



COMPARATIVE STUDY OF GRANULATION TISSUE FORMATION IN DIABETIC FOOT ULCER BY PHENYTOIN VS POVIDONE DRESSING

General Surgery

Dr Vivek Rajana* 3rd Year General Surgery Resident At Dr. S.N. Medical College, Jodhpur.
*Corresponding Author

Dr Bharti Saraswat Senior Professor At Dr. S.N. Medical College, Jodhpur.

Dr Anant Kumar 3rd Year General Surgery Resident At Dr. S.N. Medical College, Jodhpur.

Dr Thanaram Patel Assistant Professor At Dr. S.N. Medical College, Jodhpur.

ABSTRACT

Background– Foot ulcers and infections are the most common reason for hospital admission in people with diabetes. Gingival hyperplasia is a typical adverse effect of phenytoin (diphenylhydantoin) treatment for epilepsy. It was possible that phenytoin may be used to stimulate the healing of wounds due to its stimulating impact on connective tissue. Aims and objectives of this study to compare granulation tissue formation by topical agents (phenytoin & povidone). **Method**- 100 patients with diabetic foot ulcer admitted in General Surgery at Dr S.N. Medical College, Jodhpur (Rajasthan) were randomly assigned into two groups, the study group consisting of 50 patients who were treated with phenytoin dressing and 50 patients into control group who were treated with povidone dressing, assessment of granulation tissue formation done at the end of 14th day **Result**- The rate of granulation tissue in phenytoin group was 90.84% as compared to control group which was 80.08% which was statistically significant (p value < 0.0001). Wound swab cultures repeated on day 14th revealed that there was 86% negative culture in phenytoin group when compared to control group of 68% which also was statistically significant. The mean hospital stay for the patient in phenytoin group was 26.46 days and in control group, it was 31.22 days. **Conclusion**- By promoting fibroblast proliferation and reducing collagenase activity, phenytoin dressing effectively accelerates the development of granulation tissue. By virtue of its inherent antibacterial activity and indirectly through their effects on anti-inflammatory cells and neovascularization, it not only accelerates granulation tissue but also decreases bacterial load as compared to conventional dressing. Phenytoin helps to improve overall results by preparing the foot ulcer for early grafting.

KEYWORDS

Phenytoin dressing, Povidone dressing, Diabetic foot ulcer, granulation tissue

INTRODUCTION

"Diabetes Mellitus - A Global Epidemic"

Diabetes Mellitus is a chronic disease and complex life long condition affecting 8.3% of the world's population globally. It is characterized by a heterogeneous group of metabolic disorders resulting in an abnormal increase of blood glucose level (Hyperglycemia) due to absolute or relative deficiency in Insulin secretion and/or action or both¹.

The global prevalence (age-standardized) of diabetes mellitus has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. In year 2000 there were 171 million people in the world with diabetes mellitus and this is projected to extend to 366 million by 2030². The American Diabetes Association (ADA) estimated the national costs of diabetes in the USA for 2002 to be \$US132 billion, increasing to \$US192 billion in 2020³. The prevalence of diabetic ulcers is 7-8%. Ulcers and amputations result in enormous societal costs, including lost wages, job loss, prolonged hospitalization, lengthy rehabilitation and an increased need for home care and social services. Non-healing (or) chronic diabetic wounds are a significant health care problem of today's practice as its healing depends on many factors such as glycemic control, vascularity, bacterial load, the location of the wound and nutritional status of the patient. Many agents have been tried in wound healing, the quest for better wound healing agent is perhaps one of the oldest challenges for medical practice.

The phenytoin, a common anticonvulsant also has been tried in wound healing (applied locally). A common side effect of phenytoin (diphenylhydantoin) is gingival hyperplasia seen during treatment of epilepsy by stimulatory effect on connective tissue and stimulating fibroblast proliferation, enhancing the rate of formation of granulation tissue, reducing collagenase activity, hastening deposition of collagen, decreasing bacterial load and decreasing wound exudates.

METHOD

This prospective randomized comparative study included 100 patients with diabetic ulcers admitted in Dr. SN Medical College, Jodhpur from March 2022 to November 2022 (9 months) satisfying all the inclusion criteria mentioned below after the clearance from the ethical committee was obtained.

The main inclusion criteria were

- grade I and II foot ulcers according to Meggitt-Wagner clinical classification⁴

- Patient with chronic ulcer of diabetes mellitus
- Wound size <5% TBSA
- control of diabetes mellitus with oral hypoglycemic agents or insulin

The main exclusion criteria for the study were

- Grade 3,4,5 foot ulcer according to Meggitt-Wagner classification
- Chronic ulcer of other etiology like Venous ulcer
- Other co-morbid conditions like End stage renal disease (CKD), CHF grade-3&4, generalized debility which adversely affect wound healing
- Patient with allergy to phenytoin
- Uncontrolled DM (if HbA1c >11%)
- Patient is known case of epilepsy disorder and taking AED

The whole sample population was divided into two equal and comparable groups based on willingness for undergoing topical phenytoin therapy for the wound.

All patients underwent general physical and clinical examination for peripheral vascular status and peripheral neuropathic changes in lower extremities. Routine hematological, biochemical, urine microscopic investigations were done for each patient. The wounds were thoroughly debrided when necessary. After slough removal, the surface area was measured, tracing the outline on butter paper. This outline was transferred to a graph paper. On each occasion ulcer areas were measured twice.

A single 100mg phenytoin sodium capsule was opened and placed in 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20mg/cm² TBSA. In control group dressing done with 5%w/v povidone-iodine solution. Dressings were done on daily basis. The patients were followed up on a daily basis for 14 days in both study and control groups. Wound culture was obtained at the start of the treatment and on the 14th day of treatment. At the end of 14 days the wounds in both the groups were inspected and compared based on the following parameters

- Rate of granulation tissue formation as percentage of ulcer surface area
- Quality of ulcer bed

RESULT

Out of 100 cases evaluated, 82% of the men and 18% of the women

who developed diabetic foot ulcers. The majority of diabetic foot patients were between the ages of 40 and 60, with a mean age of presentation to our hospital of 52. The 22-year-old youngest patient arrived with a sole ulcer.

Table 1: Age wise distribution

Age (yrs)	Male	Female	Total
31-40	17	2	19
41-50	20	2	22
51-60	27	9	36
≥61	18	5	23
Total	82	18	100

Table 2: Comparison of granulation tissue formation, Negative wound culture, Hospital stay

Comparison of	Phenytoin dressing	Povidone dressing
Granulation tissue formation (In Percentage)	90.84%	80.08%
Negative wound culture (In Percentage)	86%	68%
Hospital stay (in Days)	31.22	26.46

The duration of the hospital was prolonged in control group when compared to study group. The mean duration of stay for phenytoin group was 26.46 days and 31.22 days for the control group. The mean hospital stay was 31.22 ± 2.75 (SD) days in the control group and 26.46 ± 2.72 (SD) days in the study group. P-value is <0.0001 which is highly significant.

The mean rate of granulation tissue formation in the study group was 90.84% (Standard deviation-4.21) of total ulcer surface and 80.08% (SD-4.28) in the control group. Results were analyzed by unpaired Student's t-test and showed a highly significant difference in the rate of granulation tissue formation ($p < 0.0001$).

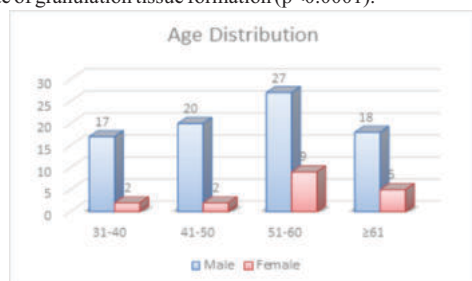


Figure 1: Age distribution

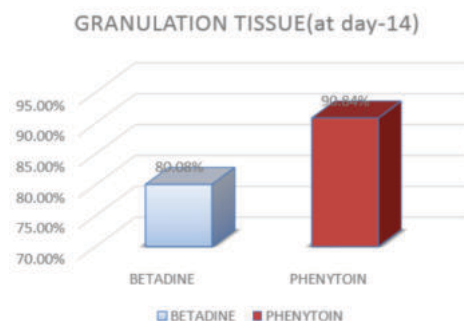


Figure 2 : Formation of granulation tissue at the end of 14 days

DISCUSSION:

With a prevalence of 25%, foot ulcers are more prevalent in diabetic patients and significantly increase morbidity and mortality in society. Since 1937, phenytoin has been used extensively to manage epilepsy. It has been employed in the management of numerous illnesses. There have been reports of unfavourable side effects like allergies. Decubitus ulcers, venous stasis ulcers, severe wounds, burns (Lodha⁴), and leprosy trophic ulcers are among the non-healing ulcers treated with phenytoin.

According to numerous studies, phenytoin promotes the formation of collagen and other connective tissue components, increases granulation tissue, decreases collagenase activity (by lowering its production or secretion or both), and stimulates fibroblast proliferation to speed up wound healing. According to a study by Tauro LF et al, Raj

R et al, Kodela SR et al, phenytoin increases the rate of granulation tissue formation (in Tauro LF) was 87% in the study group compared to 74% in the control group.

Table 3: Comparison between Result of Different Studies

STUDY	Granulation tissue formation	
	Study	Control
Present study	90.84	80.08
Tauro LF et al ⁷	87.94	74.64
Raj R et al ⁸	88.21	71.32
Rao S et al ⁹	85.21	70.32
Gunasekaran V et al ¹⁰	90.36	82.03

CONCLUSION

Phenytoin dressing is effective in increasing the rate of granulation tissue by virtue of its action on stimulating fibroblast proliferation and decreasing collagenase activity in wound surface. It not only hastens granulation tissue but also decreases bacterial load as when compared to conventional saline dressing by virtue of its intrinsic antibacterial activity and indirectly through their effects on anti-inflammatory cells and neo vascularization. Phenytoin prepares the foot ulcer for early grafting thereby improving the overall outcome. In our present study, it was concluded that the rate of granulation tissue formation was significant in topical phenytoin dressing group as compared to conventional dressing group. It was also seen that the overall hospital stay was less in the topical phenytoin dressing group. Therefore, topical moist wound dressing with phenytoin can be consider in the treatment of diabetic ulcer. However in the future, further studies in larger population will be needed before topical phenytoin dressing to added to the broad range of treatment modalities available in the management of diabetic ulcer



Figure 3- Diabetic foot with phenytoin dressing and grafting

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