

Original Research Article

Role of topical phenytoin in treatment of chronic venous ulcers

Santosh Kumar Singh, Sneh Lata*, Anil Kumar Gupta, Rajkumar

Department of Dermatology, Venereology and Leprosy, Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh, India

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***Correspondence:**

Dr. Sneh Lata,

E-mail: ysneha2008@gmail.com

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ABSTRACT

Background: Venous leg ulcers are a common cause of significant morbidity leading to compromised quality of life and a huge financial burden on patients. Apart from the systemic therapy, many topical agents are available to accelerate healing in these ulcers. Topical phenytoin is one such agent which has been studied for promotion of wound healing. The aim of the study was to study the efficacy of topical phenytoin in healing of chronic venous ulcers.

Methods: 56 patients of chronic venous ulcer were randomly divided in two groups of 28 each. First group was given daily dressing of phenytoin in normal saline (group A) and second group was given only normal saline dressing (group B) for a period of 8 weeks. After 8 weeks the reduction in size of ulcer was measured, on the basis of which results were calculated.

Results: The mean age of the patients was 50.29 ± 13.37 years. The mean duration of ulcer was 10.13 ± 4.66 weeks. Compared to the conventional normal saline dressing, patients given phenytoin and normal saline dressing showed far greater tendency to heal ($p=0.02$). 35.7% patients in phenytoin group showed excellent response out of which 21.42% achieved complete healing, while in normal saline group only 14.28% patients showed excellent response and none of patient showed complete healing. No significant adverse effects were observed in either of the group.

Conclusions: Topical phenytoin appears to be a safe, easy, effective and inexpensive option to promote wound healing and can be used as an adjuvant for treatment of chronic venous ulcers. Further studies with larger population are merited.

Keywords: Topical phenytoin, Chronic venous ulcer, Management

INTRODUCTION

Venous ulcers are the most common cause of leg ulcers worldwide. As they tend to become chronic, they cause a significant morbidity and distress to the patients. Venous ulcers arise from the effects of compromised venous return. Two main causes are venous valve incompetence and calf muscle pump failure. The resultant retrograde blood flow causes venous hypertension which leads to leakage of fibrinogen producing “fibrin cuffs” that interfere with tissue nourishment. Besides this, leaked white blood cells get trapped in soft tissues leading to

injury and inflammation. All these factors result in stasis dermatitis and eventually ulceration.^{1,2} Veins can be damaged by surgery, trauma, or deep vein thrombosis (DVT), which causes a backflow of blood in the venous system at the point of damage. Other causative factors include multiple pregnancies, obesity, congenital vein abnormalities, and varicose veins. Out of these the two main causes are varicose veins and postphlebotic syndrome following deep vein thrombosis.³ Multitude of treatment options and strategies have emerged over years including mechanical (leg elevation and compression bandages etc.), systemic drugs (aspirin, penntoxifylline

etc.), surgical (sclerotherapy, vein stripping and vein ligation) and topical. In the topical wound care, there are many options like wet and dry dressings, unna boots, hydrocolloid dressings and phenytoin.

Phenytoin (diphenylhydantoin or dilantin) was introduced as an effective agent for treatment of convulsive disorders. Since one of the side effects of phenytoin is gingival hypertrophy, its stimulatory effect can be used to promote wound healing.⁴ A study by Shapiro et al reported healing of gingival ulcers in non-epileptic patients by use of oral phenytoin in non-epileptic patients in 1958.⁵ The first double-blind, placebo-controlled clinical study involving the use of phenytoin in leg ulcers demonstrated that, when compared with controls, the use of phenytoin promoted wound healing.⁶ Since then many studies have shown the effect of phenytoin in promotion of different types of wounds like diabetic foot ulcers, trophic ulcers in leprosy, chronic leg ulcers, pressure ulcers, superficial burn wounds and traumatic wounds.⁷⁻¹⁵

In the present study we aim to assess the role of topical phenytoin in chronic venous ulcers.

METHODS

The study was conducted on 56 patients of chronic venous ulcer in the department of Dermatology, Venereology and Leprology, Nehru Hospital, BRD Medical College, Gorakhpur in east Uttar Pradesh, India. Study was conducted from April 2018 to September 2018 after taking due approval from institute ethics committee and proper consent from patients.

The inclusion criteria were patients with chronic venous ulcer (duration ≥ 6 weeks), wound size ≤ 25 cm², ulcers with active infection, patient giving written informed consent.¹⁶

The exclusion criteria were chronic non-healing wounds of other etiology, venous ulcer with gangrenous changes, wounds with osteomyelitis, other co-morbid conditions like uncontrolled diabetes mellitus, renal failure, generalized debility and other factors, which adversely affect wound healing, pregnancy, lactation, known allergy to phenytoin.

The patients were divided into two groups A and B of 28 each by 2:2 block randomization.

All patients underwent detailed clinical examination and relevant investigations after taking complete medical history. All patients were given systemic calcium dobesilate 500 mg BD and advised leg elevation. In both the groups the wounds were thoroughly debrided (surgically under local anesthesia) and the baseline ulcer dimensions were measured using centimeter scale and surface area was calculated. In group A, a single 100 mg phenytoin sodium capsule was opened and placed in 1 ml

of sterile normal saline to form a suspension. This suspension was directly applied over ulcer which was then covered with a sterile gauze and dressing was done. In the other group, the dressing was done with gauze soaked only in normal saline. In both the groups dressing was done once a day, until complete healing of ulcer or completion of 8 weeks whichever was earlier. Weekly assessment of ulcer healing was done and at the end of 8 weeks response was classified as excellent, good, fair and poor, if the percentage reduction in ulcer size was $>90\%$, 70% to 90%, 50% to 70% and $<50\%$ respectively.

The percentage of change in ulcer surface area was calculated as:

$$\% \text{ change} = \frac{\text{Pretreatment surface area} - \text{final surface area}}{\text{Pretreatment surface area}} \times 100$$

Results were analyzed using student's *t*-test for quantitative variables while Chi square test was used for qualitative variables. A probability value (p value) less than 0.05 was considered statistically significant.

RESULTS

The mean age of the patients in phenytoin group (group A) was 50.29 ± 13.37 years and 51.34 ± 14.57 years in normal saline group (Group B). Females outnumbered the males in both the groups with 17 females and 11 males in the group A and 14 females and 11 males in group B. Age and sex distribution was comparable in both the groups. There was no statistical difference between the two groups in terms of age or gender. The mean duration of ulcer in study group and control group was 12.53 ± 5.66 weeks and 12.07 ± 4.23 weeks respectively and the mean size was 4.16 ± 1.87 cm² and 3.26 ± 1.73 cm² respectively. The major cause of ulcers was varicose veins in both the groups with 63% patients affected in phenytoin group and 59% in normal saline (NS) group. The other main factor was post-phlebotic syndrome following DVT. The housewives, teachers, cooks and security guards were most commonly affected.

Table 1: Age and sex distribution with reference to ulcer size and duration.

Characteristics	Group A (phenytoin+NS)	Group B (NS only)
Age (in years)	50.29±13.37	51.34±14.57
Sex		
Male	17	14
Female	11	11
Duration (weeks)	12.53±5.66	12.07±4.23
Size (cm²)	4.16±1.87	3.26±1.73

NS: normal saline.

At the end of treatment period (8 weeks) percentage reduction in surface area of the ulcer was calculated (Table 1). 35.7% patients in phenytoin group showed excellent response out of which 21.42% achieved

complete healing, while in normal saline group only 14.28% patients showed excellent response and none of patient showed complete healing. The patients in study group showed significant reduction in ulcer size as compared to control group (p=0.02). There were no significant side-effects except mild burning sensation in 41.61% patients in phenytoin group and 23.47% in normal saline group.

Table 2: Percentage improvement in ulcer size.

Response	Group A (phenytoin+NS) (n=28)	Group B (NS) (n=28)
	N (%)	N (%)
Complete healing	6 (21.42)	0
>90%	10 (35.7)	4 (14.28)
70%-90%	12 (42.86)	7 (25)
50%-70%	4 (14.28)	9 (32.14)
<50%	2 (7.14)	8 (28.57)

NS: normal saline.



Figure 3: Pretreatment.



Figure 1: Pre-treatment.



Figure 4: After treatment with phenytoin.



Figure 2: Healthy granulation tissue after treatment with phenytoin.

DISCUSSION

Phenytoin has been in therapy for a very long time as anticonvulsant. Among its many side effects, one major unwanted effect is gingival hyperplasia, as reported by Kimball et al.⁴ These effects of phenytoin lead many investigators to try it in wound healing. In 1958, a clinical study by Shapiro demonstrated that phenytoin sodium accelerates gingival wound healing compared with controls. Since then, the efficacy of phenytoin has been confirmed in several clinical trials for different types of wounds.

Phenytoin promotes wound healing through multiple mechanisms, including stimulation of fibroblast-proliferation, facilitation of collagen deposition, inhibition of glucocorticoid activity, direct and indirect antibacterial activity, neovascularization and increasing the gene expression of platelet derived growth factor in β chain in macrophages and monocytes.^{7,17-20} Antibacterial activity of topical phenytoin on wounds was investigated and confirmed by many clinical studies.^{7,21,22} It is not known if phenytoin has intrinsic antibacterial activity, or whether the effect of phenytoin on the bacterial load of wounds is mediated indirectly by effects on inflammatory cells and neovascularization.¹⁵

The first double-blind, placebo-controlled clinical study on role of phenytoin in leg ulcers was conducted by Simpson et al.⁶ They used oral phenytoin sodium to treat 28 patients of venous leg ulcers and demonstrated that, when compared with controls, the use of phenytoin promoted wound healing. Our study showed similar results except in our study, topical phenytoin was used instead of systemic phenytoin. Topical phenytoin has similar wound healing effects without the side-effects of systemic phenytoin.⁸ In a study conducted by Pendse et al, seventy-five in-patients with chronic skin ulcers were included in this controlled trial.²¹ Forty patients were treated with topical phenytoin, and 35 patients with conventional saline dressings. Wound area reduction was greater in the phenytoin group than in controls. Healthy granulation tissue appeared earlier with phenytoin. At the end of the fourth week, 29 of 40 (72.5%) phenytoin treated ulcers had healed completely versus 10 of 35 (28.57%) controls. In comparison our study showed complete healing in 21.42% phenytoin treated ulcers whereas none of the ulcers in saline group showed complete healing, both of which are lower than reported by Pendse et al.²¹ 35.7% of phenytoin treated group showed >90% healing compared to 14.28% of saline group.

Adverse effects with topical phenytoin are mild and far less than oral route. Some patients have a burning sensation initially on application.²³ In our study 23.47% patients complained of burning sensation which was transient and resolved within few minutes without intervention. A generalized rash that resolved when treatment was stopped has also been reported by Rhodes et al.¹³ Hypertrophic granulation tissue was noted in few studies.^{7,21} Stopping treatment when the wound area is covered with a granulation base can prevent this effect.⁶ Systemic absorption of topical phenytoin is not significant. Most studies that have monitored serum phenytoin levels during topical application have shown the levels to be undetectable.²⁴

CONCLUSION

Topical phenytoin promotes wound healing with minimal side effects and appears to be a better option than the conventional saline dressing. In our study it was used as

an adjuvant to the systemic therapy for venous ulcers and proved to be safe, easy, effective, inexpensive and easily available topical agent to promote wound healing. Further studies with larger population are merited.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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