Abstract. Potassium permanganate has been reported to be an effective treatment for certain types of wounds. The aim of the present study was to evaluate the use of potassium permanganate in the treatment of diabetic foot ulcers. A single-blind, randomized, controlled clinical trial was conducted on patients with type 2 diabetes mellitus that presented with a foot ulcer persisting for >3 months. The control group (n=10) was treated with the current standard treatment, which comprises of measures for reducing pressure in the ulcerated area, daily cleansing of the ulcer with potable water and antiseptic wash solution, and the application of a disinfectant solution on the entire surface area of the ulcer; while the intervention group (n=15) received the standard treatment plus 5% topical potassium permanganate solution applied once a day for 21 days. In the intervention group, 1 patient did not tolerate the treatment and was eliminated from the study on the first day. The remaining patients tolerated the interventions well. At the end of the treatment period, ulcers in the control group had decreased by 38% whereas those in the intervention group decreased by 73% (P<0.009). The degree of decrease was also investigated; the ulcer size was ≥50% decreased in 40% of patients in the control group and in 86% of patients in the intervention group (P=0.02). In conclusion, the results of the present study indicate that topical potassium permanganate is well tolerated and significantly accelerates the healing process of diabetic foot ulcers.

Introduction

Type 2 diabetes mellitus (DM2) is a systemic, chronic-degenerative disease with a global prevalence of 9% in adults (1). It has been reported that 22-33% of adults >65 years of age in the United States have DM2 (1,2). Metabolic, vascular and neurologic complications are common in patients with DM2 and it is the most frequent cause of lower limb amputation (3). Approximately 25% of diabetic patients develop foot ulcers, which, if left untreated, may result in amputation (4).

Delayed wound healing in the diabetic foot is due to a number of factors, including elevated blood glucose levels, immune system deficiencies, peripheral arterial disease, peripheral neuropathy, foot deformity and secondary bacterial infection (4). In addition, the microenvironment of lesions in patients with diabetes is abnormal and pathogenic factors result in delayed closure of the ulcer and deficient formation of granulation tissue (5). Specifically, a persistent inflammatory infiltrate associated with bacterial colonization in the lesion may contribute to delay (5).

Despite recent advances in antimicrobial therapy (6,7), diabetic foot lesions continue to be a serious problem. Foot ulcer treatments are lengthy, costly and require intensive care (8,9). Alternative therapies, including topical treatments, have therefore been adopted to treat wounds (6-10). The use of several topical and systemic antibiotic agents has been halted due to the emergence of resistant strains (11). Given the increased prevalence of antibiotic-resistant pathogens, the use of mineral substances with antimicrobial activity, including potassium permanganate, may have potential as alternative treatments (12-15).

Potassium permanganate solution is a strong oxidizing agent that alters the cell walls of pathogenic organisms, interfering with their DNA structure and exerting potent microbicidal

Topical 5% potassium permanganate solution accelerates the healing process in chronic diabetic foot ulcers

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activity on bacteria, fungi, viruses and protozoa (13). It acts as an astringent and has a strongly alkaline pH, producing immediate oxidation (13). In addition, it promotes the formation of granulation tissue and collagen synthesis, which are essential for the healing process (13,15).

Potassium permanganate has previously been used to treat exuding wounds in dermatology and there is evidence that it acts on microbial species, fungi and the human immunodeficiency virus (13,15). Despite its growing popularity in the treatment of exuding lesions and its contributions to their healing, to the best of our knowledge, there are limited studies on the effect of potassium permanganate on diabetic foot ulcers have been performed. The aim of the present study was to determine whether the topical application of 5% potassium permanganate solution could increase the efficacy of the current standard treatment for chronic diabetic foot ulcers.

Patients and methods

Patients. Adult patients with Wagner stage I (uninfected superficial ulcer) or II (deep ulcer, often infected, no bone involvement or abscesses) diabetic foot ulcers were enrolled in the present study (5,11). The study was a simple-blind, randomized, controlled clinical trial conducted from March 2015 to November 2015. All patients had DM2 and presented with a chronic ulcer with a history of progression >3 months. Patients were recruited from an outpatient setting at the Medical Specialties Unit for Chronic Diseases at the Department of Health (Colima, Mexico) for diabetes control. A total of 25 patients (age range, 18-65 years; male-to-female ratio, 1:1.5) were enrolled in the present study. The clinical characteristics of the patients are presented in Table I. All patients signed statements of informed consent, and the present study was approved by the Ethics Committee of the Instituto Estatal de Cancerología (Colima, Mexico).

Groups and treatments. The 25 participating patients were randomly divided into 2 groups: The standard treatment group (control) and the experimental treatment group (intervention). The control group (n=10) received the standard treatment for diabetic foot ulcers administered by the Colima State Health Services at the Department of Health (Colima). The standard treatment comprises measures for reducing pressure on the ulcerated area, daily cleansing of the ulcer with potable water and antiseptic wash solution, and the application of a super-oxidized disinfectant solution (Microdacyn™; TeArai BioFarma, Auckland, New Zealand) on the entire surface area of the ulcer. The patients were assessed every 7 days to evaluate the wound and debride the lesion if necessary. The ulcer area was measured upon admission (day 0) and on days 7, 14 and 21 by placing a piece of transparent acetate over the ulcer and outlining it with a permanent ink marker. The contour of the ulcer was digitalized as previously described (16,17) and the area calculations were made using ImageJ v1.51 software following the manufacturer's instructions (National Institutes of Health, Bethesda, MD, USA). The ulcer area at day 0 was recorded as 100%. The physician who assessed ulcer areas was blinded to the patient group.

Ulcer assessment. The ulcer area was measured upon admission (day 0) and on days 7, 14 and 21 by placing a piece of transparent acetate over the ulcer and outlining it with a permanent ink marker. The contour of the ulcer was digitalized as previously described (16,17) and the area calculations were made using ImageJ v1.51 software following the manufacturer's instructions (National Institutes of Health, Bethesda, MD, USA). The ulcer area at day 0 was recorded as 100%. The physician who assessed ulcer areas was blinded to the patient group.

Statistical analysis. Normal distribution of data was confirmed using the Shapiro-Wilk test. The Student's t-test was used to make comparisons between groups. Categorical values were compared using Fisher's exact test. Relative risk (RR) was calculated to determine the probability of a ≥50% reduction of the ulcer area at day 21 in the intervention group compared with the control. The number-needed-to-treat (NNT) was defined as the number of individuals receiving the experimental treatment necessary to give an additional beneficial effect (a 50% ulcer reduction on day 21) compared with the control group. The 95% confidence interval (CI) was calculated for the RR and NNT. Statistical analysis was performed using SPSS software, version 20 (IBM Corp., Armonk, NY, USA) with the exception of the NNT, which was calculated using MedCalc v17.7.2 software (MedCalc Software bvba, Ostend, Belgium).

Table I. Clinical characteristics of the study subjects.

| Clinical characteristics | Standard (n=10) | Experimental (n=14) | P-value |
|--------------------------|---------------|--------------------|---------|
| Men (%)                  | 50.0          | 35.71              | 0.50    |
| Age (years)              | 58±4.70       | 53.50±2.34         | 0.36    |
| Diabetes duration (years)| 12.81±3.78    | 12.14±3.43         | 0.90    |
| High blood pressure (%)  | 50.0          | 21.40              | 0.10    |
| Hyperlipidemia (%)       | 10.0          | 21.40              | 0.54    |
| Alcoholism (%)           | 10.0          | 21.40              | 0.54    |
| Smoking (%)              | 10.0          | 7.14               | 0.75    |
| Fasting glucose (mg/dl)  | 140.11±19.81  | 161.50±15.40       | 0.40    |
| HbA1c (%)                | 6.65±0.42     | 7.83±1.35          | 0.38    |
| Body mass index (kg/m²)  | 30.61±1.74    | 28.02±1.09         | 0.20    |
| Ulcer area (mm²)         | 5.38±1.24     | 6.20±1.23          | 0.65    |
| Days with ulcer          | 114.00±61.95  | 169.16±58.39       | 0.56    |
| Wagner stage I (%)       | 50.0          | 50.0               | 0.82    |
| Wagner stage II (%)      | 50.0          | 50.0               | 0.82    |
| Local infection (%)      | 20.0          | 64.28              | 0.03    |

HbA1c, glycated hemoglobin. *Of the 15 patients initially included, 1 was withdrawn from the trial due to potassium permanganate intolerance; this patient's clinical data was not included in analysis.
and other in addition to the standard treatment and cleansing regimen, Topical application of 5% potassium permanganate solution, Discussion Progression after day 21 was not analyzed. any control patients during the study period (data not shown). of treatment, whereas complete healing was not observed in 14 patients (29%) in the intervention group following 3 weeks 21 was 2.18 (95% CI, 1.26-8.25; data not shown). The NNT with potassium permanganate to produce the benefit of ≥50% reduced ulcer size at day 0.02; data not shown). The NNT with potassium permanganate solution was applied 3 or 4 times a day to infected and fetid ulcerations in advanced tumors (21). No quantitative data on patient improvement was included, however the authors reported a clinical improvement of the infection and fetidness without the use of local or systemic antibiotics (21). The benefits of potassium permanganate include lower cost, a reduced rate of allergies and a significantly higher healing rate compared with other medications (18-20). However, the 5% concentration of potassium permanganate used in the present study was higher than other reported concentrations (0.01 and 1%) (20-22), which should be considered in future studies or comparisons. The patients in the intervention group had a 3-fold greater probability of a ≥50% ulcer reduction following 3 weeks of treatment compared with patients receiving standard treatment. The standard treatment used in the control group included a disinfectant (a super-oxidized solution with a neutral pH) that has previously been reported to effectively improve granulation and ameliorate ulcer infections in the diabetic foot (22), making it a good reference for evaluating the effectiveness of 5% potassium permanganate solution. Amputations are used to delimit systemic damage caused by gangrene or infection. Complicated diabetic foot ulcers often result in major or minor amputations that greatly impact patient life expectancy and quality of life (20), as well as having serious economic repercussions (9,22). Potassium permanganate is a strong oxidizing agent that may help to eliminate the anaerobic microenvironment necessary for the growth of bacteria, including those of the genus Clostridia and other pathogenic bacteria (20). It has previously been demonstrated that lavages with potassium permanganate solution have a therapeutic effect, even in mixed infections (20). The application of potassium permanganate may therefore be beneficial for fighting infections, possibly reducing their progression in addition to accelerating the healing process of diabetic foot ulcers. The present study included patients with superficial and deep ulcers with no abscesses, classified as Wagner stages I and II. One limitation was that ulcer depth was not assessed. Future studies should include this measurement and also investigate the effect of potassium permanganate solution on severely infected ulcers with concomitant abscesses or gangrene (Wagner stages III or IV).
In the intervention group, 1/15 patients did not tolerate the potassium permanganate treatment, however they experienced no adverse effects once the application was stopped. A high tolerance for topical potassium permanganate treatment has been described in previous studies (18-21). There is no evidence that topical application of potassium permanganate raises plasma potassium levels (20). However, when used at higher concentrations than described in the present study, topical application may cause chemical burns and there have been studies of harmful effects associated with the accidental ingestion of potassium permanganate solution (23,24). Studies on homemade potassium permanganate solutions, prepared by dissolving commercially available tablets or crystals intended for nonmedical use, have indicated that solid fragments of potassium permanganate may come into contact with the skin and cause caustic burns if the tablets or crystals are not completely dissolved (24).

The present study had several limitations, including the small sample size and the fact that ulcer progression was not analyzed beyond day 21. Future studies should include a larger number of patients with a longer follow-up period to further investigate the treatment response of diabetic foot ulcers.

In conclusion, the present study demonstrated that 5% potassium permanganate solution as a complementary treatment for diabetic foot ulcers is well tolerated and viable, effectively accelerating the healing process of diabetic foot ulcers of Wagner stages I and II. These data support the use of Potassium permanganate as a topical alternative to conventional antibiotics and antiseptic agents.

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