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Topical Phenytoin: Role in Diabetic Ulcer Care

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ABSTRACT

Foot complications are a major cause of hospitalization in patients with diabetes mellitus. The optimal topical therapy for diabetic foot ulcers remains ill-defined. Saline-moistened gauze has been the standard method; however, it has been difficult to continuously maintain a moist wound environment with these dressings. Phenytoin was introduced into therapy in 1937 for effective control of convulsive disorders with a common side effect being gingival hyperplasia. This stimulatory effect of phenytoin on connective tissue suggested possibility for its use in wound healing. The objective of this study was 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. In this randomised control trial, the data from 50 patients with diabetic ulcers was collected, 25 patients underwent topical phenytoin dressing while remaining 25 underwent conventional wound care. Following parameters were calculated and compared for both groups: (1) Rate of granulation tissue formation (at the end of 14 days); (2) Graft survival and take up (fifth post-op day after split thickness skin grafting); and (3) Duration of hospital stay. Statistical analysis was done by SPSS ver. 20 and p-value of <0.05 was considered as significant. The following were observed : in study group, the mean rate of granulation tissue formation was 88.21%, mean graft take up was 93.78% of total ulcer surface area and mean hospital stay was 32.21 days. The control group showed, the mean rate of granulation tissue formation was 71.32%, the mean graft take up was 85.98% of total ulcer surface area and mean hospital stay was 38.76 days. It was concluded that Topical phenytoin helps in faster healing with better graft take up and reduces hospital stay.

Keywords: Conventional Dressing, Diabetic Ulcer, Phenytoin

INTRODUCTION

Foot complications are a major cause of hospitalization in patients with diabetes mellitus (DM), which consumes a high number of hospital days because of multiple surgical procedures and prolonged length of stay [1]. Patients with DM have up to a 25% lifetime risk of developing a foot ulcer [2], which precedes amputation in up to 85% of cases [3]. A mainstay of diabetic foot ulcer (DFU) therapy is debridement of all necrotic, callus, and fibrous tissue [4, 5], with a primary goal to obtain wound closure. The management of the DFU is largely determined by its severity (grade), vascularity of the limb, and the presence of infection [6–8].

In India habits like walking barefooted, lack of knowledge regarding diabetic foot, hot climate leading to increased perspiration, poor hygiene, poor sanitation, diet poor in proteins, general poverty, lack of basic medical infrastructure, etc have worsened the problem.

Over the years the life expectancy of diabetic patient with gangrene of foot has not changed much. Advances in treatment of diabetes have caused increase in life span of diabetic patient which has resulted in an increase in complications of Diabetes Mellitus like vasculopathy, neuropathy, nephropathy. This in return has increased the prevalence and incidence of diabetic foot.

The optimal topical therapy for DFU remains ill-defined. Saline-moistened gauze has been the standard method; however, it has been difficult to continuously maintain a moist wound environment with these dressings.

Subsequently, various 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 favour of their efficacy [9].

Phenytoin (diphenylhydantoin) was introduced into therapy in 1937 for effective control of convulsive disorders with a common side effect being gingival hyperplasia. This stimulatory effect of phenytoin on connective tissue suggested possibility for its use in wound healing. The beneficial effect of phenytoin has been shown in promoting healing of decubitus ulcers, venous stasis ulcers, traumatic wounds, burns, leprosy trophic ulcers [10].

The present study was conducted to assess the efficacy of topical phenytoin dressing as compared to conventional moist wound dressing in the healing process of diabetic ulcers and to check whether it is a better alternative in the management of diabetic ulcers.

MATERIALS AND METHODS

An open labelled randomised control trial was conducted including 50 patients with diabetic ulcers admitted in the department of Surgery of a tertiary care hospital of Jaipur, India. All diabetic ulcers where conventional dressings are indicated were included in the study.

The inclusion criteria were:

- (1) Patients with chronic ulcers (ulcers of 8 weeks duration) with diabetes mellitus.
- (2) Wound size <5% TBSA.

The exclusion criteria were:

- (1) Chronic non-healing wounds of other etiology
- (2) Diabetes mellitus with gangrenous changes
- (3) Wounds with osteomyelitis.
- (4) Wounds with poor vascularity determined by arterial Doppler study.
- (5) Other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing.

The data was collected from 50 patients who were having diabetic ulcers satisfying all the inclusion criteria mentioned above. Selection of patients was done from consecutive series of prospective patients. The patients were allocated randomly into the study and the control group. The study group included the patients undergoing wound care with topical phenytoin therapy while control group patients were subjected to conventional wound care. We have included 25 patients in each group.

All patients underwent detailed clinical examination and relevant investigations. The wounds were thoroughly debrided (surgically under anesthesia) and the ulcer dimensions as well as the surface area were assessed using vernier calipers, immediately after debridement and reassessed after 14 days in either type of dressings. Both the groups underwent wound dressings twice a day. The patients were followed up on a daily basis for 14 days in both the study and the control groups.

A single 100 mg phenytoin sodium capsule was opened and placed in 5 ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20 mg/cm² TBSA. Conventional Dressing was done with 5% w/v povidone – iodine solution. Before applying the dressing, the wound was cleaned with normal saline.

At the end of 14 days the wounds in both the groups were inspected and compared. Once these desired parameters were assessed, both the groups were subjected to split thickness skin grafting. Both the groups were given the same systemic antibiotics (ceftriaxone 1 g intra-venous for 5~7 days with metronidazole 100 ml t.i.d. for 3 days) during the postoperative period. The wounds were again assessed and compared at the end of the fifth postoperative day. The follow-up of these patients was done in the outpatient department after one month of discharge to assess post skin grafting complications like contractures, itching, pain and infection, wound dimensions. Following parameters were calculated and compared for both groups:

- (1) *Rate of granulation tissue formation (at the end of 14 days),*
- (2) *Graft survival and take up (fifth post-op day after split thickness skin grafting),*
- (3) *Duration of hospital stay.*

Statistical analysis was done using SPSS ver. 20 and p-value <0.05 was considered as significant.

RESULTS

The mean age in the study group was 55.71 ± 11.5 years and in the control group was 54.31 ± 12.24 years ($p > 0.05$). In the study group, 21 patients were males and 4 were females while in control group, males were 19 and females were 6 ($p > 0.05$). Both the groups had comparable age and sex distribution.

The efficacy of the dressing was assessed as the percentage of ulcer surface area covered by granulation tissue after 14 days. The mean rate of granulation tissue formation in study group was 88.21 ± 6.98 % and in the control group was 71.32 ± 7.9 % ($p < 0.01$) (Table 1).

The patients in both the groups were subjected to split thickness skin grafting as the final treatment modality. The graft take up was then assessed at the end of 5th post-operative day as the percentage of ulcer surface area. The mean graft taken up in the study group was 93.78 ± 5.41 % and in the control group was 85.98 ± 6.91 ($p < 0.01$) (Table 2).

The total hospital stay (the total number of days of admission in the hospital) was assessed in both groups. The mean hospital stay in the study group was 32.21 ± 3.11 days and that in the control group was 38.76 ± 4.2 days ($p < 0.01$) (Table 3).

DISCUSSION

Phenytoin has been investigated as a treatment for more than 100 diseases. Numerous allergy and proliferative, idiosyncratic cutaneous side effects have been reported with its use [11]. A frequent observed and unwanted side effect of phenytoin, an anticonvulsant medication, is gingival hyperplasia, especially in children [12]. This side effect suggested that phenytoin can induce the growth of connective tissue, and may have the ability to promote wound healing. In 1939 Kimball and Horan first observed that gingival hyperplasia occurred in some patients treated with phenytoin. This stimulated the first controlled clinical trial in 1958, which found that the periodontal patients with surgical wounds who were pretreated with oral phenytoin had less inflammation, less pain, and accelerated healing when compared with controls [13]. Phenytoin has been investigated to treat ulcers in epidermolysis bullosa and other inflammatory conditions. Since then, the effectiveness of topical phenytoin has been confirmed by several clinical trials for different types of wounds.

The earliest clinical study of phenytoin in cutaneous wound healing used oral phenytoin sodium to treat venous stasis ulcers in 28 patients in a double-blind, placebo-controlled trial [14]. Phenytoin promotes wound healing by following mechanisms: Stimulation of fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity, inhibition of glucocorticoid activity, direct or indirect antibacterial activity by affecting

inflammatory cells, neovascularisation [15-18] and phenytoin increases gene expression of the platelet derived growth factor β chain in macrophage and monocytes [19].

A number of clinical studies indicate that phenytoin decreases the bacterial load of wounds [15,20,21]. 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 neovascularisation [22]. Local pain relief has also been observed with topical phenytoin therapy, which can be explained by its membrane-stabilizing action and the reduced inflammatory response [17,23].

The prospective, controlled trial by Muthukumarswamy et al. [15] examined the use of topical phenytoin versus control therapy in 100 non-insulin dependent diabetic patients with foot ulcers. In the control group (n=50), a sterile occlusive dressing was applied daily. In the phenytoin group (n=50), phenytoin powder was applied in a "thin layer" to the ulcer surface, and then dry dressing applied daily. Mean healing time was 21 days in the phenytoin group compared to 45 days in the control group ($p < 0.05\%$).

Tauro LF et al. [10] observed 200 patients with diabetic ulcers. Hundred patients underwent topical phenytoin dressing while remaining underwent conventional wound care. The results were compared after 14 days. In study group, mean rate of granulation tissue formation was 87.94%, mean graft take up was 92.31% and mean hospital stay was 32.26 days with negative culture sensitivity was 70%. The control group showed, the mean rate of granulation tissue formation was 74.64%, the mean graft take was 86.15% of total ulcer surface area and mean hospital stay was 54 days with negative culture sensitivity was 54%. They concluded that topical phenytoin aids in faster healing of diabetic wounds with better graft take up and decreased hospital stay. A study conducted by Pai et al. [24] also showed good granulation tissue with topical phenytoin.

CONCLUSION

We conclude that topical phenytoin dressing helps in better graft take up than the conventional dressing. Because of enhanced healing, overall hospital stay and post-operative complications were less in topical phenytoin dressing group. Thus, topical phenytoin moist wound dressing can be considered as superior option in the management of diabetic ulcers. But further studies with larger sample will be needed in the future before topical phenytoin dressing can be added to the wide spectrum of treatment modalities available in the management of diabetic ulcers.

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Tables

Table 1. Rate of granulation tissue formation as percentage of ulcer surface area

| Group | N | Mean (%) | SD | p- value |
|---------|----|----------|------|----------|
| Study | 25 | 88.21 | 6.98 | < 0.01 |
| Control | 25 | 71.32 | 7.9 | |

Table 2. Graft take up as percentage of ulcer surface area

| Group | N | Mean (%) | SD | p- value |
|---------|----|----------|------|----------|
| Study | 25 | 93.78 | 5.41 | < 0.01 |
| Control | 25 | 85.98 | 6.91 | |

Table 3. Duration of hospital stay

| Group | N | Mean (days) | SD | p- value |
|---------|----|-------------|------|----------|
| Study | 25 | 32.21 | 3.11 | < 0.01 |
| Control | 25 | 38.76 | 4.20 | |