Effects of Pentoxifylline on Healing Times in Diabetic Foot Ulcers

Katie Landry, DPM[3]; Zackary Clor, BS[1,2]; Derek Talbot, DC[2]; Adam Fleischer DPM, MPH, FACFAS[1,2,3,4]

[1] Center for Lower Extremity Ambulatory Research (CLEAR), [2] Dr. William M. Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine and Science, [3]Advocate Illinois Masonic Medical Center, [4] Weil Foot and Ankle Institute

♦ Introduction

Over recent years, the number of people living with diabetes has increased in the United States and worldwide, inevitably increasing the burden to the healthcare system. The average cost for treating a diabetic foot ulcer was conservatively estimated at $3927 per episode in 2012 [1]. Nearly 15% of all diabetics will be affected by a diabetic foot ulcer (DFU) [2]. Ulceration in diabetics results from the culmination of neuropathy, decreased vascular status, and increased chance of infection, which can occur in nearly 58% of new foot ulcers, and can foreshadow roughly 85% of people who require partial or full foot amputation [2,3]. The five-year mortality rate for patients with diabetic ulcers can be as high as 55% for ischemic related ulcers and 45% for neuropathic related ulcers [3]. With the numerous effects DFUs can have on patients and the healthcare system there is a need for treatment methods which can help improve the healing time of foot ulcers and wounds in diabetic patients.

Pentoxifylline alters the viscosity of blood and allows for increased erythrocyte flexibility allowing for better delivery of blood to the tissues being deprived. Ulcers are typically categorized into ischemic (15%), neuropathic (35%), or neuroischemic (50%) ulcers [4]. The odds of a diabetic developing a first-time foot ulcer increases by seven times when the patient has moderate or severe lower extremity sensory loss commonly seen in diabetic patients [5]. Neurovascular structure impairment, as a result of diabetes, in vasculature of the foot and distal lower extremity can prevent the adequate flow required to prevent and/or repair DFUs [4,5]. With many DFUs having a vascular related component, it's believed by altering the properties of the blood flow, pentoxifylline may help increase its delivery to the tissues requiring it for repair.

Mills *et al.* (2014) introduced the WIfI ulcer classification system which assesses the Wound, Ischemia, and foot Infection, to grade the ulcers. This classification method attempts to provide a uniform system that can assess three of the most common variables which typically lead to amputation in patients with DFUs. The wound score is graded from 0 to 3 and factors in depth, size, severity, and anticipated difficulty achieving wound healing. Ischemia grades range from 0 to 3 which can use ankle-brachial index, ankle systolic pressure, or toe pressure to determine the grade. Infectious Disease Society of America (ISDA) score was implemented to score the foot infection portion of WIfI [6]. Due to the WIfIs implementation of a multifactorial system, we used this system to account for foot ulcer severity in this study.

♦ Statement of Purpose

To analyze the effects of adjunctive pentoxifylline on wound healing rates in patients with DFUs.

♦ Methods

70 consecutive patients treated for DFUs from 2014 to 2019 within a large, urban-based advanced center for wound healing served as the study population. 16 patients were prescribed pentoxifylline and 54 patients were treated without pentoxifylline. Conventional ulcer treatment, which typically consisted of total contact casting and serial sharp debridement, was used on all patients irrespective of pentoxifylline regimen. The decision to start pentoxifylline was practitioner-patient dependent and, when initiated, was dosed at 400 mg three times daily. Healing rate and other covariates were obtained through chart review. Cox regression analysis was used to test for differences in healing rate while controlling for potential confounders. All patients in this study were diabetic and ulcers were scored using the WIfI classification scale as outlined by Mills et al. [6]. Wounds with WIfI ischemia classifications of 0 or 1 were included while dysvascular wounds (ischemia grades 3 and 4 were excluded). Wound size and foot infection levels were not considered as inclusion/exclusion criteria. SAS version 9.4 was used for statistical analyses.

♦ Results

Seventy patients (16 pentoxifylline, 54 no pentoxifylline) were included. The groups were similar with respect to age, ulcer duration, baseline ulcer size, comorbidities, and ulcer severity (WIfI classification) at the start of treatment (p>0.05 for all). Among those patients who healed (9/16 Tx group, 39/54 control), wound healing was significantly faster in subjects receiving oral pentoxifylline in addition to conventional ulcer treatment (mean 64 +/- 37 days versus 117 +/- 84 days, Wilcoxon p<0.05). The probability of healing was also higher in the pentoxifylline group compared to those not receiving pentoxifylline (**Figure 1** below).

Table 1. Baseline characteristics of patients within the control group and those treated with pentoxifylline 400 mg three times daily (n=70) .

Variable	Pentoxyfylline (n=16)	No Pentoxyfylline (n=54)	p Value
Male gender	12 (0.75)	34 (0.63)	0.3730
BMI (kg/m^2)	31.3 (9.0)	35.2 (15.8)	0.3900
WIfI			
Wound	1.68 (0.79)	1.53 (0.69)	0.4044
Ischemia	0.81 (0.98)	0.46 (0.88)	0.1799
Foot Infection	0.75 (0.93)	0.51 (0.79)	0.3137
Wound size (cm^2)	3.63 (7.0)	7.74 (21.5)	0.4561

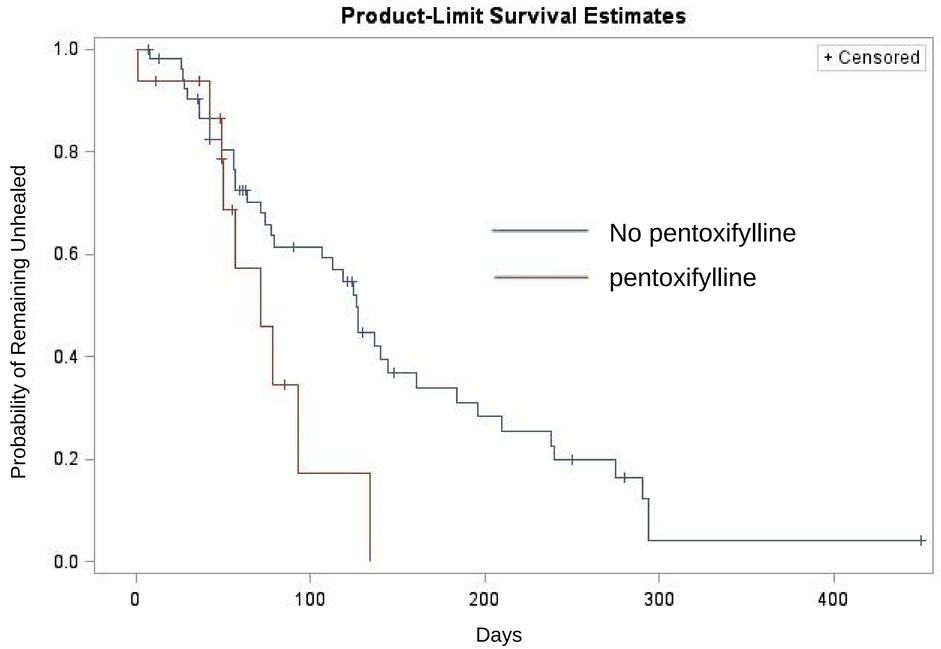

Figure 1. Kaplan Meier plot demonstrating a significantly greater probability of ulcer healing among patients treated with pentoxifylline (red line) versus those not receiving pentoxifylline (blue line) [Log-Rank Chi Square 3.925, p=0.0476).

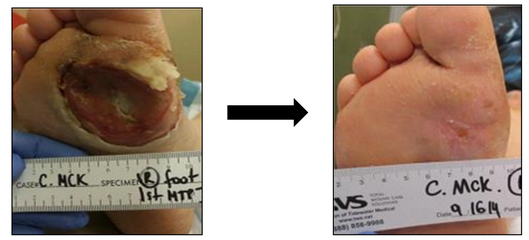

Figure 2. This patient was treated with advanced wound therapy (including total contact casting and serial wound debridement) plus PO pentoxifylline. Her time to closure was 120 days.

♦ Discussion

A recent Cochrane database review found that pentoxifylline significantly improves healing rates in patients with venous leg ulcers [7]; however, little work has been published on its efficacy in the treatment of DFUs. The analysis presented in this study suggests pentoxifylline 400 mg prescribed three times daily in conjunction with conventional ulcer treatment increases the healing time of DFUs when compared to patients undergoing just conventional ulcer treatment (mean 64 +/- 37 days versus 117 +/- 84 days respectively, Wilcoxon p<0.05, log-rank p<0.05). Additionally, patients were more likely to heal when adjunctively treated with pentoxifylline. With the cost that DFUs burden the healthcare system with, we suspect that adding pentoxifylline 400 mg three times daily might help to reduce a patient's time with an ulcerated foot thus ultimately decreasing morbidity, time and cost to the patient and healthcare system. Pentoxifylline is generally well tolerated, with approx. 10% of subjects reporting GI disturbances [7.] Prospective comparative work may be warranted at this time.

♦ References

1. Fife CE, Carter MJ. Wound care outcomes and associated cost among patients treated in US outpatient wound centers: Data from the US wound registry. *Wounds : a compendium of clinical research and practice*. 2012; 24(1): 10.
2. Farooq S, Javed S, Jahan N. Diabetic foot ulcers. *The professional medical journal*. 02;26(2).
3. Boulton AJM. The diabetic foot: A global view. *Diabetes Metab Res*. 2000;16(S1):S2-S5.
4. Armstrong DG, Cohen K, Courric S, Bharara M, Marston W. Diabetic foot ulcers and vascular insufficiency: Our population has changed, but our methods have not. *Journal of Diabetes Science and Technology*. 2011;5(6):1591-1595.
5. Del Core MA, Ahn J, Lewis RB, Raspovic KM, Lalli TAJ, Wukich DK. The evaluation and treatment of diabetic foot ulcers and diabetic foot infections. *Foot & Ankle Orthopaedics*. 2018;3(3):247301141878886.
6. Mills JL, MD, Conte MS, MD, Armstrong, DG, et al. The society for vascular surgery lower extremity threatened limb classification system: Risk stratification based on wound, ischemia, and foot infection (WIfI). *Journal of Vascular Surgery*. 2014;59(1):220-234.e2.
7. Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD001733. DOI: 10.1002/14651858.CD001733.pub3.

♦ Acknowledgements

This project was partially supported by grant number 2T35DK074390 from the National Institute of Diabetes and Digestive and Kidney Disease. The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.