



## A STUDY ON TOPICAL USE OF PHENYTOIN SODIUM IN GRADE I AND GRADE II DIABETIC FOOT ULCERS

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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 grade I and II.

**Materials and Methods:** The entire sample population 100 was divided into two equal groups that can be comparable, which is further divided into 3 subgroups: moderate and poor control based on HbA1C value assigned regular saline dressing for the control group and phenytoin sodium powder application for 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 and sensitivity, effect of granulation tissue formation based on HbA1C value and graft uptake to assess the healing process.

**Results:** The wound healing was assessed by the formation of granulation tissue, decrease in surface area, wound swab for culture and sensitivity, duration of hospital stay and graft uptake post surgery. At the end of 14 days, the presence of healthy granulation tissue were markedly noted in 90% 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 the control group. Graft uptake in study group post surgery was 95.3% superior compared to the control group which was 66.6%. Mean duration of time in the hospital is also significantly reduced in phenytoin group which was 21 days compared to control group which was 40 days.

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

### KEYWORD

Phenytoin Sodium, HbA1C value

### ARTICLE HISTORY

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#### INTRODUCTION:

Diabetes is one of the major non-communicable diseases in the world. People with diabetes mellitus have a higher risk of developing many serious health problems, of which Diabetes causing peripheral neuropathy is a very important manifestation which when prevented and managed, can cause reduced ulcer formation rate and other morbidities. The commonest cause for hospital admissions among diabetics is due to diabetic foot ulcer or gangrene contributing to 32% of admissions among type 2 DM. About 15% of diabetic patients have ended up with surgery following diabetic ulcer complications.

Considering the devastating nature of the diabetic ulcer various approaches are tried since long time such as wound dressing with povidone iodine solutions, applications of epidermal and fibroblast growth factors, dalteparin. Use of phenytoin among epileptic patients had resulting in gingival hyperplasia. This property of phenytoin has lead to try this drug as topical application for diabetic ulcer by the researchers. However, there is not much evidence to prove this phenomenon in the current setting. Hence, this study was

planned to determine the effectiveness phenytoin regimen compared to the conventional diabetic wound management.

#### AIMS AND OBJECTIVES:

**Primary objective:** To find out the effectiveness of topical use of phenytoin sodium over other conventional dressing.

**Secondary objective:** To find out the length of hospital stay, rate of granulation tissue growth, rate of reduction in mean ulcer surface area. To find out the effect of topical phenytoin on ulcer infections with serial bacterial culture and sensitivity studies.

To find out the effect of phenytoin sodium over development of granulation tissue based on HbA1c levels of patients

#### MATERIALS AND METHODOLOGY:

This prospective case control study - sample size : 100 patients with diabetic ulcers admitted in Chettinad hospital and research institute, Kelambakkam, Tamil Nadu from June 2017 to June 2018 satisfying all the inclusion and exclusion criteria mentioned below after the clearance from ethical committee

was obtained. All diabetic ulcers were conventional dressings are indicated were included in the study.

**Main inclusion criteria :-**

- Patients with age between 25-75 years
- Patients with diabetic foot ulcers with - Merritt classification grade 1 and grade 2.

**Main exclusion criteria :-**

- Chronic non-healing wounds of other etiology
- Type 2 DM with gangrenous changes.
- Wounds with osteomyelitis.(grade3)
- Wounds with poor vascularity(grade 4) and (grade 5).
- Other co-morbid conditions like renal failure, generalized debility and patient requiring intensive care monitoring.
- Patients who do not want to complete the 14 day treatment course.

The entire sample population was divided into two equal groups that can be comparable, which is further divided into 3 subgroups :-good moderate and poor control based on HbA1C value :-

- Good control - 6-7%
- Moderate control - 7-9 %
- Poor control - > 9 %

**Application of dressing :-**

In all patients, at the beginning and end of the trial, the following were recorded: general physical examination, local examination of the ulcer, peripheral vascular status, neurological examination in the lower extremities for neuropathic changes if any and ophthalmological examinations along with lab investigations like - routine hematological and biochemical investigations and wound swabs for culture and sensitivity. In each patient wound debridement was performed when required. After the removal of slough, the surface area was measured, tracing the outline using sterile gauze. When identical the reading was recorded. After gentle wash with saline, topical phenytoin was applied and sterile dry dressing done daily for 2 weeks or until complete healing (defined as intact skin indicated as complete cure) whichever occurred earlier. Observations were made based on the rate of granulation tissue formation, quality of the ulcer bed, reduction in the surface area and swab for culture and sensitivity. The reported side effects were graded as :nil, mild, moderate and severe .

**Topical phenytoin :-**

A suspension was made with powdering a 100mg phenytoin tablet and mixing it with normal saline. A sterile gauze was soaked in the suspension and applied over the raw area of ulcer. In other group, Conventional dressing was done with normal saline

Both these wounds were compared after daily dressing of 2 weeks .The comparison study was based on :

- 1) The rate of granulation formation
- 2) The reduction / contraction of the wound surface area
- 3) Inspecting the floor of the ulcer
- 4) Wound swab for c/s
- 5) Effect of phenytoin sodium over development of granulation tissue based on HbA1c levels of patients

In both the groups, some patients underwent split skin grafting with patient's consent and given same parenteral antibiotics post operatively. After post operative day 4, the percentage of taken up of the graft and the surface area of the wound were noted in both the groups. The duration of hospital stay was also taken into account. Follow up was made in these patients on Out patient basis and looked for any graft complications. After completing the entire study, the results were statistically evaluated and analysed on major parameters mentioned above

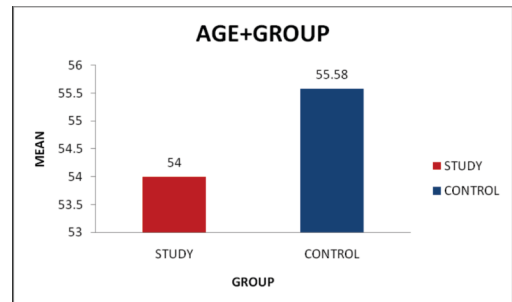
These parameters were compared in both the groups. The comparison of these variables was done with unpaired students t - test. A P value < 0,05 was considered as significant.

**OBSERVATION AND RESULTS:**

After completing the entire study, the results were statistically evaluated and analysed on major parameters.

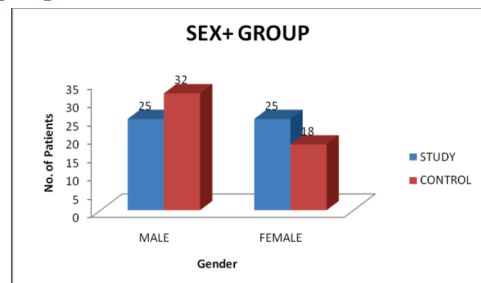
- Duration of stay in the hospital
- Rate of granulation tissue
- Reduction in wound size
- Graft uptake
- Rate of granulation tissue formation in comparison with HbA1c levels. These parameters were compared in both the groups. The comparison of these variables was done with unpaired students t - test. A P value < 0,05 was considered as significant.

**Age group:**



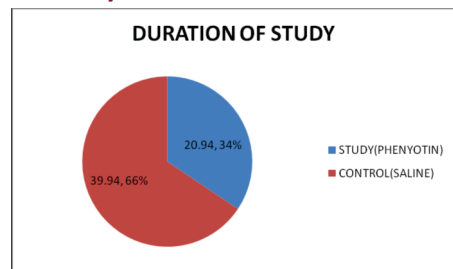
The Age+ group were compared between study and control groups. The study group age mean value is 54 whereas the control group age mean value is 55.58.

**Sex group:**



In both the study and control groups diabetes is more common among males compared to females. In present study out of 100 patients 57 were male and 43 were females. This constitutes about 63% in the male sector and 38% in the female sector.

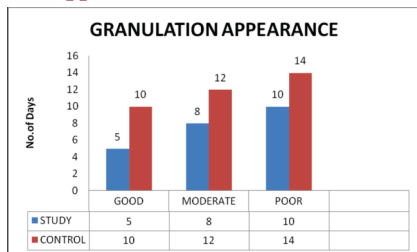
**Duration of study:**



The duration of hospital stay is considered as parameter++ in comparison between study and control groups. Each group consists of 50 patients where totally 100 patients were recruited for study. The study group stayed at hospital approximately 21 days, treated with phenytoin and control group stayed at hospital approximately 40 days, where treated with saline. The duration of stay in hospital is lesser in

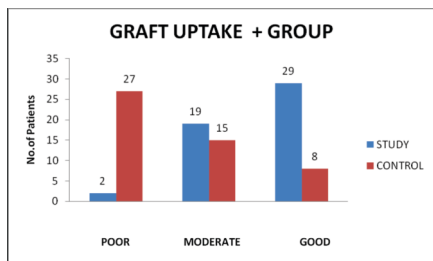
study group compare to control group. From this study group showed faster recovery compared to control group.

**Granulation appearance:**



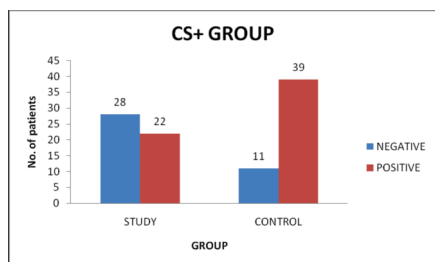
The granulation appearance was observed in range of good , poor and moderate between study and control groups. The good range of granulation appearance range between 5-7 days in the study group and good range of granulation appearance was found to be 10-11 days in the control group. . The moderate range of granulation appearance range between 8-10 days in the study group and moderate range of granulation appearance was found to be 12-13 days in the control group. .The poor range of granulation appearance range between 10-13 days in the study group and poor range of granulation appearance was found to be >14days in the control group

**Graft uptake:**



The Graft uptake + group were compared between study and control groups. The study group good graft uptake was higher than compare to moderate and poor level of graft uptake, which indicates 58% of graft uptake was found in good level of study group. In control group poor level of graft uptake was higher than compare to moderate and good level of graft uptake which indicates that 50% of graft uptake was found in poor level of control group

**CS+ group:**



The CS+ group parameter were compared between study and control groups to determine the graft uptake is whether positive or negative. In study group 28 patients were negative where has 22patients were positive. In control group 11 patients were negative and 39 patients were positive.

At the end of 14 days, the presence of healthy granulation tissue were markedly noted in 90% 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 the control group. Graft uptake in study group post surgery was 95.3% superior compared to the control group which was 66.6%. Mean duration of time in the hospital is also

significantly reduced in phenytoin group which was 21 days compared to control group which was 40days.



**DISCUSSION:**

The main aim of wound dressing is to provide Protection to the raw area, prevent infections and absorbing the exudates in the wound. The new advancement in topical application over wounds is that they promote the rate of granulation tissue formation. After evolution of moist dressing, many such topical application substance techniques have been researched. Non conventional methods like application of aloe vera, benzoyl peroxide, insulin etc have also been tried. The adoption of dressing technique which provides better outcome in all the aspects is needed.

This study is similar to the study that was conducted by Muthukumarswamy MG et al. The difference between the current study and the one done by him was that he used a thin layer of phenytoin powder over the wound. The sample size of the study was 100 with fifty in each group, the mean age of study group was 56.4 and 58.4 years in control respectively. Graft uptake was found to be 72% and 58.43% respectively. Duration of hospital stay was 21 days in the study group and 45 days in the control group.

In the study, the mean age group was 54 years in the study group and 55 years in the control group. The graft take-up was found to be 95.3% and 66.6% respectively. Duration of hospital stays 21 days in study group and 40 in control group . The main difference is that, HbA1c levels were also measured in both the groups. The granulation appearance was observed in range of good, poor and moderate between study and control groups. The good range of granulation appearance range between 5 -7 days in the study group and good range of granulation appearance was found to be 10 -11 days in the control group. The moderate range of granulation appearance range between 8 10 days in the study group and moderate range of granulation appearance was found to be 12 -13 days in the control group. The poor range of granulation appearance range between 10 -13 days in the study group and poor range of granulation appearance was found to be >14days in the control group.

The quantitative assessment of the some post operative parameters like wound contracture , pain and residual raw ulcer area s were not included in the present study, which if have been included, might have given a much better analysis of the efficacy of topical phenytoin dressings over Saline dressing.

**Future trends:**

Development of wound dressing systems that stimulates faster granulation formation and invention of artificial skin replacements like genetically engineered keratinocytes and growth factors that are under experimental phase now. Development of artificial substitutes like dermal analogues -

Alloderm, integra etc. Are under extensive research. All approaches are being made in development of successful chronic wound care management. 30,74 Clinical trials in diabetic foot ulcer healing are notoriously difficult and hence tend to be neglected. Randomization alone will not provide for equivalent groups unless the pool of patient randomized is very large. In this randomized 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 and 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: early appearance of healthy granulation tissue, early disappearance of wound discharge, post treatment wound cultures were negative in phenytoin treated ulcers, better graft uptake and reduction in the duration of the hospital stay. It also shows reduction in bacterial colonization and infective confirming the findings of data from this study and 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 mcg/ml).

The mechanism of action of phenytoin maybe 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. 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. Phenytoin enhances wound healing by stimulating lymphocytic chemotaxis and up-regulation of angiogenesis.

#### SUMMARY:

- Increased rate of granulation tissue formation was seen topical phenytoin dressing group when compared to conventional dressing group.
- Better graft take up was seen in topical phenytoin dressing group as compared to the conventional dressing group.
- Shorter duration of hospital stay was observed in the topical phenytoin dressing group.
- Follow up observations revealed that topical phenytoin dressing group suffered lesser post skin grafting complications like wound contractures, residual raw area and pain compared to the saline dressing group.

#### 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. It was also seen that hospital stay and post operative complications were less in topical phenytoin dressing group. Thus topical phenytoin moist wound dressing can be considered as a superior option in the management of diabetic ulcers. but further studies with larger population will be needed in the future before topical phenytoin dressing can be added to the wide spectrum of treatment modalities available in the management of diabetic ulcers of other etiology.

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