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Feature: Super-Oxidized Solution (SOS) Therapy for Infected Diabetic Foot Ulcers

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Abstract: Objective: This study evaluated the efficacy of a novel super-oxidized solution (SOS; Dermacyn® Wound Care, Oculus Innovative Sciences, Petaluma, Calif, USA) compared with a standard treatment (10% povidone iodine solution [PI]) in treating diabetic foot lesions. Research and design methods: This was an open-label, nonrandomized study. Patients had type 1 or 2 diabetes mellitus and grades 2–3 infected foot ulcers according to the University of Texas classification. Patients were alternately assigned to receive treatment with either SOS (n = 110) or PI (n = 108) with daily dressing changes. Samples were taken from the lesions at baseline and during elective surgery carried out after clinical evidence of infection control. Outcome measures included reduction in bacterial load from the lesion, healing time, and incidence of skin reactions. Results: The baseline number of bacterial strains at study entry was similar between the 2 groups. During final elective operative treatment, there were significantly more patients without bacterial strains in the SOS group compared with the PI group (P < 0.001), and patients were more likely to be successfully treated with SOS relative to PI (odds ratio 3.4 [95% confidence interval 1.7–7.0]). Patients in the SOS group had significantly shorter median healing time compared with patients in the PI group (43 days versus 55 days, P < 0.0001). No skin reactions occurred in the SOS group in contrast to 18 patients in the PI group who did experience skin reactions. Conclusions: This study shows SOS is effective and safe in treating infected foot lesions when included within a comprehensive wound care regimen.

Chronic wounds are a great burden to the healthcare system and account for approximately \$20 billion in healthcare costs annually in the United States.¹ Foot ulceration is the precursor to approximately 85% of all diabetic amputations, and it is estimated that 14%–20% of patients with foot ulcers will have to undergo amputation.² Infection of the ulcer increases the risk of amputation.³ If patients with ulcers are initially treated by a multidisciplinary team, major amputations can be prevented in 80%–90% of cases of limb-threatening ischemia and in 95% of patients with infection.^{4–7} This is significant, because amputations are related to high morbidity and mortality, costing up to \$60,000 per patient.^{8,9}

The most widely used therapies for treating foot ulcers are operative procedures and systemic antibiotics, highlighting the importance of infection control.^{10–13} Topical antiseptics are used to reduce the microbial load in both intact skin and in wounds, but their role in the treatment of diabetic foot ulcers has yet to be determined.¹⁴ Antiseptics have been used in preference to topical antibiotics because of concerns about the development of bacterial resistance. However, the cytotoxic effects of these agents on the host's dermal and epidermal cells may affect the wound healing process.¹⁵

Super-oxidized solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and

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wounds. These solutions are electrochemically processed aqueous solutions manufactured from pure water and sodium chloride (NaCl). During the electrolysis process, water molecules are pulled apart, and reactive species of chlorine and oxygen are formed.²⁰ Different super-oxidized solutions have different properties.²¹ Increased acidity or alkalinity and high concentrations (> 100 ppm) of free available chlorine (FAC) correlate with increased corrosiveness and toxicity of a solution. Another problem with these solutions has been stability, which can range from a few hours to several days.

Recently, a neutral pH super-oxidized solution (SOS; Dermacyn® Wound Care, Petaluma, Calif, USA) became available in Europe. According to the manufacturer, this solution has a low FAC (< 80 ppm) and is stable for more than 1 year. This solution has shown broad antimicrobial activity even against antibiotic-resistant strains.^{20,22} It has also been reported that this solution does not induce skin, dermal, or systemic toxicities in animal models.²⁰ Preliminary data in humans also suggest efficacy and safety.^{23,24}

To evaluate the role of this novel solution in infected diabetic foot lesions, the authors compared SOS with 10% povidone iodine solution (PI) as the adjuvant local antimicrobial therapy in a standard treatment program. The program included operative procedures, systemic antibiotic therapy, and offloading techniques.

The main objective was to evaluate the reduction in the number of bacterial species during the course of treatment. Other variables evaluated included the time to lesion healing, the incidence and types of operative outcomes, and adverse events.

Patients and Methods

Study design. This was an open-label, nonrandomized study of consecutively enrolled adult patients with type I or II diabetes mellitus and grades 2–3 infected foot ulcers according to the University of Texas classification.^{25,26} Grade 2 wounds penetrate to tendon or capsule, and grade 3 wounds penetrate to bone or into the joint. Infection was diagnosed using predefined criteria.²⁶ Wounds were considered to be infected if they had purulent discharge, warmth, erythema, lymphadenopathy, edema, or pain, were involved with structures deeper than skin and subcutaneous tissues, or had systemic inflammatory response syndrome. For all wounds, depth was evaluated using a sterile blunt probe.

A working diagnosis of neuropathy and ischemia was made by a combination of clinical and noninvasive studies. For neuropathy, Achilles tendon reflex, vibration perception threshold measured at the malleolus using a biothesiometer (Neurothesiometer SLS, Nottingham, UK), and tactile sensitivity using a 10-g Semmes-Weinstein monofilament in 9 foot areas were recorded.¹² Vascular assessment included measuring the pulse, transcutaneous oximetry, and duplex scanning.¹³

Study solutions. The SOS is a stable, no-rinse, pH-neutral solution with a longer shelf life (> 12 months) than any other similar solution tested thus far. The SOS formula is based on Microcyn® technology and contains sodium hypochlorite (35.7 mg/L), hypochlorous acid (25.2 mg/L), sodium chloride (110.6 mg/L), and 999.8 g/L oxidized water. The general product specifications are pH 6.2–7.8, oxidation-reduction potential (ORP) > 800 mV, and osmolality 13 mOsm/Kg. The antimicrobial spectrum has been reported elsewhere.^{20,22} The control, 10% PI solution (v/v), was purchased from Farmac SPA, Verona, Italy.

Treatment protocol. Patients were assigned alternately in a 1:1 ratio to receive either standard treatment plus daily treatment of the lesion with 10% PI (control group) or standard treatment plus daily treatment of the lesion with SOS (test group).

At enrollment, target lesions were assessed by a probe-to-bone test, plain radiograph, and debridement, which included collection of a sample for microbiological culture. Microbiological samples were obtained during sharp debridement, collecting deep soft tissues and bone, if exposed. Patients presenting with absent posterior tibial and dorsalis pedal pulses, transcutaneous oxygen tension (TCpO) < 50 mmHg, and > 50% stenosis of the vessel

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lumen were referred for endoluminal revascularization, which included percutaneous transluminal angioplasty (PTA) or vascular bypass if PTA was not feasible. Patients with cellulitis, abscess formation, or wet gangrene received operative treatment to maintain the intervention site open in the post-operative period to allow daily antiseptic medications. Patients with plantar lesions were treated with an appropriate weight-bearing relief.

Study treatment consisted of debridement followed by daily dressing changes. Patients in the control group received topical treatment with 10 x 10 sterile gauze soaked with PI, and patients in the test group were treated with sterile gauze soaked in SOS. No secondary dressing was used in both groups. After clinical improvement of infection, the target lesion was operatively closed, and a second sample was collected during the operation for microbiological culture. Osteomyelitis was treated during elective operative treatment. Any skin reactions, such as rash or itching, were recorded for all patients.

All patients received antibiotic treatment (oral or parenteral) according to the severity of their infections. Antibiotic treatment, according to international guidelines on the treatment of diabetic foot infections, included the use of a protected penicillin (amoxicillin plus clavulanic acid or piperacillin plus tazobactam) or a fluoroquinolone plus clindamycin. Methicillin-resistant *Staphylococcus aureus* (MRSA) was treated with glycopeptides (vancomycin-teicoplanin). There were no fixed doses of antibiotics for patients, and dosing was decided according to the severity of the infection, the strain(s) of bacteria present, and renal function, which was ascertained using patients' creatinine levels. Antibiotic treatment started before the microbiological results were available, and broad-spectrum antibiotics, such as clindamycin plus floxacillin, were given. Antibiotic treatment was later adjusted after data regarding the bacterial cultures isolated were obtained and was continued for 3 to 4 weeks.

Type of surgery. For the purpose of this study, the type of elective surgery was classified according to 1 of the following 3 groups: conservative, minor amputations, or major amputations. Conservative operation included dressing, debridement, skin graft, ulcerectomy, ulcerectomy with exostectomy, and panmetatarsal head resection. Minor amputation included single and multiple toe amputation, single and multiple ray amputation, transmetatarsal amputation (TMA), Lisfranc and Chopart amputation (midfoot), and partial calcanectomy. Major amputations were those conducted below the knee (BKA) and above the knee (AKA).

Outcome variables. The outcome variables were reduction in bacterial load from the lesion at operative closure, the type of operation required, healing time (days), frequency of wound dehiscence after eradication of infection, and the incidence of skin reactions. Bacterial reduction was assessed by measuring the number of strains quantified at enrollment and at the time of operative closure of the lesion.

Statistical analysis. All analyses were done using Stata Version 8.2 (Stata Corporation, College Station, Tex, USA).

To analyze the effect of treatment on bacterial strains at operation, the microbial load at operative procedure was dichotomized into a successful or unsuccessful outcome, where zero bacterial strains was considered successful, and any non-zero number of bacterial strains was considered unsuccessful.

The number of bacterial strains at baseline was compared using Fisher's exact test. In the baseline analyses, the numbers of bacterial strains were not dichotomized and were considered separately.

The difference between the 2 treatment groups in the proportion of successful microbiological outcomes was tested for statistical significance using Fisher's exact test. In addition, the odds ratio (OR) of a successful outcome was calculated by logistic regression.

Healing times were evaluated with a 1-way analysis of variance (1-way ANOVA). Since the data violated the important assumption of normality that underlies the ANOVA, healing time data were transformed using a log transformation. Data were analyzed for response differences between groups (1-way ANOVA) on the log scale, and results were transformed back to the original

metric for reporting.

Results

Patients. A total of 218 patients were enrolled and treated at a single center with 110 patients enrolled into the test arm (SOS) and 108 patients enrolled into the control arm (PI). The mean age of the patients was 69.6 years, and 33.5% were women (Table 1). The mean duration of diabetes was 17.4 years. Demographic characteristics were well balanced between the 2 groups. More than half of the patients in both treatment groups suffered peripheral vascular disease (PVD, [55.5% for the test group and 52.8% for the control group]), and more than 80% had neuropathy. Approximately half of the patients underwent PTA (44.5% for the test group and 43.5% for the control group).

Bacteria present before treatment and at operation. The median number of bacterial strains at enrollment was the same in the 2 treatment groups (2 for both groups, Table 2). However, more patients in the SOS group had only 1 bacterial strain (39 patients in the test group versus 27 patients in the PI group). The differences between the groups were not statistically significant ($P = 0.109$, Fisher's exact test).

At the time of elective operation, there were more patients without bacterial strains in the SOS group compared with the PI group (Table 2). The differences between the treatment groups in the proportion of microbiological success with SOS were highly significant ($P < 0.001$, Fisher's exact test). Consistent with this, the odds ratio for a successful outcome was 3.4 (95% confidence interval [CI] 1.7–7.0) for patients treated with SOS relative to PI.

Figure 1 shows the bacterial strains isolated from the ulcers of patients in both treatment groups at entry (Figure 1A) and at operative closure (Figure 1B). The total number of positive cultures for *S aureus*, MRSA, *P aeruginosa*, *Streptococcus sp*, and other bacteria were similar at entry for both treatment groups. However, for the samples taken at operation, there were fewer cultures for all types of bacteria in the ulcers treated with SOS compared with those treated with PI.

Type of operation. A summary of the type of operation performed in patients in both treatment groups is shown in Table 3. The types of operation were grouped into 3 categories: conservative operation and minor or major amputations (Figure 2). In general, more patients in the SOS group than in the PI group had conservative operative treatment. Whether or not this result was due to the effect of SOS on the wounds cannot be established from this study. Other than that, the groups were well balanced for baseline characteristics of the operation.

Figure 1

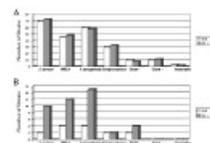


Figure 1. Stenotrophomonas isolated from infected foot ulcers. A, Total number of bacterial strains isolated from the ulcers of patients at entry, compared to SOS (n = 110) and PI (n = 108) groups. B, Total number of bacterial strains isolated from ulcers after at operative closure from SOS (n = 110) and PI (n = 108) groups. Green = SOS and blue = PI. Data are shown as mean and standard deviation.

Table 1

Table 1. Patient demographics

| Feature | Test (SOS) n = 110 | Control (PI) n = 108 |
|------------------------------|--------------------|----------------------|
| Gender | | |
| Male (%) | 66 (60.0) | 59 (54.6) |
| Female (%) | 44 (40.0) | 49 (45.4) |
| Age (years) | 69.6 ± 8.43 | 69.8 ± 7.10 |
| Mean ± SD | 69.6 ± 8.43 | 69.8 ± 7.10 |
| Median | 70 | 70 |
| Range | 45-90 | 50-90 |
| Duration of diabetes (years) | | |
| Mean ± SD | 18.2 ± 13.3 | 16.7 ± 13.8 |
| Median | 10 | 10 |
| Range | 0-70 | 0-70 |
| PTA (%) | 44 (40.0) | 47 (43.5) |
| Mean ± SD | 44 (40.0) | 47 (43.5) |
| Median | 0 | 0 |
| Range | 0-100 | 0-100 |

Abbreviations: PTA, percutaneous transluminal angioplasty; PI, percutaneous transluminal angioplasty; SOS, percutaneous transluminal angioplasty; PI, percutaneous transluminal angioplasty.

Table 2

Table 2. Number of bacterial strains in infected diabetic foot ulcers at entry and at operative closure

| Number of Bacterial Strains | SOS | | PI | |
|-----------------------------|-----|------|-----|------|
| | n | % | n | % |
| At entry | | | | |
| 0 | 28 | 25.5 | 37 | 34.3 |
| 1 | 48 | 43.6 | 35 | 32.4 |
| 2 | 34 | 30.9 | 38 | 35.2 |
| 3 | 7 | 6.3 | 7 | 6.5 |
| 4 | 3 | 2.7 | 3 | 2.8 |
| Total | 120 | 100 | 107 | 100 |
| At operation | | | | |
| 0 | 27 | 24.5 | 24 | 22.3 |
| 1 | 12 | 10.9 | 15 | 13.9 |
| 2 | 1 | 0.9 | 3 | 2.8 |
| Total | 40 | 36.3 | 42 | 39.0 |

Table 3

Table 4

Healing time. The

Figure 2

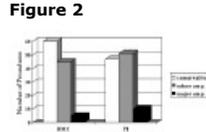


Figure 2. Type of operation conducted in infected foot ulcers. Operative procedures in this study were categorized as conservative, minor amputations, or major amputations and are described in more detail in Table 3.

Figure 3

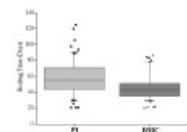


Figure 3. Analysis of wound healing time after operation. Box and whisker plot of healing time for the 2 treatment groups. The box ranges from the 25th to the 75th percentile, the middle of the box shows the median, and the whiskers show the 5th and 95th percentiles. Data values are also shown on the plot. The plot shows the significantly shorter healing time for patients in the SOS group.

by the fact that 11.8% of ulcers in the SOS group had microbiological cultures at operation versus 31.5% of ulcers in the PI group. In addition, 16.7% of the patients using PI had a local skin adverse event versus none in the SOS group. There is evidence that neutral-pH SOSs could also directly accelerate the wound healing process.³³ This potential effect cannot be concluded from the data presented here and requires further investigation.

Approximately 80%–85% of major amputations are preceded by ulcers and deep infections, which suggests that these may play a significant role in the requirement for amputation.² In this study, there was an increase in conservative and minor operations and a decrease in major amputations in the SOS group compared with the PI group (Table 3, Figure 3). Although this study was not designed to have adequate statistical power to show statistical significance, these results could have profound consequences on the quality of life of the patients and on treatment cost.^{1–8} Whether limb preservation in the SOS group could be due to better infection control or to the lack of toxicity of the solution will also need to be addressed in future trials with a larger number of patients.

In addition to the cost of the dressing, the global cost of treatment included hospitalization, revascularization, antibiotic therapy, and operative procedures. The cost of topical treatment (dressing) did not significantly influence this global cost. Based on the treatment protocol and clinical results of this study, an independent cost-effectiveness analysis for SOS versus PI was performed (Bridgehead International, UK). Following the NICE guidelines, it was appropriate to use cost minimization as the basis of choice in wound care. This approach took into account the total cost, including the nurse time required for dressing changes (Technical Appraisal 24). The dressing and other costs were adapted from Derbyshire.³⁴ It was assumed that gauzes were soaked in 20 mL SOS per treatment and that dressings were changed on a daily basis.

Using these assumptions, the cost-effectiveness calculation showed that although using SOS rather than PI increases the daily dressing costs (euro 4.35 versus 2.93), the reduced time to complete healing leads to an overall equality in the mean cost per ulcer healed (euro 187.05 versus 161.15).

In addition, there were other factors in favor of SOS usage that are not quantifiable in cost-saving terms. The patients' quality of life apparently improved as a result of using SOS due to faster healing time, the elimination of the unpleasant odor from necrotic tissue and bacterially colonized wounds, and the elimination of local adverse effects from the antiseptic.

Conclusion

This study shows for the first time in a large population that this SOS is effective and safe for the treatment of infected foot lesions. The use of SOS as an adjunct local antimicrobial treatment produced improved outcomes over PI when used within a comprehensive wound care regimen in the treatment of infected, diabetic foot ulcers.

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