The Effectiveness of Stable pH Neutral Super-oxidized Solution for the Treatment of Infected Diabetic Foot Wounds

Amar P.S. Suri, MBBS, CPP

Department of Podiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Consultant Podiatrist and Director, Diabetic Footcare Center, New Delhi, India

Email: suriamar@hotmail.com

Abstract

Objective: Foot ulcers are common in diabetic patients, and most become infected, thereby increasing the risk of amputation. Successful treatment requires a comprehensive program of metabolic control, wound debridement and antibiotics. The role of topical antimicrobials remains undefined. Dermacyn (Oculus Innovative Sciences, Petaluma, CA) is a stable, nonirritating, pH-neutral super-oxidized solution (nSOS) that contains oxychlorine compounds and is highly active in vitro against numerous microorganisms.

Study Design: We evaluated the clinical efficacy and microbial load reduction of topical therapy with nSOS or saline in diabetic patients with mild foot infections. This randomized trial enrolled 100 patients (81 men and 19 women) with either type I or type II diabetes and solitary infected foot ulcers 2 cm to 15 cm in diameter. Patients were randomized into two groups and were instructed to bathe their wounds in either 20-50 mL of nSOS or normal saline for 45 minutes once a day for 16 weeks. Debridement was performed as needed. Cultures were obtained from the base of the wounds on days 1, 7, and 21 of the treatment period. Off-loading was achieved in all patients. Patients were evaluated weekly by an examiner who was blinded to the solution the patient was using for wound cleansing. All 100 patients completed the 16-week study. At entry, the most common isolates in both groups were *Staphylococcus aureus* and *E. coli*.

Results: A 5-log reduction in bioburden was documented at some point in 38 patients (76%) in the study group, whereas only 16 patients (32%) in the saline group achieved a 2-log reduction in bioburden ($p=0.01$). In addition, better growth of granulation tissue was noted at the base of the ulcers in patients in the study group than in those in the saline group (8 cm^2 versus 2 cm^2, $p<0.05$). At the conclusion of the trial, the wounds had healed in 39 patients (78%) in the nSOS group versus only 20 patients (40%) in the saline group ($p<0.05$).

Conclusion: This study demonstrates for the first time that nSOS is superior to saline for treating mildly infected foot wounds in diabetic patients and that mechanical eradication of bacteria is not the sole explanation for its efficacy.

Introduction

Foot ulcers are common among diabetic patients, with an estimated lifetime risk of 25%.[1] Most of these ulcers become infected, primarily with *Staphylococcus aureus*,[2] although polymicrobial infections are not uncommon.[3] Infection increases the risk that amputation will become necessary. In addition, the formation of biofilms within the wound can inhibit antibiotic action.[4]

Treatment of foot ulcers in this population is imperative to reduce the risk of amputation, which leads to loss of independence, greatly diminished quality of life, and sometimes death.[5] Successful treatment requires a comprehensive program of blood glucose control, smoking cessation,[6] appropriate antibiotics, proper wound cleansing and debridement, off-loading of pressure and, sometimes surgical intervention that focuses on revascularization of the affected foot.[7] Even with these measures however, success is not assured.

Dermacyn is a new super-oxidized pH-neutral solution containing active oxychlorine compounds with a total free chlorine concentration of <30 ppm. Unlike earlier formulations of super-oxidized water, this preparation is stable (it has a shelf-life of one year or longer) and nonirritating. In vitro, it is highly active against numerous gram-positive and gram-negative bacteria, fungi and viruses, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Bacillus* spores and human immunodeficiency virus. It also is active against many antibiotic-resistant organisms.[8] In the study reported herein, we compared the clinical efficacy of and microbiological response to nSOS with saline in a population of diabetic patients with mild foot infections.

Methods & Materials

This prospective, open-label trial was conducted at the **Diabetic Footcare Center in New Delhi, India**. Consenting men and women (age >18 years) with type I or II diabetes mellitus and a mild to moderate infected foot ulcer that had been present for at least six weeks were eligible for the study.

On presentation, all patients underwent podiatric assessment, Doppler ankle-brachial index (ABI) measurement, neuropathic screening with a 10-g monofilament & biothesiometer, and plantar pressure measurements. Mild infections were defined by clinical signs according to the classification of the Infectious Disease Society of America (IDSA).[10] Lesions were further documented as grade I, II or III following the University of Texas Wound Classification System.[7] Patients could have undergone debridement or other minor surgical procedures as long as the infected area was not resected or amputated.

The trial enrolled 100 patients (81 men and 19 women) with a mean age of 54.5 years and foot ulcers that had been present for a mean of two months.[6] They were randomly assigned to receive either normal saline (n=50) or nSOS (n=50) for use at home to clean and irrigate their wounds once a day for 16 weeks. They were no significant differences between the two groups with respect to age, duration of diabetes mellitus, wound grade, ulcer size or incidence of peripheral vascular disease or neuropathy (Table 1). The clinical characteristics of the infected sites were similar in the two groups according to the IDSA classification. Lesions sites were also similar (Table 2).

The volume solution used for each dressing ranged from 20 ml to 50 ml. Wounds were cleaned by swabbing them lightly with a gauze pad that had been soaked in the assigned solution. Patients with more severely infected wounds were instructed to bathe them in either nSOS or normal saline for 4 to 5 minutes daily for 3-4 days. Extensive debridement was performed on day 1 in all patients who had necrotic tissue and draining pus; suitable tissue wound specimens were obtained for bacterial cultures. Small debridements were performed regularly on subsequent days in all patients, as necessary (mean, five per patient). Cultures were repeated at day 7 and day 21 after the initiation of therapy. Off-loading was achieved in all patients with the Deaconess felted foam system, which was applied with glue around the ulcers. Surgical shoes, AFT orthotics, or offloading sandals were given to all patients. Off-loading pads were changed during weekly visits to the clinic, and photographs of the lesions were taken regularly.

Clinical response was evaluated weekly for 16 weeks for signs of progression of infection, growth of granulation tissue and complete wound closure. The persons evaluating the wounds were blinded to the solution the patient was using for wound cleansing. The data were analyzed based on the chi-square test with Yates correction.

Results

All 100 patients completed the 16-week follow-up. At wound culture on days 1, 7 and 21, the most common isolates in both groups were *S. aureus* (isolated from more than 60% of the wounds), *E. coli* (isolated from 50% of the wounds), *Streptococcus agalactiae*, *K. pneumoniae*, and *P. aeruginosa* (Table 2). The number of conservative surgical procedures (e.g., debridement, ulcerectomy) and minor amputations (e.g., Ray's single, toe amputation) performed during the study was similar for the two groups . No major amputations were necessary during the course of this study.

Patients in the nSOS group showed a considerable reduction in cellulitis surrounding the wound, and less fetid odor was apparent a few days after the start of therapy. There was a 5-log reduction in bioburden (from 1.0×10^7 cfu/mL to 1.0×10^2 cfu/mL) documented at some point between days 7 and 21 in 38 patients (76%) in the study group, whereas only 16 patients (32%) in the saline group achieved a 2-log reduction in bioburden (from 2.0×10^7 cfu/mL to 1.0×10^5 cfu/mL) during the same period ($p=0.01$; Table 5). At the conclusion of the trial, 45 patients (90%) in the nSOS group had eradication of all bacterial strains from the wound compared with 32 (64%) of the saline group ($p=0.01$). Patients in the nSOS group also experienced better growth of granulation tissue at the base of the ulcers at 16 weeks than those in the saline group (8 cm^2 versus 2 cm^2, $p<0.05$). At the conclusion of the trial, the wounds had completely healed in 39 patients (78%) in the nSOS group versus only 20 (40%) in the saline group ($p<0.05$). The median time to healing was significantly less in the nSOS group (44 days; range 1864 days) than in the saline group (62 days; range 2281 days) ($p<0.05$). Neither solution caused irritation of the wounds.

Discussion

In order to increase the likelihood that diabetic wounds will heal, patients need to follow a comprehensive treatment program that includes control of serum glucose concentration and ideally, smoking cessation, in an effort to improve local blood flow and immune function.[1,7] The wound should be cultured and an appropriate antibiotic given until the infection has resolved.[7] Wound care including regular cleansing and debridement of callus and necrotic material, is required; for deeper wounds, evaluation and appropriate treatment by a surgeon is recommended.[7]

Because these measures may be insufficient, the value of topical agents has been explored. Povidone - iodine is one choice. However, in vitro, it inhibits the growth of human fibroblasts,[11] and, clinically, it is capable of causing chemical burns in some patients,[12] although it may not interfere with wound healing.[13] Nevertheless, it is objectionable to many patients because it can cause skin irritation and it stains. The super-oxidized solution used in this study is a pH-neutral (7.27.8) preparation of water containing active oxychlorine compounds with <80 ppm of free chlorine. Thus, it is non-irritating and does not need to be rinsed off after application, a step suggested for Povidone - iodine.[12]

Two clinical trials have compared nSOS with povidone - iodine in patients with diabetic foot ulcers. The nSOS solution was significantly more effective than povidone - iodine in reducing the bacterial burden in the wounds and in promoting healing. Not only were the wounds treated with super-oxidized water more likely to heal but they healed more rapidly.

The current study demonstrates for the first time that nSOS is superior to saline in healing mildly infected foot wounds in diabetic patients. Significant reductions in bioburden were achieved in more than twice as many patients using nSOS (76% versus 32%, $p<0.01$), and, at the conclusion of the trial, the wounds had healed in 78% of the patients using nSOS compared with only 40% of those using saline ($p<0.05$). These results suggest that mere washing of the wound, although beneficial, does not account for all of the therapeutic effect of nSOS. Further trials with larger numbers of patients with a greater variety of lesion types are needed to determine the most appropriate use of this topical agent.

References

1. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885-95.
2. Nelson EA, O'Meara S, Golder S, et al. Systematic review of antimicrobial treatments for diabetic foot ulcers. Diabet Med 2006;23:348-59.
3. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. Diabet Care 1998;21(5):855-9.
4. Landa-Solis C, Gonzalez-Espinosa D, Guzman-Soriano B, et al. MicrocynTM: a novel super-oxidized water with neutral pH and disinfectant activity. J Hosp Infect 2005;61:291-9.
5. Tanaka H, Hirakata Y, Kaku M, et al. Antimicrobial activity of superoxidized water. J Hosp Infect 1996;34:43-9.
6. Gutierrez AA. The science behind stable, super-oxidized water: exploring the various applications of super-oxidized solutions. Wounds 2006;18(suppl):7-10.
7. Yahagi N, Koto M, Kitahara M, et al. Effect of electrolyzed water on wound healing. Artif Organs 2000;24:984-7.
8. Gonzalez-Espinosa D, Pérez-Romano L, Guzman-Soriano B, Arias E, Bongiovanni CM, Gutiérrez AA. Effects of neutral super-oxidized water on human dermal fibroblasts in vitro. Int Wound J (UK) 2007;4:241-50.
9. Dalla-Paola L, Brocco E, Senesi A, et al. Super-oxidized solution (SOS) therapy for infected diabetic foot ulcers. Wounds 2006;18(9):262-70.
10. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of North America's diabetic foot infection classification. Clin Infect Dis 2007;44:562-5.

Table 1. Characteristics of study and control patients

	nSOS group (n=50)	Saline group (n=50)
Male/Female (%)	39 (78)/11 (22)	42 (84)/8 (16)
Mean age (years)	55.5	53.5
Mean duration of DM (years)	22	21
UTC n (%)		
I	31 (62)	32 (64)
II	14 (28)	15 (30)
III	5 (10)	3 (6)
Ulcer size (cm^2)	4-12	2-11
N (%) with PVD	10 (20)	9 (18)
N (%) with neuropathy*	34 (68)	35 (70)

nSOS=Dermacyn®, saline solution=0.9% NaCl solution
UTC=University of Texas Wound Classification System, PVD=peripheral vascular disease
* Loss of sensation on 5 of 10 of places on evaluation by a 10 gm SW monofilament and Biothesiometer (Neurobiometric SES-UK)

Table 2. Pathogens isolated on initial culture

Bacterium	nSOS group (n=50)	Saline group (n=50)
Staphylococcus aurous	31	32
E. coli	18	32
Streptococcus agalactiae	12	9
Klebsiella sp.	12	0
Pseudomonas aeruginosa	3	1

Table 3. Results after 16 weeks of treatment

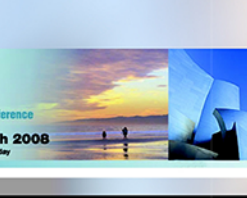
Parameter	nSOS group	Saline group	P-value
No. (%) with significant reduction in bioburden*	38 (76%)	16 (32%)	0.01
No. (%) with eradication of all bacterial strains	45 (90%)	32 (64%)	0.01
Mean growth of granulation tissue (cm^2)	8	2	0.05
No. (%) with wounds healed at conclusion of trial	39 (78%)	20 (40%)	0.05

* Results from cultures on days 7 through 21.

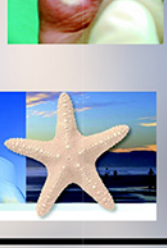
48yrs, Diabetic pt with Neuropathy, Exudating Staph aureus positive wound on Day 1. Treated with sos washing with debridement of the wound, Offloading done

Diabetic Burn injury with scab tissue, Severe diffuse PVD, Daily Dermacyn dressings, Granulation started at 2" week, wound ready for grafting in 4 weeks.

Diabetic Neuropathic Midfoot Ulcer, Collapse medial arch, Daily Super oxidized solution dressings with Offloading, Wound closure with good Epithelization in 12 weeks.



Dermacyn wash and dressings in cavity wound daily for 6 weeks, Curretage of IP joint with debridement, Good granulation tissue formation, wound healed in 6-8 weeks.



DFCon 08 Diabetic Foot Global Conference
Los Angeles 13 - 15 March 2008
Thursday - Saturday
RENAISSANCE HOLLYWOOD HOTEL