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Jordan Byrd

Philadelphia College of Osteopathic Medicine, jordanby@pcom.edu

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Is topical phenytoin effective in healing diabetic foot ulcers in patients over age 18?

Jordan Byrd, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not topical phenytoin is effective in healing diabetic foot ulcers in patients over age 18.

Study Design: Systematic review of three randomized controlled trials, published in 2011, 2013 and 2014.

Data Sources: Three randomized controlled trials comparing the effectiveness of topical phenytoin to placebo in healing diabetic foot ulcers. Data sources found using PubMed and Google Scholar.

Outcomes Measured: Greater than 50% reduction in ulcer area measured via graph paper tracings and area reduction calculations, discontinuation of slough and discharge from ulcers via blind observer decision, complete wound closure measured via wound measurement with elliptical method and statement of closure or non-closure.

Results: In the study by Ahmed et al. (2014), 70% of patients treated with topical phenytoin experienced greater than 50% closure of their ulcers, compared to 43% of patients in the control group. Patil et al. (2013) found that 78% of ulcers treated with topical phenytoin stopped producing slough and discharge, compared to 16% of ulcers in the control group. Shaw et al. (2011) found that 62% of ulcers treated with a phenytoin dressing had complete wound closure, compared to 74% in the control-dressing group.

Conclusions: There is conflicting evidence for whether topical phenytoin is effective in healing diabetic foot ulcers in patients over age 18. Two studies found significant evidence to support the efficacy of topical phenytoin in healing diabetic foot ulcers. One study did not find a significant difference in ulcer healing between patients treated with phenytoin and control dressings.

Key Words: Topical phenytoin, diabetic foot ulcer

INTRODUCTION

Diabetic foot ulcers are a common complication of diabetes mellitus (types 1 and 2). The decreased ability of patients with diabetes to heal wounds results from the altered functionality of their cells, nerves and blood vessels. Diabetic foot ulcers are a major cause of non-traumatic amputations in the United States. This systematic review evaluates three randomized controlled trials (RCTs) discussing the efficacy of topical phenytoin in healing diabetic foot ulcers.

The incidence of diabetes and its complications is increasing. This means that physician assistants must be familiar with the preventative measures and treatments associated with diabetic foot ulcers. Diabetes mellitus (types 1 and 2) affects approximately 25 million Americans. A foot ulcer will affect 15% of patients with diabetes in their lifetime. In 2007, an estimated 116 billion dollars were spent in the United States for the care of diabetes mellitus.¹ The care of diabetic foot ulcers makes up 33% of this cost.¹ In 2007, there were 113,000 patients discharged from hospitals in the United States with a primary diagnosis of diabetic foot ulcer.²

Diabetes type 1 most commonly presents during childhood. These patients are said to be insulin dependent because they usually do not produce any endogenous insulin. Diabetes type 2 tends to affect patients predominately over 45 years of age, but the occurrence in younger patients is rising due to poor dietary habits and decreased exercise. Type 2 diabetics are called insulin independent because many patients continue to produce some insulin, allowing them to augment their endogenous supply with drugs. In either case, patients with diabetes are at a greater risk of being hyperglycemic. The hyperglycemia seen in diabetics is thought to play a large role in the pathogenesis of many complications of diabetes, including diabetic foot ulcers. The higher incidence of peripheral neuropathy in the diabetic population leads to more frequent injuries, structural deformity and altered weight distribution to the foot because of decreased

sensation present in the lower extremity. Vascular insufficiency in the diabetic population leads to decreased perfusion of the lower extremity and altered healing ability in the event of an injury or ulceration.

Prevention of diabetic foot ulcers through blood sugar control and regular foot care is important because the efficacy of non-invasive treatments for established ulcers is limited. Once a patient develops a diabetic foot ulcer, early intervention includes decreased weight bearing of the affected part of the foot, debridement and wound dressing. Frequently, ulcers are subject to constant stress from activities such as walking. Interventions such as casting, custom footwear and bed rest are available to off-load the ulcers. In some cases, ulcers will need to be debrided with a surgical blade to allow neovascularization and new granulation tissue to be formed.³ Following debridement, ulcers are covered with a protective dressing, which may include a topical antimicrobial or other agents depending on the patient's individual needs. Infection in a diabetic foot ulcer is an indication for the use of systemic antibiotic therapy. Signs of infection include erythema, edema, tenderness and purulent discharge. The choice of antibiotic should be made based on the severity of ulceration and whether the clinician suspects the involvement of resistant bacteria.³ Commonly used agents for mild infections include monotherapy with PO clindamycin, cephalosporins or augmentin.⁴ In severe infections, intravenous monotherapy with a carbapenem or a 2-drug regimen such as vancomycin plus a beta-lactam/beta-lactamase inhibitor may be considered.⁴ Ulcers that have not responded to less invasive measures may require revascularization therapies or amputation.

Many patients with diabetic foot ulcers experience significant losses of mobility and quality of life. While there are a variety of treatments available, more research must be done to find effective, minimally invasive options for these patients. Phenytoin is an anti-epileptic drug

that has caused gingival hyperplasia as an adverse effect when used systemically. Research has shown mixed results on whether topical phenytoin may be an effective option for healing diabetic foot ulcers.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not topical phenytoin is effective in healing diabetic foot ulcers in patients over age 18.

METHODS

Studies were selected based on the population, intervention and comparison addressed in each article. This review selected for RCTs that compared the application of topical phenytoin dressing to control dressing in healing diabetic foot ulcers in patients over age 18. The three RCTs studied in this systematic review measured outcomes including the number of patients experiencing greater than 50% reduction in ulcer area, discontinuation of slough and discharge from the ulcers, and complete closure of ulcers.

The data sources were found using searches through PubMed and Google Scholar, with key words including “diabetic foot ulcer” and “topical phenytoin”. All articles used were in the English language and published in peer-reviewed journals. It was necessary for all articles to be relevant to the research question and to include outcomes that mattered to patients (POEMs). The inclusion criteria used for this review was RCTs published since 2011. This review excluded RCTs that included patients less than the age of 18. In order to determine the significance of the results published in each article, the relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), and p-values were calculated.

Table 1 - Demographics & characteristics of included studies

| Study | Type | # Pts | Age (yrs) | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---------------------------|------|-------|-----------|--|---|------------|--|
| Ahmed ⁵ (2014) | RCT | 60 | 35-68 | -Wagner grade I/II foot ulcers for >4 weeks. -Controlled diabetes (Fasting blood sugar 110-130, within 2 days prior to study) | Pts with necrosis, osteomyelitis, history of hepatic/ renal disease, steroid use, impalpable dorsalis pedis or posterior tibial pulses | 0 | Wound dressing with phenytoin powder each day or every other day |
| Patil ⁶ (2013) | RCT | 100 | >22 | -Pts with grade I/II diabetic foot ulcers | Pts with grade III/IV/V diabetic foot ulcers, ulcers with signs of ischemia, tropic ulcers caused by neuropathy/ MS, varicose ulcers, Marjolin's ulcers | Not stated | Wound dressing with topical phenytoin each day of the study |
| Shaw ⁷ (2011) | RCT | 65 | >18 | -Pts with DM 1 or 2, peripheral neuropathy, ABI > 0.5 and a diabetic foot ulcer for 4 weeks or longer | Pts with signs of ischemia (ABI < 0.5, rest pain and necrosis), grade III/IV ulcers, osteomyelitis/ exposed bone | 9 | Topical phenytoin dressing application to wound 3 times per week |

OUTCOMES MEASURED

Each RCT looked at several aspects comparing healing in the topical phenytoin group to the placebo group. This review focused on the evidence published in each RCT that matters to patients.

In the article by Ahmed et al., treatment was considered to be effective if there was greater than 50% reduction in ulcer area. To measure this outcome, the ulcers were traced onto graph paper at the beginning and end of the 8-week study. The number of squares within the tracings was counted, representing the area of the ulcer. The percent reduction was then calculated to decide whether greater than 50% of the ulcer had closed.

In the article by Patil et al., the number of ulcers that stopped producing slough and discharge was measured. This outcome was determined via a blind observer, who made notes on ulcer slough and discharge weekly and ultimately decided whether slough and discharge was present at the end of a 14-day timeframe.

In the article by Shaw et al., the outcome measured was whether the diabetic foot ulcers had completely closed. A blind observer measured the ulcers each week using the elliptical method and stated whether complete closure occurred by the end of a 16-week period.

RESULTS

This systematic review used three RCTs that displayed dichotomous data comparing phenytoin dressings versus control dressings. Each RCT studied patients greater than 18 years old with a diagnosis of diabetic foot ulcer. Each RCT had inclusion and exclusion criteria for the selection of patients, which may be found in Table 1. None of the RCTs in this review reported issues with compliance.

In the study by Ahmed et al., 60 patients with grade 1 or 2 diabetic foot ulcers were studied at the Benazir Bhutto Hospital surgical unit. The study took place from January 2013 to June 2013. The 60 patients were randomized into two groups of 30. One group was given dressings with topical phenytoin and the other received control dressings. Ahmed et al. found that 70% of patients that received phenytoin dressings had greater than 50% closure of their ulcers, compared to 43% of patients in the control group.⁵ A chi-square test was used to evaluate the results and they were found to be statistically significant with a p-value of 0.037.⁵ Relative benefit increase (RBI) was calculated to be 63% and absolute benefit increase (ABI) was calculated to be 27%. Numbers needed to treat (NNT) was calculated to be 3.70, (see table 2) meaning that for every 4 ulcers treated with topical phenytoin, one more will have greater than 50% reduction in area as compared to control dressing at the end of an 8 week period. No patients were lost to follow up and adverse effects experienced by research subjects were not reported in this RCT.

In the RCT by Patil et al., 100 patients admitted to the Shri B.M. Patil Medical College Hospital in India with a diagnosis of grade 1 or 2 diabetic foot ulcers were studied. The trial took place from October 2009 to May 2011. Two groups of 50 patents were formed. The experimental group received topical phenytoin dressing and the control group received a standard saline dressing. This RCT reported that 78% of ulcers treated with topical phenytoin stopped producing slough and discharge, compared to 16% of ulcers in the control group.⁶ This finding was analyzed with a chi-square test and found to be statistically significant, with a p-value of less than 0.005.⁶ RBI was calculated to be 388%, and ABI was calculated to be 62%. NNT was calculated to be 1.61, (see table 2) meaning that for every 2 ulcers treated with topical phenytoin dressing, one more ulcer will stop producing slough and discharge at the end of a 14-day period,

compared to control. Mild itching was experienced by 5 patients treated with topical phenytoin dressings.⁶ Losses to follow up were not reported in this RCT.

In the RCT by Shaw et al., 65 patients with grade 1 or 2 diabetic foot ulcers were selected from the vascular surgery and diabetic foot clinics in the Royal Victoria Hospital of Belfast. The RCT was conducted between February 2006 and February 2008. During the study, 9 patients were removed for reasons including infection, death or loss to follow up. Shaw et al. reported that all 65 patients were included in the data analysis. For the purposes of this review, only the patients that finished the study will be examined. Of the 56 patients that completed the study, 29 patients were given phenytoin dressings and 27 patients were given control dressings to treat their ulcers over a 16-week timeframe. This RCT found that 62% of ulcers in the phenytoin-dressing group experienced complete wound closure, compared to 74% in the control-dressing group.⁷ A Kaplan-Meier test was used in order to produce a survival analysis. A p-value of 0.96 was reported, meaning that topical phenytoin and control dressings showed no statistically significant difference in ulcer healing.⁷ RBI was calculated to be -16%, ABI was calculated to be -12% and NNT was calculated to be -8.33 (see Table 2). This means that for every 9 ulcers that are treated with phenytoin dressing, one less ulcer will completely close as compared to control dressing at the end of a 16-week period. There were no adverse effects in either group studied. The systemic absorption of topical phenytoin was significantly less than phenytoin's therapeutic range when used as an anti-epileptic agent.⁷

Table 2: Analysis of treatment efficacy and statistical significance

| RCT | CER | EER | RBI | ABI | NNT | P-value |
|------------|------------|------------|------------|------------|------------|----------------|
| Ahmed | 43% | 70% | 63% | 27% | 3.70 | 0.037 |
| Patil | 16% | 78% | 388% | 62% | 1.61 | <0.005 |
| Shaw | 74% | 62% | -16% | -12% | -8.33 | 0.96 |

DISCUSSION

Phenytoin is an anticonvulsant medication approved for the treatment of generalized tonic-clonic seizures, complex partial seizures and status epilepticus.⁸ It has also been approved for the prevention of seizures in some patients with a decreased threshold for seizures. Phenytoin works for seizures by blocking sodium transport across nerve membranes, thereby decreasing the rate of conduction.⁸ Phenytoin has a black-box warning for cardiac arrhythmias such as ventricular fibrillation and ventricular tachycardia especially when it is given intravenously at a rate greater than 50 mg/min.⁸ Phenytoin, when given systemically, is associated with many other adverse reactions including Stevens-Johnson syndrome, hypotension, hepatotoxicity, suicidal ideation, gingival hyperplasia, decreased bone density and seizures if the drug is quickly stopped.⁸ Previous studies have shown that phenytoin, when used topically, is able to promote new growth of blood vessels and connective tissue.⁷ Fortunately, Shaw et al. reported minimal systemic absorption and no adverse reactions in patients treated with topical phenytoin.

Phenytoin is available in IV and PO forms, but topical phenytoin is not widely available in the US. Each of the articles studied in this systematic review had to manufacture their own topical phenytoin dressings using a gel or saline base, mixed with phenytoin powder. This poses some inconvenience for widespread use on diabetic foot ulcers. Insurance should not be a barrier to treatment with topical phenytoin because it is a relatively inexpensive treatment option as compared to the standard treatments for diabetic foot ulcers.

A limitation of the RCTs by Ahmed et al. and Shaw et al. is that the margins of diabetic foot ulcers can be difficult to approximate, meaning that there could be observer error when measuring the area of an ulcer. A limitation to the studies by Ahmed et al. and Patil et al. is that the articles failed to mention specifics of patient randomization and blinding techniques used for

clinicians and observers. These are important in assessing the validity of the RCTs. The study by Shaw et al. was limited by sample size. It was calculated that 144 patients would need to be studied in order to show a 20% benefit increase related to the usage of topical phenytoin for healing diabetic foot ulcers.⁷ Only 56 patients completed the RCT.

CONCLUSIONS

There is conflicting evidence as to whether topical phenytoin is effective in healing diabetic foot ulcers in patients over the age of 18. The RCTs by Ahmed et al. and Patil et al. reported significant improvement in patients treated with phenytoin dressings as compared to control dressings. The RCT by Shaw et al. could not demonstrate significant improvement in the healing of diabetic foot ulcers treated with topical phenytoin over control.

Improvements can be made for future studies regarding the outcomes that are measured. The studies by Ahmed et al. and Patil et al. tested the efficacy of topical phenytoin in healing diabetic foot ulcers though statement of 50% closure or discontinuation of slough and discharge. While these outcomes are applicable to the research question, future studies should be directed toward the number of patients that experience complete closure of their ulcers, as this could be considered the best measurement of effective healing.

In order to increase the generalizability of future studies, the population of participants recruited should be broader. In each RCT studied, the research subjects were selected from the surgical unit of one hospital. By including patients from a variety of locations the results will be more generalizable to answering the question of whether topical phenytoin is effective in healing diabetic foot ulcers in patients over age 18.

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