Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/396

Original Article

Role of Topical Phenytoin in the Management of Diabetic Foot Ulcers

M S Varadarajan[1], M Gobinath[2], Heber Anandan[3]

[1]Professor, Department of General Surgery, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India, [2]Junior Resident, Department of General Surgery, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India, [3]Senior Clinical Scientist, Department of Clinical research, Dr. Agarwal's Healthcare Limited, Tirunelveli, Tamil Nadu, India

Abstract

Introduction: The management of the diabetic foot ulcer (DFU) is largely determined by its severity (grade), vascularity of the limb, and the presence of infection. In India, habits such as walking barefooted, lack of knowledge regarding diabetic foot, hot climate leading to increased perspiration, poor hygiene, poor sanitation, diet which has low proteins, and general poverty have worsened the problem.

Aim: To study the effect of topical phenytoin in the management of DFU.

Materials and Methods: A total of 40 patients with DFU were studied. 20 patients underwent surgical debridement, and conventional povidone-iodine dressing and 20 others received surgical debridement followed by topical phenytoin dressing.

Results: DFU was common in patients with the duration of diabetes 5-10 years >70% belong to Wagner's Grade 3 and 4 ulcers. On topical application of phenytoin, there was a significant decrease in pain but this was more subjective. There was a decrease in purulent discharge at the end of 1 week and significant negative culture at the end of 2 weeks.

Conclusion: Considering phenytoin in accelerating wound healing it can be used as a safe, effective easy to use and inexpensive management in the treatment of DFU.

Key words: Conventional dressings, Diabetic foot ulcer, Granulation tissue, Topical phenytoin

INTRODUCTION

In this millennium where man has succeeded in deciphering human genetic code, the issue of management chronic wound still continues an enigmatic challenge. Diabetic ulcers,[1] particularly nonhealing types, are one of the most common surgical issues. From time immemorial doctors are trying different methods to treat these kinds of ulcers. The difficulty in a chronic ulcer, is its refusal to heal,[2] whatever management given, especially diabetic ulcers. The notion that ulcers should be kept dry, although still held by a considerable number of clinicians, is steadily losing ground. We now know that ulcers re-epithelialize[3] much faster or develop granulation tissue faster when treated with dressings which allow moist wound healing.[4] We recognize that occluding ulcers does not lead to infection. Many techniques have been tried over the centuries to heal diabetic leg ulcers. Although wound dressings have been used for at least two millennia, there exists no ideal dressing. During the past 2½ decades, a wide range of innovative dressings has been introduced. People have tried various nonconventional topical therapies in wound healing, such as *Aloe vera*, benzoyl peroxide, collagen,[5,6] gentian violet, impregnated gauze, topical phenytoin, mercurochrome, oxygen therapy,[7] sugar, and vinegar. Studies have also proven that topical sucralfate promotes healing of decubitus ulcers, venous stasis ulcers,[8] traumatic wounds, burns, and trophic ulcers and was seen to be superior management of diabetic ulcers. Sucralfate,[9] an oral gastrointestinal medication primarily indicated for the treatment of active duodenal ulcers, is also used for the treating gastroesophageal reflux disease and stress ulcers. It shows potential utility in the healing of skin wounds.[10-12]

Access this article online

www.ijss-sn.com

Month of Submission : 06-2017
Month of Peer Review : 07-2017
Month of Acceptance : 08-2017
Month of Publishing : 08-2017

Corresponding Author: M Gobinath, Department of General Surgery, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India. Phone: +91-9894447700. E-mail: gobi.kmc@gmail.co

Aim

The aim of the study was to study the effect of topical phenytoin in the management of diabetic foot ulcers (DFU).

MATERIALS AND METHODS

This prospective study was Department of Surgery at Tirunelveli Medical College 40 patients with DFU was studied. 20 patients underwent surgical debridement, and conventional povidone-iodine dressing and 20 others received surgical debridement followed by topical phenytoin dressing.

Inclusion Criteria

Patients with DFU with ulcer involvement limiting to the food and DFU of Wagner's grade from Group 1 (superficial involvement) to Group 4 (gangrene limited to forefoot or heel, DFU with no vascular compromise) were included in this study.

Exclusion Criteria

Patients with diabetic ketoacidosis, poor compliance, vascular compromise, and with Wagner's Grade 5 ulcer (extensive gangrene of foot and leg) were excluded from the study.

RESULTS

Of the 40 DFU patients, the majority of the patients belong to 60-70 years of age and the next common presentation was between 50 and 60 years. Of the 40 patients, 32 patients were male and 8 were female. Of the patients having DFU majority of them had diabetes for 5-10 years. Of the patients, 10 patients had some form of renal dysfunction as elevated renal parameters or USG showing medico renal disease. Of the 40 patients, 26 patients had strict glycemic control with insulin and 14 patients had moderate glycemic control (blood glucose: 200-300 mg).

Of the 40 patients majority of the patients were of Grade 3 and 4 (abscess with osteomyelitis and DFU with forefoot/toe gangrene). Patients presenting with Grade 1 and 2 ulcers are relatively rare (Table 1). The wound swab from DFU showed that most common organism isolated from the wound was proteus (Table 2).

Phenytoin has membrane stabilizing action and hence an analgesic effect (Table 3). At the end of 2 weeks of monitoring of topical phenytoin these were the end results; unhealthy wound-14, healthy granulating tissue-23, ascending infection-Bk amputation-2, and death due to comorbid illness-1. The discharge from the ulcer was observed for 2 weeks, and the following observations were made (Table 4). Wound culture and sensitivity were seen for the patients on admission and at the end of the 2nd week (Table 5). The healing rate as observed by the formation healthy granulation tissue is given in Table 6.

Table 1: Grading of ulcer

Grades of ulcer	Number of patients
Grade 1	1
Grade 2	10
Grade 3	17
Grade 4	12

Table 2: Microbial culture

Organism isolated	Number of persons
Proteus	18
Escherichia coli	10
Staphylococci	8
Pseudomonas	4

Table 3: Regression of pain

Assessment day	Treatment group	Severe pain	Bearable pain	No pain
Admission day	Phenytoin group	16	4	0
	Control group	15	5	0
Day 7	Phenytoin group	9	10	1
	Control group	12	8	0
Day 14	Phenytoin group	6	6	8
	Control group	8	10	2

Table 4: Clearance of ulcer discharge

Assessment day	Treatment group	Purulent discharge	Serous discharge	No discharge
Admission day	Phenytoin group	17	3	0
	Control group	16	4	0
Day 7	Phenytoin group	10	9	1
	Control group	14	6	0
Day 14	Phenytoin group	2	12	6
	Control group	8	10	2

Table 5: Wound culture test

Assessment day	Wound C&S	Phenytoin group	Control group
Admission day	Positive for organisms	20	20
End of 2 weeks	No growth in culture	11	6

Table 6: Healthy granulation tissue formation rate

Assessment day	Presence of HEALTHY Granulation tissue	Phenytoin group	Control group
Admission day	Yes	0	0
	No	20	20
Day 7	Yes	7	4
	No	13	18
Day 14	Yes	12	8
	No	8	12

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.[13] A frequent observed and unwanted side effect of phenytoin, an anticonvulsant medication, is gingival hyperplasia, especially in children.[14] 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.[15] 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, neovascularization and phenytoin increase gene expression of the platelet-derived growth factor β chain in macrophage and monocytes. 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.[16-19]

CONCLUSION

In our present study, it was concluded that the rate of granulation tissue formation, overall graft survival and patient compliance was better in topical phenytoin dressing group as compared to conventional dressing group. Topical phenytoin has a role in the healing of diabetic ulcer by decreasing the pain and decreasing the purulent discharge and early formation of granulation tissue. Surgical debridement and glycemic control remain the cornerstones in the treatment of DFU. Considering phenytoin in accelerating wound healing it can be used as a safe, effective easy to use and inexpensive management in the treatment of DFU.

REFERENCES

1. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic ulcer study group. J Am Coll Surg 1996;183:61-4.
2. Cohen IK. A Brief History of Wound Healing. 1st ed. Yardley, PA: Oxford Clinical Communications Inc.; 1998.
3. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature 1962;193:293-4.
4. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med 1999;341:738-46.
5. Donaghue VM, Chrzan JS, Rosenblum BI, Giurini JM, Habershaw GM, Veves A. Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers. Adv Wound Care 1998;11:114-9.
6. Sai PK, Babu M. Collagen based dressings-a review. Burns 2000;26:54-62.
7. Landau Z. Topical hyperbaric oxygen and low energy laser for the treatment of diabetic foot ulcers. Arch Orthop Trauma Surg 1998;117:156-8.
8. Santilli SM, Valusek PA, Robinson C. Use of non-contact radiant heat bandage for the treatment of chronic venous stasis ulcers. Adv Wound Care 1999;12:89-93.
9. Szabo S, Hollander D. Pathways of gastrointestinal protection and repair: Mechanisms of action of sucralfate. Am J Med 1989;86:23-31.
10. McGee GS, Davidson JM, Buckley A, Sommer A, Woodward SC, Aquino AM, *et al.* Recombinant basic fibroblast growth factor accelerates wound healing. J Surg Res 1988;45:145-3.
11. Gospodarowicz D, Ferrara N, Schweigerer L, Neufeld G. Structural characterization andbiological functions of fibroblast growth factor. Endocr Rev 1987;8:95-114.
12. Folkman J, Szabo S, Shing Y. Sucralfate affinity for fibroblast growth factor. J Cell Biol 1990;111:223a.
13. Meritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. J Am Med Assoc 1938;111:1068-73.
14. ASHP Drug Information 2001. Bethedsa MD: American Society of Health System Pharmacists; 2001. p. 2081.
15. Shapiro M. Acceleration of gingival wound healing in non-epileptic patients receiving diphenylhydantoin sodium (dilantin, epanutin). Exp Med Surg 1958;16:41-53.
16. Muthukumarasamy MG, Sivakumar G, Manoharan G. Topical phenytoin in diabetic foot ulcers. Diabetes Care 1991;14:909-11.
17. Anstead GM, Hart LM, Sunahara JF, Liter ME. Phenytoin in wound healing. Ann Pharmacother 1996;30:768-5.
18. Talas G, Brown RA, McGrouther DA. Role of phenytoin in wound healing-a wound pharmacology perspective. Biochem Pharmacol 1999;57:1085-94.
19. Genever PG, Cunliffe WJ, Wood EJ. Influence of the extracellular matrix on fibroblast responsiveness to phenytoin using *in vitro* wound healing models. Br J Dermatol 1996;133:231-5.

How to cite this article: Varadarajan MS, Gobinath M, Anandan H. Role of Topical Phenytoin in the Management of Diabetic Foot Ulcers. Int J Sci Stud 2017;5(5):70-72.

Source of Support: Nil, **Conflict of Interest:** None declared.