

A COMPARISON OF EFFICACY OF TOPICAL USE OF PHENYTOIN AND VASELINE GAUZE DRESSING WITH VASELINE GAUZE DRESSING ALONE IN HEALING OF DIABETIC FOOT ULCERS

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Date Received:

August 22, 2013

Date Revised:

June 11, 2014

Date Accepted:

June 18, 2014

ABSTRACT

Objective: To compare efficacy of topical use of Phenytoin and Vaseline Gauze dressing with Vaseline Gauze dressing alone in healing of diabetic foot ulcers.

Methodology: This randomized controlled trial was carried out in Surgical unit I of Benazir Bhutto Hospital from January to June 2013. Study included 60 diabetic patients with Wagner grade 1 & 2 ulcers on foot for more than 04 weeks with adequate control of diabetes. Patients with history of hepatic and renal diseases; on steroid use; or with impalpable foot arteries; were excluded. Thirty each were randomized to phenytoin and vaseline gauze dressing and vaseline gauze alone groups, respectively. At baseline and after 08 weeks, area of wound was measured using graph paper tracings and healing percentage was calculated.

Results: Mean age of the sample was 53.83 ± 6.66 years. Thirty six (60%) were males. Twenty five (41.67%) patients had Wagner grade 1 and 35 (58.33%) had grade 2 foot ulcers. Age, gender distribution and severity of foot ulcers according to Wagner grades were similar between two groups. In phenytoin & Vaseline group, the mean baseline ulcer area decreased from 1310 ± 489.2 mm² to 492.53 ± 460.9 mm² at 8-weeks. In vaseline alone group, the mean baseline ulcer area decreased from 1107.53 ± 486.58 mm² to 662.63 ± 497.8 mm². In phenytoin & vaseline group, the treatment was effective in 21 (70%) patients, whereas in vaseline alone group, the treatment was effective in 13 (43.3%) patients; $p = 0.037$.

Conclusion: Phenytoin and vaseline dressings were significantly more effective as compared to vaseline alone dressings.

Key Words: Diabetic foot; Wound healing; Wound dressings; Phenytoin; Vaseline

This article may be cited as: Ahmed A, Ahmed MI. A comparison of efficacy of topical use of phenytoin and vaseline gauze dressing with vaseline gauze dressing alone in healing of diabetic foot ulcers. *J Postgrad Med Inst* 2014; 28(3):297-302.

INTRODUCTION

Diabetic foot ulceration is estimated to occur in 5-10% of diabetic population¹. Wound healing may be delayed due to abnormal cell function, hyperglycemia, peripheral neuropathy, peripheral vascular disease, susceptibility to infections and abnormal planter foot pressures. Delayed wound healing causes prolong morbidity and may ultimately end up in loss of part or whole of the foot. The 5-5dipenyl 2-4 imidazolidione sodium, with generic name of Phenytoin, was synthesized in 1908 and is in clinical use as a potent anti-epileptic drug since 1937². A frequently observed and unwanted side

effect of phenytoin, an anticonvulsant medication, is gingival hyperplasia, especially in children³. This side effect suggested that phenytoin can induce the growth of connective tissue, and may have the ability to promote wound healing. The beneficial effect of phenytoin has been shown in promoting healing of decubitus ulcers⁴, venous stasis ulcers⁵, traumatic wounds⁶, burns⁷, leprosy trophic ulcers⁸.

Topical application of Phenytoin has been used successfully in the management of diabetic foot ulcers. It stimulates the development of granulation tissue formation within 2 to 7 days after beginning treatment.

Its wound healing promoting effect has been attributed to many mechanisms including increasing fibroblast proliferation, inhibiting collagenase activity, promoting collagen deposition, enhancing granulation tissue formation, decreasing bacterial contamination, reducing wound exudates formation and up regulating growth factor receptors⁹. Biopsies of Phenytoin treated wounds show neovascularization, collagenization and decreased polymorphnuclear and eosinophil cell infiltration¹⁰. Topical Phenytoin can enhance wound healing in diabetic foot ulcers but further research is required to establish Phenytoin as healing agent^{11, 12}.

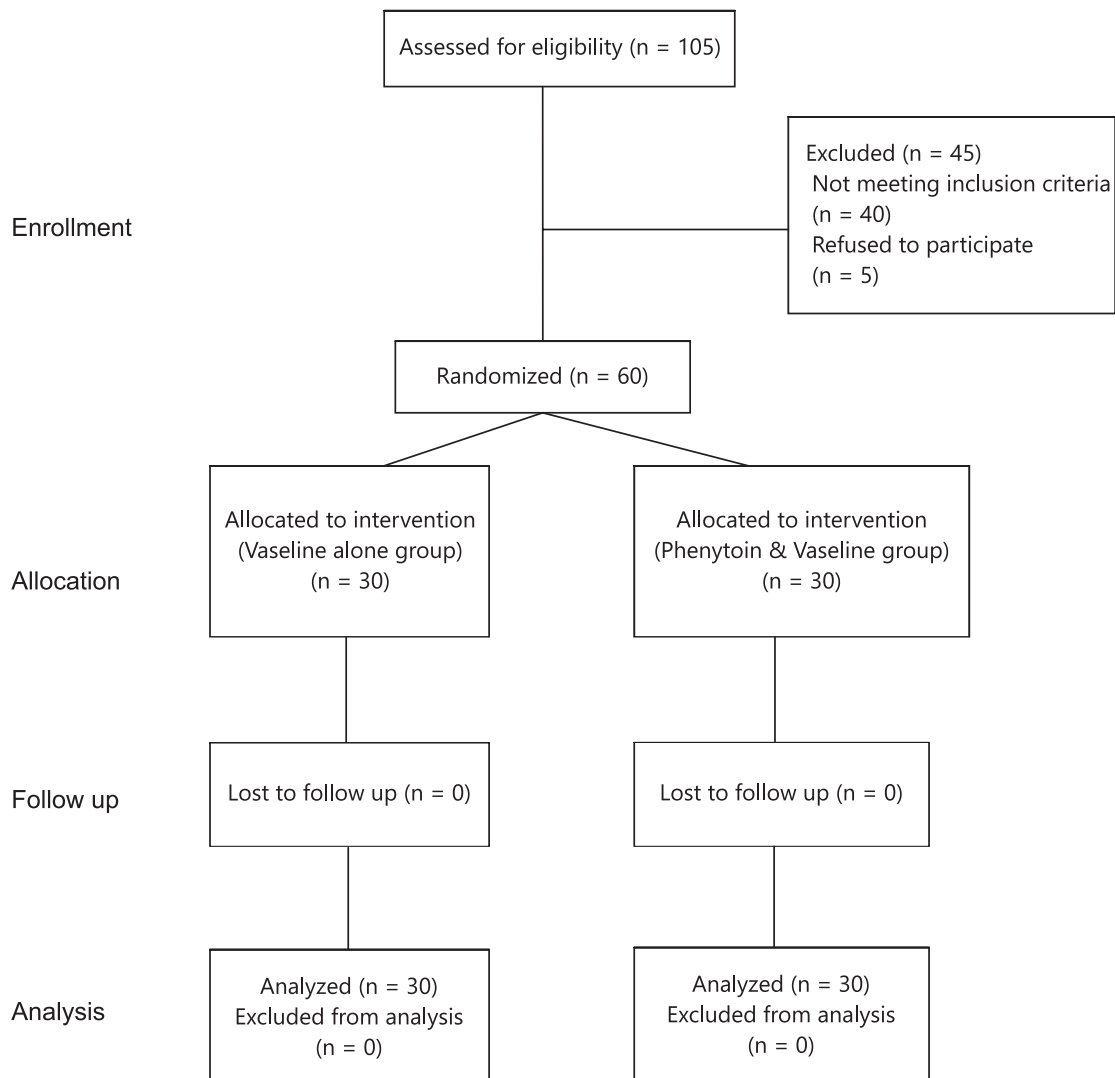
The rationale of this study was to determine the efficacy of Phenytoin in our population as topical use of Phenytoin is not in routine use in the treatment of diabetic foot ulcers and different studies have shown conflicting results. Vaseline Gauze dressing is in com-

mon practice for diabetic foot wound care. Phenytoin capsules are available in the market and powder from these capsules can be topically applied.

METHODOLOGY

This randomized control trial was conducted at Surgical unit I of Benazir Bhutto Hospital from January to June 2013 to compare efficacy of topical use of Phenytoin and Vaseline Gauze dressing with Vaseline Gauze dressing alone in healing of diabetic foot ulcers. Efficacy was measured in terms of > 50 % reduction in area of diabetic foot ulcer after 08 weeks time. The study included 60 patients of Grade 1 & 2 Maggot-Wagner Diabetic Foot Ulcers of more than 4 weeks (i.e. without necrosis or osteomyelitis) who had adequately controlled diabetes with fasting blood sugar of 110-130 mg/dL on two consecutive days prior to recruitment in the study.

Figure 1: CONSORT diagram showing the flow of participants through each stage



Patients with history of hepatic and renal disease, those on steroid use and those with impalpable dorsalis pedis or posterior tibial arteries were excluded. Area of ulcer was measured by drawing the size of ulcer on a transparent paper and then shifting it to a graph paper for measurement of area by adding squares with in marked lines on first day of treatment.

Sample size was calculated by using WHO calculator, level of significance was 5 % and power of test was 90%. The study patients were divided in two equal groups randomly by Lottery method; 30 in the phenytoin and Vaseline gauze dressing group and 30 in Vaseline gauze dressing alone group. Systemic antibiotics were given according to culture and sensitivity report. Group A received routine dressing with Pyodine bath and normal Saline and Vaseline gauze dressing was placed. Group B was given Phenytoin powder from capsules in thin uniform layer in addition to wound care mentioned for group A. The amount of powder dusted was dependent on surface area: 0-5 cm - 100mg, >5.1-9 cm - 150 mg, 9.1-15 cm - 200mg, >15 cm - 300 mg Dressings were done daily or on alternate days depending upon dressing soakage and patients comfort. After 08 weeks, area of the wound was measured using graph paper tracings and healing percentage was calculated. The number of small squares inside the tracing was measured. This gave the area in mm. It was assessed at the baseline (A₀) and at 8th week (A₈). The percentage reduction in the area over 8 weeks was assessed as follows;

$$\text{Percentage reduction in wound area} = \frac{(A_0) - (A_8)}{(A_0)} \times 100$$

Figure 1 shows CONSORT diagram of the study.

Collected data was recorded and analyzed on SPSS version 13.0. Chi Square test was used to compare efficacy between two groups. P value < 0.05 was significant.

RESULTS

The age ranged from 35 to 68 years with a mean age of 53.83±6.66 years. The study included 36 (60%) males and 24 (40%) females. All were Wagner grade 2 foot ulcers. This means that the age and gender distribution were similar between the two groups; p= 0.432 for age and p= 0.598 for gender distribution respectively. Hence the difference in efficacy cannot be biased by differences in demographic characteristics or severity of foot ulcer.

The mean baseline ulcer area (A₀) of patients in the phenytoin & Vaseline group was 1310±489.2mm² and that of patients in Vaseline alone group was 1107.53±486.58 mm² respectively. The mean baseline ulcer area (A₀) of patients was not statistically different between the two groups; p= 0.113. The mean 8-week ulcer area (A₈) of patients in the phenytoin & vaseline group was 492.53±460.9 mm² and that of patients in Vaseline alone group was 662.6±497.8 mm² respectively. The mean percentage reduction in ulcer area at 8-weeks of patients in the phenytoin & Vaseline group was 66.1±34.1% whereas that of patients in vaseline alone group was 46.64±39.4% respectively. This difference was statistically significant; p= 0.045. Hence at the 8-weeks percentage reduction in ulcer area was significantly higher in the phenytoin group. In the phenytoin & vaseline group the treatment was effective in 21 (70%) patients, whereas in the vaseline alone group the treatment was effective in 13 (43.33%) patients (Figure 2); p= 0.037 (Table 1). Hence the phenytoin & Vaseline

Table 1: Comparison of ulcer healing parameters between the two groups

Parameter	Phenytoin & vaseline group	Vaseline alone group	P value
Baseline ulcer area in mm ² (A ₀)	1310.10±489.2	1107.53±486.5	0.113♣*
Ulcer area at 8-weeks in mm ² (A ₈)	492.53±460.9	662.63±497.8	0.175♣*
Percentage reduction in ulcer area at 8-weeks in %	66.15±34.1	46.64±39.4	0.045♣♠
Efficacy (> 50% reduction in area) in N (%)	21 (70%)	13 (43.3%)	0.037¥♠

♣ Calculated using independent sample t-test

¥ Calculated using chi square test

* Not significant

♠ Statistically significant

Figure 2: Reduction in size of diabetic foot ulcer 08 weeks after Phenytoin and vaseline dressing in one patient



a: Pre-treatment



b: Post-treatment

dressings were significantly more effective as compared to vaseline alone dressings.

DISCUSSION

A wide array of dressings is now commercially available for treatment of diabetic foot ulcers. New products are frequently being released, each targeted at different aspects of healing. An appropriate dressing will control exudate and odor, alleviate pain, and contain wound infection. Whatever dressing is chosen, there is no substitute for adequate wound debridement, appropriate systemic antibiotic therapy, and frequent (daily) dressing changes and wound inspection. Phenytoin appears to be useful as a topical agent in promoting the healing of diabetic foot ulcers. Topical phenytoin appears to be an effective and inexpensive therapeutic agent in wound healing.

In our study phenytoin & vaseline dressings were significantly more effective as compared to vaseline alone dressings. Our results were similar to the study by Muthukumarasamy et al¹ where mean time to complete healing was 21 days with phenytoin and 45 days with control i.e., ulcers treated with topical phenytoin healed more rapidly ($p < 0.05$). Similar results were reported by Tauro et al¹⁴ where wound area reduction and bacterial clearance was greater in the phenytoin group than in controls. At the end of the fourth week, 72% phenytoin-treated ulcers had healed completely versus 28.5% controls. El-Nahas et al⁵ demonstrated that topical phenytoin significantly improved healing of recalcitrant neuropathic diabetic foot ulcers. In this study baseline wound area was $319.3 \pm 340.4 \text{ mm}^2$, reducing to $286.1 \pm 341.1 \text{ mm}^2$ and $269.1 \pm 341.2 \text{ mm}^2$ after four and eight weeks respectively. Overall reduction in ulcer size was $18.3\% \pm 27.5\%$ and $25.7\% \pm 38.6\%$ respectively. Of the 32 patients evaluated, only eight (25%) achieved more than 50% reduction in ulcer size after eight weeks of treatment. Pai et al⁶ conducted a double blind controlled trial on the effectiveness of phenytoin in diabetic neuropathic ulcers. At completion of the study the mean percentage reduction of ulcer area was 78.3% vs. 73.5% in the phenytoin vs. control group ($P > 0.05$). In study by Tauro et al² in 100 patients of phenytoin group as compared to 100 patients in control group, the mean rate of granulation tissue formation was 87.94% vs. 74.64%, mean graft take up was 92.31% vs. 86.15%, mean hospital stay was 32.26 vs. 54 days with negative culture sensitivity in 70% vs. 54% respectively. Carneiro et al³ compared topical phenytoin in 50 patients with EUSOL in 52 patients. Phenytoin caused significant reduction in pain, clearance of ulcer discharge ($p < 0.05$). The rate of formation of healthy granulation tissue was highly significant in the phenytoin group, however bacterial

colonization clearance was not statistically different between the two groups. In 2007 Shaw et al¹ conducted a meta-analysis of 14 trials of phenytoin on wound healing. There was a positive percentage treatment effect in favor of the phenytoin-treated group in one study investigating diabetic foot wounds and one study on chronic wounds but there was limited evidence for the use of phenytoin in burns and war wounds.

The assessment of wound healing is, in many cases, subjective and difficult to interpret⁴. We used the simplest method of tracings on the graph paper to measure the ulcer area. Tracing is cheap, quick and easy to use and requires no special skills⁵. Manual tracings prevent magnification and positioning errors; and therefore makes them fairly accurate⁶. However, problems occur with wounds with undermined margins. In addition, area measurements do not reflect early changes in deep wounds as they start the healing process by building up granulation tissue from the base of the wound. This issue was dealt with by taking all patients with grade 2 ulcers.

CONCLUSION

Phenytoin plus Vaseline dressings were significantly more effective as compared to vaseline alone dressings in healing of diabetic foot ulcers. Phenytoin powder is cheap and easily applied topically on ulcers thereby enabling its use in resource-poor environments. Further clinical use and evaluation is merited.

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CONTRIBUTORS

AA planned the study, did data analysis and wrote the manuscript. MIA helped in data collection and manuscript writing. Both authors contributed significantly to the final manuscript.