



Efficacy of Phenytoin on Chronic Non Healing Diabetic Ulcer - A Prospective Study

Authors

Vijay Kumar. N^{*1}, Mohan K², Sunil Kumar M³, Mano Ananth A.B

^{1,2,3}Department of Plastic and Reconstructive Surgery, Mysore Medical College and Research Institute, Irwin road Mysore 570 001, Karnataka, India

*Corresponding Author

Vijay Kumar. N

Telephone: +919980134235, Email: drvijay17281@gmail.com

Abstract

Background: Chronic non healing ulcer is one of the major cause for morbidity in diabetic patients. In spite 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: This is a prospective study conducted in the Department of plastic surgery, K R Hospital on 100 patients with non-healing chronic diabetic ulcer during the period of November 2013 to June 2015. The patients are randomly divided into two groups study (phenytoin) and control (5% povidine iodine group). 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: There was no statistical difference in the baseline characteristics like age, sex, initial and final wound area of the ulcer between the two groups. The mean reduction in wound area was 6976.1 ± 1441.5 mm in patients treated with topical phenytoin dressings and 1960.7 ± 280.4 mm in patients treated with 5% povidine iodine dressings, which is statistically significant ($p < 0.001$).

Conclusions: 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.

Keyword: Diabetic ulcers, povidine iodine, topical phenytoin, Wound area.

Introduction

Chronic non healing ulcers are one of the common surgical conditions encountered, which is more commonly occurs in diabetic patients and nearly one fifth of diabetic patients admitted in hospitals are suffering from non-healing foot ulcers and leading

to lower limb amputations in many cases¹. Various methods has been proposed by many authors over a period of time for healing and prevention of diabetic ulcer. Since diabetes is a systemic disease which causes neurological, vascular and immunological complications favoring the foot ulcers to get

arrested in inflammatory stage of healing. Nearly 15% of all diabetic develop ulcers in their life time and the risk of lower limb amputations is 15 fold increases when compared to non-diabetics². Management of Non healing diabetic ulcer is challenging. The quest for better wound healing is one of the oldest challenge for the medical practice. During the last two decades a wide variety of innovative dressings have been introduced.

Basic requirements of the ideal ulcer dressing³;

1. Maintain high humidity between wound and dressing.
2. Absorbent, removes excess exudates.
3. Non-adherent, allowing easy removal without trauma at dressing change.
4. Safe and acceptable to patient (non-allergic).
5. Permit gaseous exchange but impermeable to micro-organism.
6. Cost-effective.

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 dressings⁴.

Few studies stated that topical phenytoin increased the healing rate of diabetic foot ulcers, 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 collagens activity.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.^{7,8}

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.

Materials and Methods

This prospective randomized comparative study included 100 patients with diabetic ulcers admitted In K.R HOSPITAL attached to Mysore medical college and research Institute, Mysore from November 2015 to June 2017

Inclusion criteria

- 1) Patients with chronic ulcers (ulcers of 4 weeks duration) with diabetes mellitus.
- 2) Wound size <5% TBSA

Exclusion criteria

- 1) Diabetes mellitus with gangrenous changes.
- 2) Wounds with osteomyelitis.
- 3) Wounds with poor vascularity
- 4) Other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing.

The data was collected from 100 patients who are having diabetic ulcers satisfying the inclusion criteria mentioned above. The whole sample population was divided into group A and group B randomly. Group A contain 50 patients and Group – B contain 50 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 is sent for culture and sensitivity. Empirical antibiotics are started with ciprofloxacin and metronidazole changed to sensitive antibiotics after sensitivity report. The patients were followed up for 2 weeks in both study and control groups.

Application of Dressing

Group A is dressed with topical phenytoin (study group) and group B with povidine iodine (control group). 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 is cleaned with normal saline and debridement is done if necessary. Ulcer size is measured initially and at the end of 14 days, size is recorded. Size is measured twice and mean of two is taken. Wound is also observed for granulation tissue, discharge at the end of 14 days are recorded, wound discharge is sent for culture and sensitivity on 14th day of treatment. All the routine blood investigations, x ray of the part, arterial Doppler done.

Statistical analysis

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

Discussion

Chronic Foot Ulcers

Acute ulcers are sometimes defined as those that follow the normal phases of healing; they are expected to show signs of healing in less than 4 weeks and include traumatic and postoperative wounds. Chronic ulcers are those that persist longer than 4 weeks and are often of complex poorly understood origin. Chronic leg ulceration affects about 1% of the middle-aged and elderly population. It most commonly occurs after a minor injury in association with chronic venous insufficiency (45-80%), chronic arterial insufficiency (5-20%), Diabetes (15-25%). Causes

of formation of chronic foot ulcer are recurrent infection, Trauma, Poor blood supply, edema, Loss of sensation.

Pathogenesis of Diabetic foot

Changes in foot caused by diabetes, 1.Dryness of skin and callus formation due to peripheral neuropathy. 2. High pressure at bony prominences due to; Decrease plantar tissue thickness, Weak intrinsic muscles of foot, Imbalances of flexors and extensors causing clawing of foot, Pulling away fat padding from metatarsal heads.3. Limited joint mobility due to; Collagen abnormality, Thickening of skin tendons and joint capsule, decreased tissue flexibility, increased plantar pressure.

Ulcer Management: Wound bed preparation removes many specific impediments to healing, including necrotic tissue, exudate, bacteria, and abnormal cells. Ulcers heal more quickly if their surface is clean and if sinuses are laid open. Vigorous and repeated sharp debridement of the wound is recommended, although evidence for efficacy is slim, complete excision of neuropathic ulcers did lead to faster healing. Necrotic material can also be removed with debriding agents (enzymes, hydrogels, and hydrocolloids) although evidence to justify their use is not available. Dressings used in chronic foot ulcer: Conventional dressings, such as gauze, impregnated gauze, gauze and cotton, packing strips have been in use for over fifty years.

Action of saline dressing

Normal saline dressing keeps the environment moist for proper healing. Normal saline dressing acts as an osmotic dressing, with time the concentration of the saline increases due to evaporation altering it from isotonic to hypertonic dressing which in turn decreases evaporation of fluid from the wound, keeping it moist.⁹ Moist wound environment that these dressings provide are best for wound regeneration and repair and increasing the velocity of healing. Effective wound management aims to strike a balance that is a moist environment to promote healing, but not so wet as to cause maceration and excoriation.

Two factors are important for natural wound healing. One is wound exudates which is generic term given to liquid produced from wounds. Exudate keeps the wound moist, supplies nutrients, and provides the medium for migration and mitosis of epithelial cells. This in turn, keeps the wound supplied with leucocytes, helping to control microorganism. Second factor is the presence of white cells in the wound. White cells play a major role in wound healing by cleaning the wound, remove potentially pathogenic microorganisms and producing collagen, the building block of new tissue. Excessive exudates can cause maceration and hence the dressing should be able to absorb excessive exudates from the wound.¹⁰

Topical Phenytoin

In 1938, Meritt and Putnam published their data using phenytoin to treat major, absence and psychic equivalent seizures. Since that time phenytoin has been considered highly effective anticonvulsant Phenytoin is type 1B anti arrhythmic and also used in treatment of trigeminal neuralgia Phenytoin has been used to treat ulcers epidermolysis bullosa and inflammatory condition.

Numerous allergy and proliferate, idiosyncratic cutaneous side effects have been reported with its use. A frequently observed and unwanted side effect of phenytoin, is gingival hyperplasia, especially in children. This side effect suggested that phenytoin can induce the growth of connective tissue, and may have the ability to promote wound healing. The beneficial effect of phenytoin in wound healing had been reported in 1945 and was observed in the first clinical trial for gingival wounds in 1958. Since then, the effectiveness of topical phenytoin has been confirmed by several clinical trials for different types of wounds.

Postulated Mechanisms of Action

Wound healing is a complicated process and the mechanism by which phenytoin promotes wound healing is not fully understood, but several theories have been proposed.

Phenytoin wound healing mechanisms may include^{11,12}: 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 p chain in macrophage and monocytes.

Topical Phenytoin Preparation Reported side effect

Topical phenytoin used in wound therapy appeared to be well tolerated. Its adverse effects were used in clinical trials. Systemic absorption was considered insignificant. Allergic reaction to topical phenytoin is rare. Formation of thin layer of phenytoin powder on the ulcer, initial burning sensation, skin rash are the other side effects of topical phenytoin which are resolved when application stopped^{13,14,15}

Systemic Side Effects^{16,17}: Long-term parenteral phenytoin can lead to a coarsening of the facies, enlargement of the lips and thickening of the scalp and face and also can cause hirsutism, Collagen Vascular Like Side Effects, can alter vitamin levels especially biotin metabolism. Has a variety of effects on copper zinc and magnesium in the hair and skin, generalized cutaneous eruptions Hypersensitivity syndrome, Pseudo lymphoma, Birth defects (fetal hydantoin syndrome).

Results

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 as 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 wounds (Venous ulcers, pressure sores, superficial burn wounds, small donor site wounds and minor abrasions). Phenytoin acts 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 phenytoin dressing in the study group and in patients who received povidone iodine dressing in the control group.

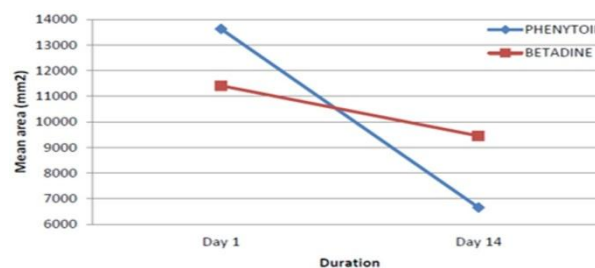
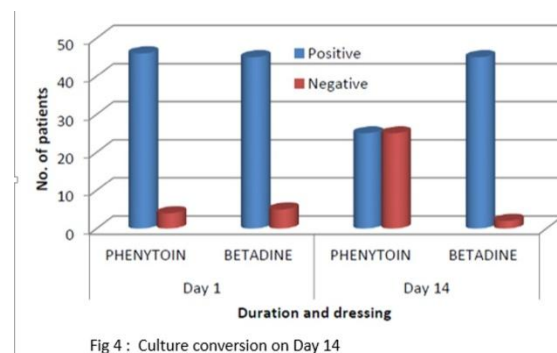
Table 1 : Culture on Day 1 and Day 14

		Dressing		ToTal
		Phenytoin	Povidine iodine	
Culture and sensitivity DAY 1	Positive	46	45	91
	Negative	4	5	9
Culture and sensitivity DAY 14	Positive	25	45	70
	Negative	25	5	30

This study is a comparative study which is aimed to document the safety and performance of phenytoin dressing in the treatment of established diabetic foot ulcers. The non-healing ulcers should be of more than 4 weeks duration and less than 5% of body surface area. The treatment period was 2 weeks. The mean wound area reduced from 13621.3 ± 1441.5 mm² to 6645.1 ± 280.4 mm² in patients dressed with topical phenytoin. Percentage of reduction in wound size is 62.1 ± 1.7 % compared to 18.5 ± 1.1 % reduction in control group. This study demonstrates that treatment of diabetic foot ulcer with topical phenytoin dressing results in considerable and rapid wound area reduction and reduces infection rate in ulcer. However, the final area of the ulcer (in mm²) was not reduced in patients with phenytoin dressing group as compared to the patients in povidone iodine group but the percentage reduction in the area of the ulcer was more in the phenytoin dressing group 62.1 ± 1.7 % as compared to the control group 18.5 ± 1.1 % and this difference was statistically significant ($p < 0.001$).

Table 2 : Mean reduction in wound area

	Dressing	N	Mean	Stardard deviation	Stardard error
Reduction in size	Phenytoin	50	6976.1380	10193.51978	1441.58139
	Povidine iodine	50	1960.7416	1982.96866	280.43412
Reduction in percentage	Phenytoin	50	62.1311	12.03716	1.70231
	Povidine iodine	50	18.5397	7.99421	1.13055



In our study it was noticed that conversion from positive culture to negative culture growth on day 14 was significant in patients dressed with topical phenytoin ($p = 0.00$). It is not a direct anti-bacterial effect, but rather a change in the pH and improvement in local circulation.

In this study it was noticed that compared to povidone iodine, topical phenytoin 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 25 of 50 patients who were treated with topical phenytoin, but there is no conversion noted in patients wound cultures in control group, who received povidone iodine dressing. Systemic absorption of phenytoin on topical use in diabetic ulcer is not significant. There were no side effects noted in the patients dressed with topical phenytoin in our study

Table 3: Independent Samples Test

		t- Test for equality Means			
		t	df	Sig. (2-tailed)	Mean Difference
REDUCTION SIZE	IN	3.415	98	.001	5015.39640
REDUCTION PERCENTAGE	IN	21.331	98	.000	43.59137

Overall this study shows that phenytoin dressing is safe and effective in treating chronic foot ulcers. This study was conducted only for 2 weeks and complete epithelialization and wound reduction was not awaited for.

**Fig 1****Fig 2****Fig 3**

Limitations of our study

Not a blinded study, Follow up is short to derive conclusion on long term healing of the ulcers.

Scope for further study

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

Conclusions

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; 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 5 % povidone iodine dressing .Topical phenytoin dressing may have anti-bacterial effect.

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