



## LOCAL APPLICATION OF PHENYTOIN SODIUM IN DIABETIC ULCERS: A RANDOMIZED PROSPECTIVE STUDY

Prashaanth M. K<sup>\*1</sup>, Ramesh R<sup>2</sup>, Junior Sundresh N<sup>3</sup>, Nirmala P<sup>4</sup>, Umapathy P<sup>5</sup> and Appu Mathi Roga Rajan<sup>6</sup>

<sup>1,2,3,5,6</sup>Department of General Surgery, Rajah Muthaiah Medical College, Chidambaram

<sup>4</sup>Department of Pharmacology, Rajah Muthaiah Medical College, Chidambaram

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### ABSTRACT

**Introduction:** Diabetic foot ulcer is the most common complication of diabetes mellitus. Most of the patients with diabetes seek hospital admission due to a diabetic foot ulcer. About 15% of diabetic patients have ended up with surgery following diabetic ulcer complications.

**Objective:** The objective of this study was carried out to assess the efficacy of topical application of phenytoin sodium powder on healing in diabetic foot ulcer Category I and II.

**Materials and Methods:** Totally, 50 patients with diabetic foot ulcer were randomized into two groups, assigned regular saline and betadine dressing for the control group and phenytoin sodium powder application for the study group. Patients fulfilled the inclusion and exclusion criteria. Both the control and study group are compared for the reduction in the surface area, granulating tissue formation, duration of hospital stay, wound swab for culture & sensitivity and graft uptake to assess the healing process.

**Results:** The wound healing was assessed by the formation of granulation tissue, decrease in the surface area, wound swab for culture and sensitivity, duration of hospital stay, and the graft uptake post surgery. At the end of 14 days, the presences of healthy granulation tissue were markedly noted in 90.08% of study group with phenytoin, and it was present only in 10% of control group. Moreover, also wound reduction was 66% in the study group, and 44% in control group. Graft uptake in study group post surgery was 87.6% compared to the control group which was 65.76%. Mean duration of time in the hospital is also significantly reduced in phenytoin group which was 35.36 days compared to control group which was 5.56 days.

**Conclusion:** Based on this study and literature review, we conclude phenytoin sodium powder topical application on diabetic foot ulcer promotes early wound healing.

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## INTRODUCTION

Diabetes is one of the major non-communicable diseases in the world. Globally 382 million people are affected by diabetes and it is predicted to exceed 592 million in another 25 years [1]. Diabetes alone caused more than 5.1 million deaths in 2013 and economic loss of 627 billion US \$ in that year. In India around 62 million people are having diabetes contributing to largest number of diabetics in the world. India is considered to be diabetic capital in the world [1].

People with diabetes have an increased risk of developing a number of serious health problems. A study from South India revealed that 20.1% of type 2 diabetes patients did not receive any treatment and 71.2% had poor glycaemic control. In fact, 41.4% did not visit a primary care provider in the previous year. Major proportions of diabetes disease outcomes are attributed to patients' ignorance and non-compliance. Over all, three percent of the diabetics were found to have foot related complications due to diabetes. Of all the foot related complications, diabetic foot ulcer alone contributes to

\*Corresponding author: Prashaanth M. K

Department of General Surgery, Rajah Muthaiah Medical College, Chidambaram

62%, followed by amputations (32%) and gangrene (8%) [2]. Duration of diabetes more than 10 years, age more than 45 years, male gender, associated macro vascular complications, poor glycaemic control are proven to be associated with increased risk of diabetic foot. These diabetic ulcers compromise the life of the patients by premature mortality and disability. If the ulcer size is more than 4cms and duration of ulcer is more than one month, it can lead to multi drug resistance for antibiotics. In this scenario, if the diabetic ulcers are not treated with proper approach it can result in grave consequences in the form of amputation.

Considering the devastating nature of diabetic ulcer various approaches are tried since long time such as wound dressing with Povidine Iodine solutions, Applications of epidermal and Fibroblast growth factors, dalteparin. Use of Phenytoin among Epileptic patients had resulting in gingival hyperplasia [2][5]. This property of Phenytoin has lead to try this drug as topical application for diabetic ulcer by the researchers [5]. However, there is no much evidence to prove this phenomena in the current setting. Hence, this study was planned to determine the effectiveness of Phenytoin sodium regimen compared to the conventional diabetic wound management.

## MATERIALS AND METHOD

50 patients with type II diabetes mellitus (ages 25-75) were hospitalised and randomised to treatment if they met the following two criteria: (a) Grade I and II foot ulcers according to Wagners clinical classification (Grade I were superficial ulcers and Grade II were deep ulcers with slough). An assessment of peripheral vascular status was made based on the presence of femoral, popliteal and dorsalispedis pulses. (b) Control of diabetes with oral hypoglycaemic agents or insulin based on fasting & post prandial blood sugar. Exclusion criteria included the presence of Grade III, IV and V foot ulcers, ulcers of other etiology, patients with comorbid factors. The ethics committee approved the study design. All participants gave informed consent.

Evaluation and treatment protocol: The following were recorded in all patients at the beginning and at the end of the trial: general & physical Examination, local examination of the ulcer, peripheral vascular state, neurological and neuropathic changes in the lower extremities and ophthalmological examinations: routine haematological and biochemical investigations, ulcer swabs for culture and sensitivity. In each patient surgical debridment was performed when necessary. After slough removal, the surface area was measured, tracing the outline. This outline was transferred to graph paper. On each occasion ulcer areas were measured twice. When identical, the reading was recorded. If not the average was recorded. Gentle saline cleaning, topical phenytoin or control application and a sterile dry dressing cover was applied daily for a period of 6 weeks or until complete healing (defined as intact skin indicated as complete cure) whichever occurred earlier. The quantity of powder dusted depended on the surface area: 0-5 cm<sup>2</sup> - 100 mg, 5.1-9 cm<sup>2</sup> - 150 mg, 9.1-15 cm<sup>2</sup> - 200 mg;> 15 cm<sup>2</sup> - 300 mg. At the end of each week the same observer measured the

surface areas of ulcers. Observations were recorded on the rate of granulation tissue formation, quality of the ulcer bed, reduction in surface area and swab for culture & sensitivity. Observed or spontaneously reported side effects were graded on a 4 point scale: nil, mild, moderate, severe.

## STATISTICS

The primary measure of efficacy was the reduction in the surface area of the ulcer. The mean ulcer surface area was determined before, during and after treatment. ANOVA - analysis of variance was carried out to see the differences in mean reduction in surface area of the ulcer over different periods namely baseline, at 1, 2, 3, 4, 5, 6 weeks. To obtain ANOVA Fisher's 'F' test was used which gives the 'F' value for each group. From the 'F' value probability was calculated. Bonferroni 't' test was applied where there were repeated measures namely to compare baseline to week 1, baseline to week 2 and so on, within each group. The 'Y' value obtained has given the probability value within each group. The student unpaired 't' test compared the reduction in ulcer areas between the two treatment groups. Level of significance was chosen at P<0.05.

## RESULTS

At completion of the study the mean percentage reduction of ulcer area was 66% VS 44% in the phenytoin vs control group (P > 0.05). The mean difference between pretreatment and post treatment values (in cms) of ulcer area of 50 enrolled patients in the phenytoin (36) vs control (14) group was 6.45 cm<sup>2</sup>±1.53 vs 5.44 CM<sup>2</sup>±1.49. The phenytoin group showed a slight acceleration of effect as compared to the control 3<sup>rd</sup> on 4<sup>th</sup> week. In this study made by me the mean age group in study group is 55.64 yrs and 48.36 yrs in control group. Graft up take was 87.6% and 65.76% respectively. Hospital stays was 35.36 days in study group and 56.56 days in control group. Written observations made during the study noted that with phenytoin there was a better quality of granulation tissue and that wound discharge ceased earlier. Among the ulcers that did not heal completely at the end of the study post treatment wound cultures were negative in phenytoin treated ulcers. Figure 1





**Figure 1** Effect of topical phenytoin in diabetic ulcers

## DISCUSSION

Clinical trials in diabetic foot ulcer healing are notoriously difficult and hence tend to be neglected. Randomisation alone will not provide for equivalent groups unless the pool of patient randomised is very large. In this randomised study there was unequal distribution in the numbers of grade I and II ulcers, peripheral vascular status and neuropathic changes. Histological examination would have given an idea of the control particularly with reference to the following findings & in the control group: The results of this study confirm that compared to the 'control' phenytoin is more effective in wound healing. This conclusion is based on the following findings: earlier appearance of healthy granulation tissue, earlier disappearance of wound discharge, post treatment wound cultures were negative in phenytoin treated ulcers, better graft uptake and reduction in the duration of hospital stay. It also shows reduction in bacterial colonisation and infection confirming the findings of Data from this study & are suggestive of a modest treatment response with phenytoin. In this study the values of phenytoin registered were consistently lower than the normal therapeutic drug monitoring range for phenytoin as seizure prophylaxis (10-20 µg/ml).

The mechanism of action of Phenytoin may be involved in the healing process at several levels including Stimulating fibroblast proliferation, Enhancing the formation of granulation tissue, Decreasing collagen activity, Promoting deposition of collagen, Decreasing bacterial contamination, Decreasing wound exudates[3][4]. The phenytoin has antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella*, and *Pseudomonas*. Another advantage of phenytoin observed is the reduction in the pain score of the ulcer.

Many studies have shown a significant reduction in the pain score of the patient from 7th day resulting in less use of analgesia. This is explained by the effect of phenytoin on the membrane stabilizing property and its ability to reduce the inflammatory response[6]. Phenytoin enhances wound healing by stimulating lymphocytic chemotaxis and up-regulation of angiogenesis[7].

## CONCLUSION

This study showed that phenytoin sodium has enhanced wound healing in diabetic foot ulcers compared with other conservative therapies. Treatment of diabetic foot ulcer with topical phenytoin is very economical and safe. The topical phenytoin showed accelerated wound healing thereby decreasing the hospital stay of the patients and reduces the expenditure in health care.

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