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A Comparative Study of Topical Phenytoin Versus Conventional Wound Care in Diabetic Ulcers

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ABSTRACT
A diabetic ulcer is a significant healthcare problem. A chronic diabetic foot ulcer remains difficult to manage., topical application of phenytoin has been used successfully in the management of diabetic foot ulcer. It stimulates the development of granulation tissue formation within 2 to 7 days after beginning treatment and is associated with non-detectable serum phenytoin levels. Aim of the study is to compare the efficacy of topical phenytoin with conventional wound dressings in healing of diabetic ulcers, in terms of Number of days required for healing, Rate of granulation tissue formation, Quality of graft bed and skin graft up take, Effect on bacterial load and Side effects of topical phenytoin dressing. This was a Prospective Comparative Observational Study which consists of 50 patients admitted with Diabetic Ulcers in Government Medical College, Ongole over a period of one year and There was male predominance as compared to female population in the study (M: F=4:1). The mean rate of granulation tissue formation in study group is 95.93cm of total ulcer surface area and in control group is 98.09cm. The mean graft uptake in the study group is 99.03cm and in the control group is 97.61cm. The total number of hospital stay for the patients, mean number of days in study group was 27.8 days and control group was 31.3 days. 45% of study group showed negative culture sensitivity at the end of 14 days whereas in control group it was 37%. Pseudomonas was the commonest organism in the study (68%) followed by MRSA (52%). Number of ulcer dressing changes were less in phenytoin group (10.68) as compared to povidone iodine group(16.52). Thus reducing the ulcer size does affects the man working hours of the patient. Early return to work does reduce the financial burden on the patient. The use of phenytoin dressing accelerates the rate of wound healing in diabetic ulcers.

INTRODUCTION

Diabetic ulcers is a significant healthcare problem with its healing depending on many factors such as glycemic control, vascularity, bacterial load, location of the wound and nutritional status of the patient[1,2]. Many agents have been tried in wound healing, one such agent is phenytoin.

Phenytoin (diphenylhydantoin) was introduced into therapy in 1937 for effective control of convulsive disorders[3,4] 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 wound, burns and trophic ulcers[5].

A chronic diabetic foot ulcer remains difficult to manage., topical application of phenytoin has been used successfully in the management of diabetic foot ulcer[6,7]. It stimulates the development of granulation tissue formation within 2-7 days after beginning treatment and is associated with non-detectable serum phenytoin levels[7,8]. There are so many wound care modalities for diabetic ulcers seen in the literature., one such is local wound care with topical phenytoin application. Hence it was planned to take up a study on the results of the efficacy of topical phenytoin in diabetic ulcer management.

Aims and Objectives of the study: To compare the efficacy of topical phenytoin with conventional wound dressings in healing of diabetic ulcers, in terms of:

- No of days required for healing
- Rate of granulation tissue formation
- Quality of graft bed and skin graft up take
- Effect on bacterial load
- Side effects of topical phenytoin dressing.

Patients and Methods: This was a Prospective Comparative Observational Study which consists of 50 patients admitted with Diabetic Ulcers in Government Medical College, Ongole over a period of one year. A series of 50 cases was compiled for this study during this period, after obtaining clearance from ethical committee. These 50 patients are divided into 2 groups for study purpose, group A (n=25) patients were treated with Phenytoin Dressing, whereas group B (n=25) patients were treated with Conventional Dressing method using normal saline and povidone-iodine. Analytical data obtained was compared and discussed with the data available in the literature.

Inclusion Criteria: Patients with Diabetic ulcers of size <5% TBSA.

Exclusion Criteria: Chronic non-healing ulcers of other etiology, with gangrenous changes, with Osteomyelitis, with poor vascularity determined by arterial Doppler study, other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing, Patients, who give prior history of hypersensitivity to phenytoin drug.

A single 100mg phenytoin sodium tablet was mixed with 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20mg/cm^2 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 7 days, 14 days the wounds in both groups were inspected[9,10].

RESULTS AND DISCUSSIONS

Number of Ulcer Dressings Changed: Minimum and maximum number of ulcer dressings changed in this study was 6 and 15 in Group A with a mean of 10.68, whereas in case of Group B, they were 10 and 23 with a mean of 16.52.

Number of Debridement: Average (mean) number of debridement required were 1.6 and 2.7 in Group A and Group B respectively. Statistically it is significant with a $P<0.05$.

Granulation Tissue Formation Time: Mean percentage of red granulation tissue by the end of 2 weeks in Group A was 90% and that of Group B was 68%. This is statistically significant with a $P<0.05$.

Number of Completely Healed Ulcers: Number of completely healed ulcers were 8 (32 %) in Group A and 6 (24%) in Group B respectively.

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates and controlling local infections by local medications to the level of providing adequate environment promoting wound healing. This has been achieved by modern wound dressing agents, which promote granulation tissue formation. As the concept of 'outcome based medicine' evolved, the need for a better wound dressing modality has become more acute.

This study was done as a prospective comparative observational study, to compare the efficacy of using phenytoin dressing to conventional wound care with debridement in management of diabetic ulcers.

Ulcer Size Comparison: In a similar study done by Leo F Tauro[12], it was found that out of 60 patients of the phenytoin group, 42 (70%) wounds showed complete closure with phenytoin dressing in six weeks or lesser.

This is comparable with the present study. In another study done by V.Patil[11], on 276 patients of diabetic foot ulcer divided equally into two groups, one group was treated with phenytoin and the second with other dressing materials. They found no significant difference in the completeness of healing of wounds when old wounds (> six months old) were compared. But the healing was better in wounds of less than six months duration treated with phenytoin dressings. Although in the present study, there was a significant improvement in ulcer size even in older ulcers after 4 weeks. A Study by S Bhattacharya[16], showed excellent results by using phenytoin on patients with Toxic Epidermal Necrolysis (TEN). Mathangi Ramakrishnan[17], used phenytoin based dressings in superficial and partial thickness burns. 73% of all cases healed without any infection and complete epithelialization was seen within 6 weeks.

Table 1: Age Wise Distribution

Age (Yrs)	Group A	Group B
31-40	7	7
41-50	7	7
51-60	4	5
61-70	7	6
Mean	49.48Yrs	49.4Yrs

Statistically it is not significant

Table 2: Sex Wise Distribution

Sex	Group A	Group B	Total
Male	20	21	41
Female	5	4	9
Total	25	25	50
Male : Female was 5.25:1	Chi-square = 0.54, P>0.05		

Table 3: Ulcer Size at Day 1, Day 7, Day 15 And Day 30

Ulcer size at (in cm2)	Group A (n=25)		Group B (n=25)		
	Mean	SD	Mean	SD	p-value
Day 1	7.98	4.0	8.6	4.51	>0.05
Day 7	6.82	3.54	7.72	4.15	>0.05
Day 15	5.27	3.0	6.4	3.68	>0.05
Day 30	2.7	1.38	3.76	2.31	<0.01

Table 4: Reduction In Mean Ulcer Size

Parameter	Group A	Group B	P value
Reduction in mean Ulcer size (%)	66%	56.7%	< 0.01

Table 5: Organisms isolated during the study

Organism isolated	Group A (n=25)	Group B (n=25)
MRSA	3 (12%)	10 (40%)
MSSA	7 (28%)	8 (32%)
E coli	2 (8%)	3 (12%)
Pseudomonas	13 (52%)	4 (16%)
Total	25	25

Table 6: Comparison of age wise distribution

Study	Group A (Mean age)	Group B (Mean age)
V.Patil *et al*[11]	56	56
Leo F Tauro *et al*[12]	43.75	43.75
Harish rao *et al*[13]	43.88	50.41
Present study	49.48	49.4

Table 7: Comparison of sex wise distribution

	Group A	Group B
V.Patil *et al*[11]	2.21	3.6
Leo F Tauro *et al*[12]	2.33	2.0
Present study	4	5.25

Table 8: Comparison of reduction in mean ulcer size

Study	Group A	Group B
Pendse *et al.*[14]	80.6%	61.1%
Pai MR *et al.*[15]	45.43%	23.4%
Present study	66%	56.7%

Table 9: Comparison of average (mean) number of ulcer dressings changed.

Study	Group A	Group B
V.Patil *et al*[11]	10.1	11.2
Karunakar reddy *et al*[18]	6.96	17.89
Present study	10.68	16.52

Table 10: Comparison of average (mean) number of ulcer debridement.

Study	Group A	Group B
Karunakar reddy *et al*[19]	2.07	2.58
Present study	1.6	2.68

Table 11: Comparison of mean % of granulation tissue formation by the end of 2 weeks.

Study	Group A	Group B
Present	90%	68%
Shankar20	93.68%	65.59

Table 12: Comparison of percentage of number of completely healed ulcers

Study	Group A	Group B
Leo F Tauro *et al*[12]	70%	63%
V.Patil *et al*[11]	51%	28%
Present study	32%	24%

Table 13: Comparison of bacteria isolated during the study

Organism isolated	Harish et al.		Present study	
	Group A	Group B	Group A	Group B
Pseudomonas	17.11%	29.17%	52%	16%
Staphylococcus (MSSA and MRSA)	42.11%	45.83%	40%	72%
Escherichia coli	12.5%	12.5%	8%	12%
Mixed infection	6.58%	4.17%	-	-

Table 14: comparison of duration hospital stay during the study

Group	Mean hospital stay	P value
Phenytoin	27.8 ± 2.4	0.02
Betadine	31.3 ± 4.2	

Table 15: Comparison of percentage of negative c/s in both the groups at the end of 14 days

Culture and sensitivity	Group		
	Group A (n=25)	Group B(n=25)	Total(n=50)
Negative	22 (88%)	18(72%)	40(80%)
Positive	3 (12%)	7(28%)	10(20%)
total	25 (100%)	25(100%)	50(100%)

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 use6. A Medline search in November of 2002 showed that 12,860 articles concerning Phenytoin have been published since 1966. In dermatology, phenytoin has been investigated to treat ulcers, epidermolysis bullosa and inflammatory conditions.

Phenytoin has been studied (mostly with inadequate controls) in the healing of pressure ulcers, venous stasis ulcers, diabetic ulcers, traumatic wounds and burns[21]. Used topically, it appears to enhance healing without side effects. Its wound-related pharmacology has been investigated[22]. Phenytoin increases gene expression of the platelet-derived growth factor B chain in macrophages and monocytes[23]. Healthy granulation tissue appears earlier with phenytoin than

with conventional saline dressings[24]. Phenytoin may promote wound healing through multiple mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism, and antibacterial activity.

Phenytoin seems promising in enhancing the healing of decubitus ulcers. In a comparison involving 47 patients with stage II decubitus ulcers, treatment with phenytoin, DuoDerm® dressings or triple antibiotic ointment applications all resulted in reduction of the ulcers. However, the phenytoin group demonstrated more rapid results in all aspects of ulcer healing[26]. Phenytoin has been used to treat ulcers that result from mycobacterial infections. It has been used orally and topically to treat the trophic ulcers of leprosy[27]. In such a role, it is more effective than saline[28]. It can be used in the treatment of the Buruli ulcer of Mycobacterium ulcerans. 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[29]. Phenytoin promotes wound healing by following mechanisms. They are 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., neovascularization30 and phenytoin increases gene expression of the platelet derived growth factor ß chain in macrophage and monocytes.

Side Effects of Topical Phenytoin Preparations: Topical phenytoin used in wound therapy appears to be well tolerated. Its adverse effects are mild and infrequent. Some patients have a transient burning sensation when the powder is initially applied, but this can be prevented by using pure phenytoin powder instead of phenytoin sodium. A generalized rash that resolved when treatment was stopped has also been reported. Hypertrophic granulation tissue was noted in 10~36 percent of patients in two studies. This is reversed by stopping treatment, and it is suggested that stopping treatment when the wound area is covered with a granulation base can prevent this effect. 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. Only one case report showed significant levels of serum phenytoin after topical phenytoin. However, in this study, there was no case with any side effects from topical phenytoin dressing.

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