Original Research Paper

Volume-8 | Issue-10 | October-2018 | PRINT ISSN No 2249-555X

General Surgery

A COMPARATIVE STUDY OF EFFICACY OF TOPICAL PHENYTOIN VERSUS CONVENTIONAL WOUND CARE IN DIABETIC ULCERS

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ABSTRACT

INTRODUCTION: Diabetic ulcer is a significant healthcare problem with its healing depending on many factors. Many agents have been tried in wound healing and one such agent is phenytoin. The aim of this prospective comparative study was to compare the efficacy of topical phenytoin with conventional wound dressings in the healing of diabetic ulcers.

PATIENTS AND METHODS: This prospective comparative study included fifty patients, with 25 patients in each group. The patients were compared in terms of number of days required for healing, rate of granulation tissue formation, effect on bacterial load and skin graft up take.

OBSERVATIONS AND RESULTS: Both the groups were comparable in terms of patient demographics. Rate of granulation tissue formation was more rapid in phenytoin group with a mean of 85.21% as compared to conventional moist dressing group with a mean of 70.32%. Hospital stay was significantly reduced in phenytoin group with a mean of 30.04 days compared to conventional moist dressing group with a mean of 45.10 days. Percentage of graft uptake is more in phenytoin group with a mean of 91.78% compared to conventional moist dressing group with a mean of 75.48%.

CONCLUSION: Rate of granulation tissue formation, overall graft uptake, patient compliance and overall hospital stay were better in the topical phenytoin dressing group. Thus, topical phenytoin moist wound dressing can be considered as a superior option in the management of diabetic ulcers.

KEYWORDS : Diabetic ulcers, Topical phenytoin, Conventional moist dressings.

INTRODUCTION:

Diabetic ulcer is a significant health care problem with its healing depending on many factors such as glycemic control, nutritional status of the patient, bacterial load, vascularity and location of the wound[1, 2]. Diabetic foot ulcers precede almost 85% of amputations in India[3]. Diabetic foot ulcers are extremely debilitating and difficult to treat. Multidisciplinary management which includes patient education, glycemic control, debridement, offloading, infection control and adequate perfusion is the mainstay of standard care endorsed by most practice guidelines.

Many agents have been tried in wound healing and one such agent is phenytoin. Phenytoin (diphenylhydantoin) was introduced into therapy in 1937 for effective control of convulsive disorders[4, 5] 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 and trophic ulcers[6].

A chronic diabetic foot ulcer remains difficult to manage. Topical phenytoin stimulates the development of granulation tissue formation within 2 to 7 days after beginning treatment and is associated with non-detectable serum phenytoin levels[7, 8]. Hence it was planned to take up a study on the results of the efficacy of topical phenytoin in diabetic ulcer management.

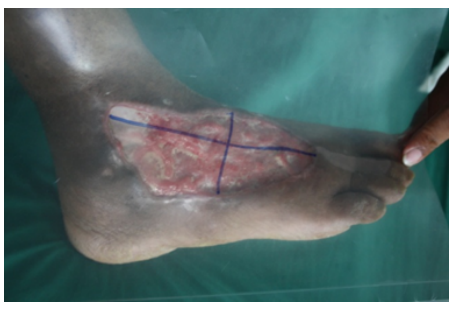
PATIENTS AND METHODS:

The present study was a single-centre, prospective, comparative study. It was conducted on patients admitted with diabetic foot ulcer in Mamata General Hospital from October 2015 to March 2017. A total of 50 patients were studied with 25 patients in each group (Group A and B). Group A were treated with phenytoin dressing and Group B with conventional dressing. Institutional ethical committee approval and informed consent from patient were taken before start of the study.

Routine pre-operative investigations were done in both the groups. In diabetic patients, glycemic control was achieved using oral hypoglycemic and/or insulin therapy. Before starting the therapeutic procedure, culture & sensitivity swabs were taken from ulcers. Debridement of dirty and crusted wound was done. Once the ulcer was free from infection and necrotic debris, it was included in the study. All patients were treated empirically with capsule amoxicillin and clavulanate potassium 625mg/TID at the time of admission. Later antibiotics were changed according to culture and sensitivity report. Dressings were changed daily. Wound swab for culture and sensitivity were sent on weekly basis during the study period.

Measurements: Ulcer was measured using a sterile transparent paper placed on the wound to mark ulcer borders. Two largest perpendicular diameters were measured using a ruler (in centimeters). To calculate the ulcer area, these two diameters were multiplied to obtain area of ulcer (cm^2).

Figure 1: Measurement of ulcer dimensions



Group A: A single 100mg phenytoin sodium tablet was mixed with 5ml of sterile normal saline and sterile gauze soaked in the suspension was placed over the wound. Phenytoin suspension was used at a concentration of 20mg/cm^2 surface area of ulcer.

Group B: Conventional dressing was done with gauze soaked in 5% w/v povidone-iodine solution.

In both the groups, the wound was cleaned with normal saline before applying the dressing. Wounds were inspected in both groups at the end of 7 and 14 days. The end point of study was taken as complete ulcer healing or appearance of red granulation tissue which was suitable for spilt skin grafting, or up to a time period of 1 month, or whichever was earlier. Rate of wound healing was calculated as the difference between the primary wound on the day 1 and wound healing at 1 week, 2 weeks and 1 month.

Statistical Analysis: Paired T test for quantitative data and Pearson chi

square test for qualitative data were used to evaluate the P value. Differences were considered statistically significant, if P < 0.05. IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) software program was used for statistical calculations.

OBSERVATIONS AND RESULTS:

There was no significant difference in terms of age, sex in both the groups (Table 1). Ulcer size from day 1 to day 30 was compared in both the groups; phenytoin group has shown a better result (Table 1). Reduction in mean ulcer size was 66% in phenytoin group and 56.7% in conventional group (Table 2).

Mean percentage of red granulation tissue formation by the end of 2 weeks was 90% in phenytoin group and 68% in conventional group. Number of completely healed ulcers was 32% in phenytoin group and 24% in conventional group. Mean duration of hospital stay in phenytoin group was 27.8 days while that of conventional group was 31.3 days. Percentage of negative culture and sensitivity at the end of 14 days was 88% in group A and 72% in group B (Table 2).

Fig 2: Red granulation tissue over ulcer after phenytoin dressing

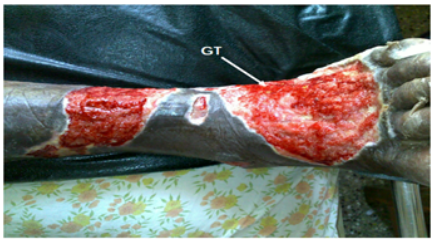


Fig 3: Grafted ulcer on follow up

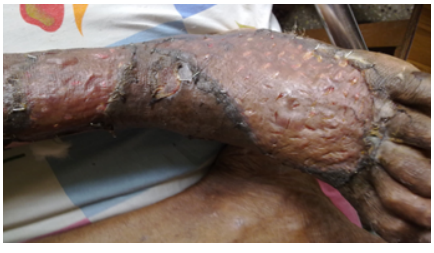


Table 1: Demographic profile and ulcer size in both groups

Variable		Phenytoin group	Conventional group	P value
Mean age in years		40.27	46.9	0.15
Sex	Male	20	21	-
	Female	5	4	
Ulcer size in cm^2	Day 1	7.98	8.6	0.565
	Day 7	6.82	7.72	0.048
	Day 15	5.27	6.4	0.03
	Day 30	2.7	3.76	0.001

Table 2: Comparison of study variables in both the study groups

Variable	Phenytoin group	Conventional group	P value (P<0.05 significant)
Decrease in mean Ulcer size	66%	56.7%	0.001
Mean % of red Granulation tissue By the end of 2 weeks	90%	68%	0.012
Number of completely healed ulcers	32%	24%	0.032
Mean duration of Hospital stay	27.8	31.3	0.05
Percentage of negative c/s by the end of 14 days	88%	72%	0.048

DISCUSSION:

In 1938, Merritt and Putnam published their noteworthy data using phenytoin to treat major, absence and psychic equivalent seizures[3]. Since that time, phenytoin (diphenylhydantoin or Dilantin) has been demonstrated to be a highly effective anticonvulsant. Even decades later, it continues to be a widely prescribed anticonvulsant agent in the treatment of grand mal and psychomotor epilepsy.

Phenytoin has been investigated as a treatment for more than 100 diseases. Numerous allergic and proliferative idiosyncratic cutaneous side effects have been reported with its use[3]. A frequent observed and unwanted side effect of phenytoin is gingival hyperplasia, especially in children on long term phenytoin therapy (more than 4 years).

Used topically, it appears to enhance wound healing without side effects. So phenytoin has been studied (mostly with inadequate controls) in the healing of pressure ulcers, venous stasis ulcers, diabetic ulcers, traumatic wounds and burns[9]. Phenytoin increases gene expression of the platelet-derived growth factor B chain in macrophages and monocytes[10].

Mechanism of action of topical phenytoin:

- Stimulation of fibroblast proliferation
- Enhances formation of granulation tissue
- Decreases collagenase activity
- Inhibition of glucocorticoid activity
- Direct or indirect antibacterial activity by affecting inflammatory cells
- Neovascularisation by increasing gene expression of the platelet derived growth factor β chain in macrophage and monocytes.

A number of clinical studies indicate that phenytoin decreases the bacterial load of wounds. 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.

Leo F Tauro et al[11] 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. 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[12] also showed good granulation tissue formation with topical phenytoin.

The present study is similar to the studies conducted by Leo F Tauro et al[11], Ritu Raj et al[13] and V.Patil et al[14] except the sample size. Sample size in studies by Ritu Raj et al al[13] and V.Patil et al[14] was 100 whereas in the present study, the sample size is 50 patients. Sample size in the study by Leo F Taura et al[11] was 200. All the above mentioned studies documented better results in phenytoin group when compared with conventional dressing group.

Table 3: Comparison with other similar studies

Variable	Leo F Tauro (2013)		V. Patil (2013)		Rita Raj (2015)		Present Study	
	Study	Control	Study	Control	Study	Control	Study	Control
Sample size (n)	100	100	50	50	50	50	25	25
Mean age (years)	50.11	51.41	48.50	49.74	55.71	54.31	47.28	49.20
Rate of Granulation (%)	87.94	76.64	78.30	73.50	88.21	71.32	85.21	70.32
Mean graft take up (%)	92.31	86.15	72.40	58.43	93.78	85.98	91.78	75.48
Mean hospital Stay (days)	32.26	54.00	20.04	26.10	32.21	38.76	27.8	31.2

CONCLUSION: Rate of granulation tissue formation, overall graft survival and patient compliance is better in topical phenytoin dressing group as compared to conventional dressing group. Thus, topical phenytoin moist wound dressing can be considered as a superior option in the management of diabetic ulcers.

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