	Highly significant
(mm ²)							

In the control group out of 16 patients who were positive for culture on day zero, 3 had no growth on culture media on day ten. The conversion form positive culture to negative culture on day 10 in control group was not statistically significant (p=0.250).

The mean area the beginning of the study was $2827.1\pm1149.1 \text{ mm}^2$ in intervention group and $3227.8\pm1791.8 \text{ mm}^2$ in the normal saline group. There was no significant difference in the initial mean area between the two groups (p=0.31).

At the end of the study the mean area were 973.2 ± 453.3 mm² in the group treated with topical phenytoin dressings and 2161 ± 1293.2 mm² in the group treated with normal saline dressings. The difference in final wound area between two groups was significant (p<0.001).

The study shows that the final wound reduction achieved between the two groups were 1856.9±724.9 mm² in patients treated with normal saline dressing and 1066.8±565.3 mm² in patients treated with normal saline dressing, which is statistically significant (p<0.001).

DISCUSSION

It is every surgeon's desire that after dressing the wound, it should heal without any complications. Successful wound dressing should keep the wound moist and be devoid of any adverse reactions such infection, maceration and allergy. Diabetic foot ulcers are stuck in inflammation phase and shows cessation of epidermal growth or migration over the wound surface.

Phenytoin dressing has shown great promise as a procedure for healing of chronic wound (venous ulcers, pressure sores, superficial burn wounds, small donor site wounds and minor abrasions). Phenytoin act by stimulating fibroblasts enhancing granulation tissue formation, decreasing collagenase activity. 6

In the present study, an attempt has been made to establish better healing rates with use of phenytoin dressing in diabetic foot ulcer. In this study the base line characteristics such as age, sex and location of the ulcer were similar in the patients who received normal saline dressing in the control group.

This study was a comparative study which was aimed to document the safety and performance of phenytoin dressing in the treatment of established diabetic foot ulcers. Participants had an ulcer size bigger than one cm². The treatment period was 4 weeks. The mean wound area reduced from 2877.1±973.2 mm² in patients dressed with topical phenytoin. Relative wound area reduced from 100% at baseline to 35% at end of 4 weeks in study group. This study demonstrated that treatment of diabetic foot ulcer with topical phenytoin dressing results in considerable wound area reduction and prevented any deterioration in maceration. The percentage of area reduction was 66.2±4.64 in patients treated with topical phenytoin dressing and 33.05±7.1 in patients treated with normal saline dressing.

However, the final area of the ulcer (in mm²) was significantly reduced in patients with phenytoin dressing group as compared to the patients in normal saline group at the end of the study (p<0.001). The percentage reduction in the area of the ulcer was more in the phenytoin dressing (66.2 ± 4.64) group as compared to the normal saline group (33.05 ± 7.1) and this difference was statistically significant (p<0.001).

The following formula was applied to calculate % reduction in area of wound after 4 weeks period in both cases and controls.

Percent reduction of wound after 4 weeks= $\frac{initial\ area-final\ area}{initial\ area} \times 100.$

In our study, it was noticed that conversion from positive culture to negative culture growth on day 10 was significant in patients dressed with topical phenytoin (p=0.004) and was not significant in patients dressed with normal saline (p=0.250). E1 Zayat in his study reported 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 Lodha et al suggested that phenytoin may have a direct antibacterial effect. Further in vivo and vitro studies are required to establish the anti-infective effect of topical phenytoin dressing and its mechanism of action. 13

In this study it was noticed that compared to normal saline, topical phenytion is more effective in inhibiting wound infection. This conclusion was based on the following findings, earlier appearance of granulation tissue, earlier disappearance of wound discharge and post treatment wound cultures were negative in 9 of 20 patients who were treated with topical phenytoin, but only in 3 of 16 patients wound cultures were negative in control group, who received normal saline dressing.

Systemic absorption of phenytoin on topical use in diabetic ulcer is not significant. Most studies that have monitored serum phenytoin levels during topical application have shown the levels to be undetectable. Other known side effect of use of topical phenytoin in diabetic ulcer are transient burning sensation initially and hypergranulation. There were no side effect noted in the patients dressed with topical phenytoin in our study.

Overall this study shows that phenytoin dressing was safe and effective in treating chronic foot ulcers. This study was conducted only for 4 weeks and complete epithelialization and wound reduction was not awaited for.

Scope for further study

There is further scope of study among infective diabetic wound with respect to anti-infective properties of topical phenytoin dressing.

CONCLUSION

Topical phenytoin dressing showed faster and better healing rates among the study group. Area reduction and percentage reduction was better in topical phenytoin dressing group. There was no adverse effect or reactions seen when topical phenytoin dressing was applied over the ulcer. Appearance of granulation tissue was earlier as compared to regular dressing. Topical phenytoin dressing may have anti-infective properties.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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