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RESEARCH ARTICLE

Microbiological and clinical response of superoxidized solution versus povidone iodine in the management of lower limb ulcers

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ABSTRACT

Background: Lower limb ulcers are debilitating and associated with significant morbidity, loss of productivity and decreased the quality of life. Currently used antiseptics are cytotoxic, damage the granulation tissue and interfere in the wound healing process. Superoxidized solution is nontoxic and contains reactive oxygen species which have bactericidal and wound healing properties. **Aims and Objective:** To compare the microbiological response and clinical efficacy of superoxidized solution versus povidone iodine in the management of lower limb ulcers. **Materials and Methods:** This was a prospective randomized open label study with 68 patients randomized into two groups of 34 each. They were assessed for pain, wound size, periwound erythema, periwound edema, appearance of granulation tissue, re-epithelialization, slough, discharge, and growth on culture on day 1, 5, 9, 12, 18, and 21. Microbiological response and clinical efficacy were assessed at the end of the study. The results were assessed by descriptive methods, ANOVA, unpaired *t*-test, and Chi-square test. **Results:** The mean duration of treatment, ulcer size, pain, periwound edema, erythema, and microbial growth were significantly reduced in the superoxidized solution treated group. Early appearance of granulation tissue and re-epithelialization was noted in superoxidized group. A superior microbiological response, statistically higher cure rate and lower rates of clinical failure were also observed with superoxidized solution compared to povidone iodine. **Conclusion:** Superoxidized solution when compared to povidone iodine was found to significantly accelerate wound healing, reduce the signs of inflammation faster and achieve better microbiological clearance.

KEY WORDS: Lower Limb Ulcers; Superoxidized Solution; Povidone Iodine; Clinical Efficacy; Microbiological Response

INTRODUCTION

Lower limb ulcers are debilitating and often difficult to treat. They cause restricted mobility, loss of productivity, impaired sleep due to pain, social distress, negative body image, and thereby reduce the quality of life. The prevalence of leg ulceration is approximately 1-2%.[1-3] They affect 0.6-3% of those aged over 60 years, increasing to over 5% of those aged over 80 years due to increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes.

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The treatment of limb ulcers presents a therapeutic challenge and requires a multidisciplinary approach. Tissue level factors such as poor blood supply, undue tension in suturing, tissue necrosis, and local infection have a deleterious effect on wound healing.[4] Optimal wound care starts with cleansing, debridement, and off-loading of the lesion.[5] Some commonly used dressing agents are povidone iodine, silver sulfadiazine,

etc. An ideal wound care product in addition to controlling the infection should also protect the normal tissues and not interfere with the normal wound healing.[2]

Broad spectrum antimicrobials like povidone iodine used for initial surgical debridement for polymicrobial infections have cytotoxic effect, thus leading to tissue damage and delayed wound healing due to abnormal inflammatory response and persistent infection.[6] Further, the resultant dry, dark, indurated skin from povidone iodine applications makes it difficult to distinguish whether the delayed wound healing is secondary to infection or chemical damage.[6]

Superoxidized solution, a new concept in wound management is an electrochemically processed aqueous solution with neutral pH, nontoxic, and dermal wound irrigant which is rich in reactive oxygen species and has a longer half-life (>12 months). Superoxide solution is stable, non-flammable and non-corrosive that is ready to use with no further dilution or mixing. It is bactericidal, fungicidal, virucidal, sporicidal and moistens, lubricates, debrides, and reduces the microbial load of lesions. It promotes healing by enhancing local blood supply, accelerating neovascularization, reducing inflammation, improving granulation tissue and epithelialization significantly and producing an environment hostile to opportunistic pathogens, thus reduces morbidity and hospital stay with its early wound healing effect.[2,4,7]

Wounds are a great burden on the health-care system and due to the limitations associated with the use of existing biocidal agents, there is a need to explore newer methods of wound care to help maintain effective microbial control, promote early wound healing, reduce hospital stay, and prevent substantial long-term morbidity.[7]

MATERIALS AND METHODS

This was a prospective randomized study conducted among selected in-patients and out-patients of Surgical Department of M. S. Ramaiah Medical College, Bengaluru, India, from June to July 2015, a tertiary care teaching hospital. Patients were eligible for the study if they had lower limb ulcer with either of the types, *viz.,* traumatic ulcer, diabetic ulcer (Grades 1 and 2)[8] or venous ulcer,[9] aged above 18 years and willing and able to give informed consent. Exclusion criteria of the study were ischemic ulcer, malignant ulcers, decubitus ulcers, trophic ulcers, patients with osteomyelitis, chronic renal failure, autoimmune disorders and those on cytotoxic drugs/corticosteroids, or any immunosuppressive medication. Routine and specific investigations, such as hemogram, blood sugar, renal function tests, swab culture and sensitivity, and X-rays when indicated were taken.

Sample Size Estimation

Based on a previous study in Bhopal by Pandey et al.,[10] it was found that the occurrence of infection in primarily sterile cases was 15% in those treated by dressing with superoxidized solution whereas in a group belonging to povidone iodine it was 36%. To achieve a desired confidence level of 95% with a power of 80%, considering minimum difference between the two proportions as 20%, the minimum sufficient sample size required were 34 in each group.

Randomization

A total of 68 patients were included in the study and randomized into two groups of 34 each in 1:1 ratio by simple randomization.

Drug Administration

One group was treated with a topical superoxidized solution while other received topical povidone iodine. The test medication in each group was applied topically once daily by the attending surgeon on affected lesion. Patients were put on antibiotic coverage according to culture and sensitivity. Insulin and oral antidiabetic agents and antihypertensives were given when indicated for good glycemic and hypertension control during the study period. Assessments were done on day 1, 5, 9, 12, 18, and 21 and the observations were noted in the study pro forma.

Efficacy and Safety Assessments

Efficacy was measured by assessing for change in signs and symptoms of wound characteristics such as pain, size, periwound erythema, periwound edema, appearance of granulation tissue, re-epithelialization, slough, discharge, organism isolated/growth on culture, and procedures done (skin grafting/debridement/no procedure).

Clinical efficacy[5] was evaluated as per clinical outcome criteria as follows:

1. Cure - resolution of all signs and symptoms, including the presence of culturable exudates, warmth, erythema, induration, tenderness, pain, swelling, as well as a healing wound (as determined by the investigator) after >5 days of treatment
2. Improvement - resolution of ≥2 signs as described above after ≥5 days of treatment
3. Failure - persistence or progression of baseline clinical signs and symptoms of infection after ≥3 days of therapy requiring a switch to an antibiotic
4. Indeterminate - circumstances preclude classification.

Pain was assessed using visual analog scale with “0” being no pain and “10” being worst pain.

Patients were classified by microbiologic response[5] as follows:

1. Eradication - elimination of the causative organism (s) from the same site during or upon completion of therapy.
2. Presumed eradication - post therapy culture was not obtained because there was no culturable material, and there is an adequate clinical response.
3. Persistence - failure to eradicate the original causative organism at all post baseline time points from sites previously cultured, regardless of whether signs and symptoms of infection are present.
4. Relapse - reappearance of the original causative organism from the original site of infection after a post baseline culture has been negative.
5. Superinfection - development of a new infection during the study that is due to a new pathogen which was not recognized as the original causative organism.

The safety of study drugs was assessed among all patients by recording adverse drug reactions (ADRs) as reported by them. The details of occurrence, intensity and causal relationship to the study drug along with the findings of physical and clinical examination were considered.

Statistical Analysis

The data collected were tabulated and analyzed using mean and standard deviation. Continuous variables were compared within the group using repeated measures ANOVA and between the groups using unpaired *t*-test. Categorical data were expressed as percentages/proportions, and Chi-square test was done to compare the categorical variables.

RESULTS

Demographic Characteristics

The demographic and baseline clinical characteristics of study patients were similar between the two groups as presented in Table 1.

In both groups, there were 13 (38.23%) traumatic and 20 (58.82%) diabetic ulcers with great toe being the most common site. All the patients in the study population had single ulcer. There was 1 (2.94%) venous ulcer in each of the groups. 25 of the diabetic ulcers were Grade 1 (12 vs. 13) while 15 of them were Grade 2 ulcers (8 vs. 7). 20 (58.8%) and 16 (47%) ulcers, respectively, in the superoxidized solution and povidone iodine groups were acute in nature whereas 11 (32.3%) and 15 (44.1%) ulcers were chronic in nature. Antibiotics were given based on culture sensitivity and local hospital policy guidelines.

Efficacy Assessment

Ulcer characteristics

The mean duration of treatment (16.15 ± 3.9 days, $P < 0.0001$) was significantly reduced in the superoxidized solution treated group compared to the povidone iodine treated group (20.65 ± 0.98 days).

The size of the ulcer at baseline was 20 ± 6.2 cm^2 and 21 ± 5.4 cm^2 ($P = 0.25$) in superoxidized solution and povidone iodine groups, respectively. Both the treatments effectively reduced the ulcer size at each of the follow-up visits ($P < 0.0001$) as presented in Figure 1.

There was a higher percentage decrease in wound size in the superoxidized solution treated group compared to the povidone iodine treated group at each assessment. The reduction on day 5 (30% vs. 14%) ($P < 0.0001$) and day 9 (49% vs. 28%) ($P = 0.02$) was significantly more in the patients treated with superoxidized solution compared to patients treated with povidone iodine. Overall reduction at the end of the study was about 94% in the superoxidized solution group as against 81% in the povidone iodine group.

Out of 34 cases, growth on culture was positive for 23 (67.6%) cases in the superoxidized solution group and 25 (73.5%) cases in the povidone iodine group. *Staphylococcus aureus* was the most common organism isolated on culture (Table 2).

There was also a significant reduction in growth on culture in the superoxidized solution group on day 9 ([12/23] 52% vs. [6/25] 24%, $\chi^2 = 4.06$, df = 1, $P = 0.04$) and day 12 ([19/23] 82.6% vs. [13/25] 52%, $\chi^2 = 5.65$, df = 1, $P = 0.025$) compared to povidone iodine as shown in Figure 2.

Pain relief was seen in 16 (47%) patients treated with superoxidized solution on day 5 as compared to 10 (29.4%) of those treated with povidone iodine which was statistically significant ($\chi^2 = 3.89$, df = 1, $P = 0.049$) as shown in Figure 3.

Patients treated with superoxidized solution group had significant reduction in periwound erythema and edema on

Table 1: Epidemiologic profile of the study population

Parameters	Superoxidized solution group (*n*=34)	Povidone iodine group (*n*=34)
Age (mean±SD)	56.4±18.6 years	52.6±18.1 years (*P*=0.3666)
Gender: Male/female	25/9	25/9 (*P*=0.3905)
Comorbidities DM DM±HTN	138	10 (*P*=0.0931) 11 (*P*=0.0985)

SD: Standard deviation, DM: Diabetes mellitus, HTN: Hypertension

Table 2: Commonly isolated organisms

Organism isolated	Superoxidized solution *n*=23	Povidone iodine *n*=25
Staphylococcus aureus	10	12
Citrobacter freundii	6	7
Pseudomonas aeruginosa	5	5
Proteus mirabilis	2	1

day 5 (17 vs. 6, 50% vs. 17.6%, $\chi^2 = 9.68$, df = 1, $P = 0.002$) and day 9 (31 vs. 24, 91% vs. 70.5%, $\chi^2 = 4.66$, df = 1, $P = 0.031$) as compared to povidone iodine.

14 patients in the superoxidized solution group and 16 in the povidone iodine group had slough and wound discharge on day 1. Both agents reduced slough and wound discharge by day 9. But on day 5, while 25 (73.5%) ulcers in the superoxidized solution treated group showed appearance of granulation tissue, only 12 (35.2%) in the povidone iodine treated group did ($\chi^2 = 7.27$, df = 1, $P = 0.007$). Also on day 9, 34 (100%, $\chi^2 = 7.8$, df = 1, $P = 0.005$) of superoxidized solution treated ulcers and 27 (79.4%) of povidone iodine treated ulcers showed appearance of granulation tissue shown in Figure 4.

Re-epithelialization was also significantly higher in favor of superoxidized solution on day 9 (24 vs. 14, 70.5% vs. 41%, $\chi^2 = 5.96$, df = 1, $P = 0.015$) and day 12 (32 vs. 22, 94% vs. 64.7%, $\chi^2 = 8.99$, df = 1, $P = 0.003$) as shown in Figure 5. A total of 7 patients in the superoxidized solution treated group and 11 patients in the povidone iodine treated group required split skin grafting during the study.

Clinical Efficacy and Microbiological Response

While complete eradication of the causative organism was seen in 33 (97%) ulcers treated with superoxidized solution, only 29 (85%) ulcers treated with povidone iodine showed complete eradication. About 26 (76.5%) patients treated with superoxidized solution were cured which was significantly higher than 18 (52.9%) patients cured in the povidone iodine group ($\chi^2 = 4.12$, df = 1, $P = 0.042$). A failure rate of 2.9% (1 patient) was noted in the superoxidized solution group as against 14.7% (5 patients) in the povidone iodine group as shown in Figure 6.

Evaluation of Safety

Both study treatments were well tolerated, and no ADRs were noted in either of the study groups.

DISCUSSION

Lower limb ulcers are debilitating and associated with significant morbidity, loss of productivity, reduced quality of life, and high cost of health care. Most of the antiseptics currently used in wound care are cytotoxic, may cause damage to the granulation tissue, interfere in the wound healing process and are far from ideal wound care products.[6] Superoxidized solution, an electrochemically processed aqueous solution with neutral pH, is a new concept in wound management. It

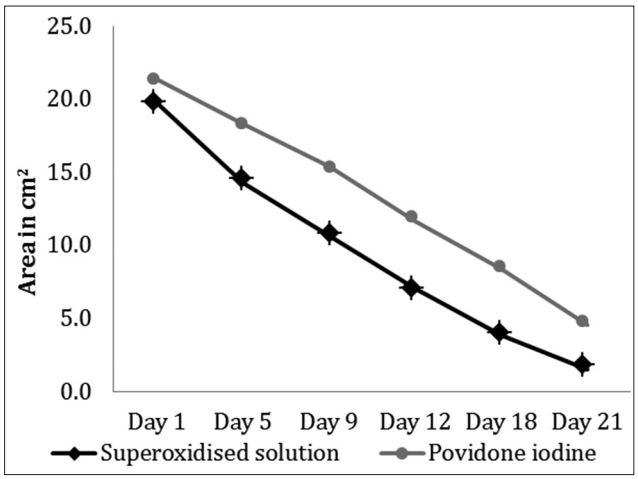

Figure 1: Reduction in the size of the ulcer in both groups

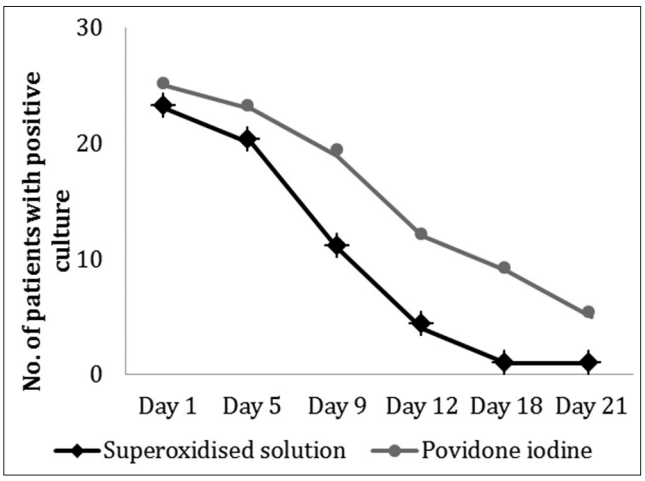

Figure 2: Growth on culture in both groups

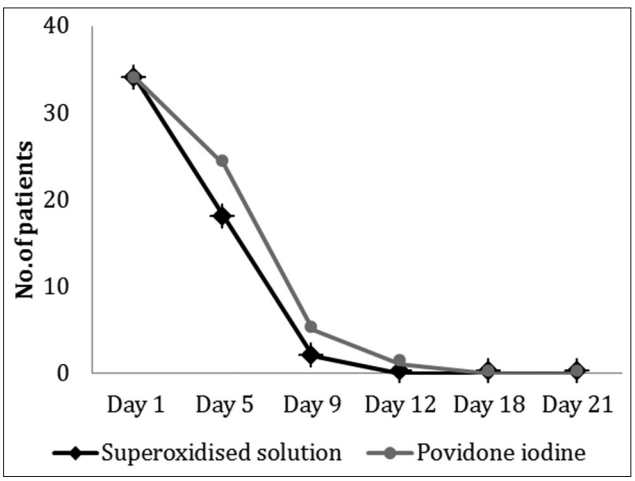

Figure 3: Reduction in pain in both groups

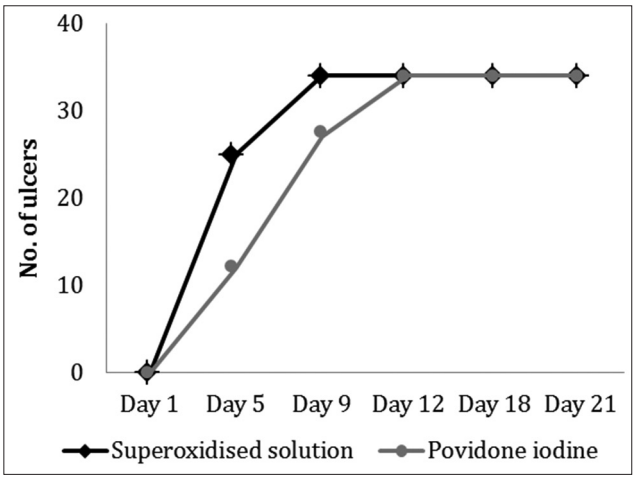

Figure 4: Appearance of granulation tissue in both groups

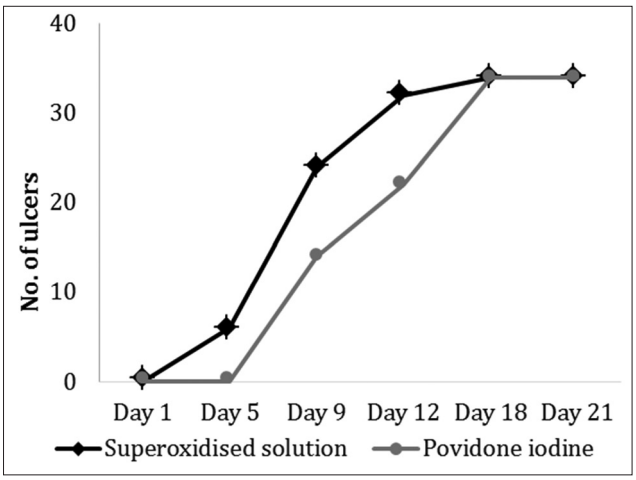

Figure 5: Re-epithelialization in both groups

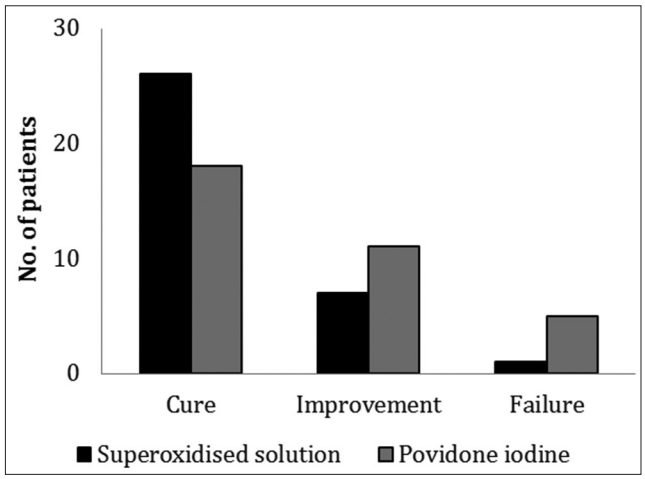

Figure 6: Clinical efficacy in superoxidized solution group versus povidone iodine group

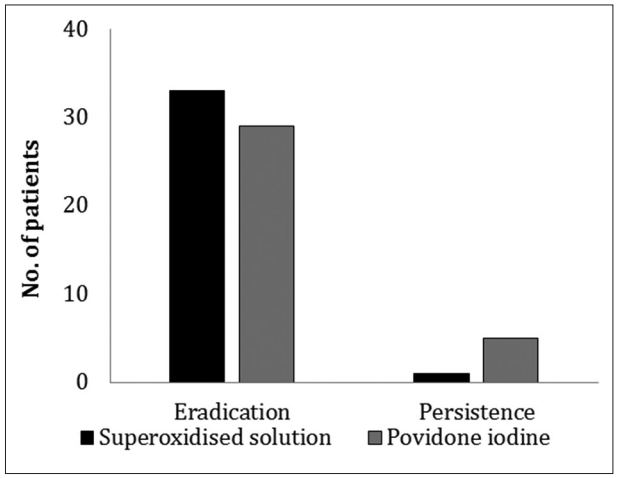

Figure 7: Microbiological response in superoxidized solution group versus povidone iodine group

is nontoxic and contains reactive oxygen species which have both bactericidal and wound healing properties.[2]

Majority of the study population were aged between 50 and 60 years, and male preponderance was noted. Diabetes was noted as the main comorbidity associated with leg ulcers. The prevalence of leg ulceration is known to be higher in elderly, and diabetes has been identified as one of the major risk factors.[11] This is similar to the observations by Satishkumar et al., but Pandey et al. from Bhopal noted younger subjects in their study. The gender distribution was similar to other studies reported from India.[2,10]

In the Western world, venous insufficiency constitutes to majority of leg ulcers, but in India, systemic conditions such as diabetes, tuberculosis, atherosclerosis, and leprosy are the main risk factors[3] The comorbid factors apart from being the cause, also adversely affect the prognosis and outcome of treatment. In this study, majority of the ulcers were diabetic. Observational studies suggest that 6-43% patients of diabetes and a foot ulcer eventually progress to amputation.[12,13] Ramsey et al. reported amputation rates of 11.2% and Nanjappa et al. noted 44.17%.[14,15]

Superoxidized solution, an effective non-toxic antiseptic agent, promotes rapid healing without damaging normal host tissues.[6] The mean duration of treatment in patients treated with superoxidized solution was significantly less than the patients treated with povidone iodine. This was consistent with the findings of Paola et al. where the median healing time for infected diabetic foot ulcers was 43 days versus 55 days in superoxidized solution and povidone iodine groups, respectively.[16] This was further confirmed by studies by Kapur and Marwaha[4] and Satishkumar et al.[2]

Overall reduction of ulcer size was about 94% in the superoxidized solution group as against 81% in the povidone iodine group. These results were similar to the observations by Kapur and Marwaha where reduction in wound size was about 70%,[4] but Satishkumar et al. noted reduction of 56%.[2] Although the percentages vary in these studies, the general trend is consistent. Superoxidized solution produces faster wound healing when compared to povidone iodine.

Majority of the patients in both groups had growth on culture at baseline, but superoxidized solution significantly reduced the growth on culture compared to povidone iodine group by day 9. This was similar to the observations by Kapur and Marwaha, Pandey et al. and Landsman et al.[4,5,10] This early reduction in microbial growth may have promoted better and rapid wound healing. In addition, superoxidized solution reduced inflammation quickly resulting in early and significant pain relief compared to povidone iodine.

Pain relief was significantly better in superoxidized solution group which could be due to a faster reduction of inflammatory changes and better wound healing.

The inflammatory phase of healing starts at the moment of injury and is followed by the proliferative or granulating phase. An ideal antiseptic is one that is rapidly lethal to all forms of bacteria and spores, capable of prolonged bactericidal activity and has no injurious effect on wound healing tissues.[4] Povidone iodine is said to cause significant cell damage and interfere with the wound healing process while superoxidized solution has shown antimicrobial efficacy without inducing toxicity.[16] Hence, superoxidized solution showed a significant reduction in periwound erythema and edema and a significantly higher number of ulcers showed appearance of granulation tissue and re-epithelialization. A significant decrease in common signs of inflammation such as edema and erythema as well as increase in signs of healing such as granulation and fibrin formation with superoxidized solution were also demonstrated by Kapur and Marwaha[4] Satishkumar et al. observed granulation tissue in 69% of the patients by day 5 and re-epithelialization in 65% of the patients by day 12.[2] A study conducted by Martınez-De Jesus et al., it was also seen that an increased percentage of patients (90.4% vs. 62.5%) advanced to the next wound healing stage, the granulating phase in superoxidized solution group.[6]

The patients were also evaluated for microbiological response and clinical efficacy. While complete eradication of the causative organism was seen in 97% of the ulcers treated with superoxidized solution, only 85% of the ulcers treated with povidone iodine showed complete eradication. About 76.5% of the patients showed clinical cure in the superoxidized solution group whereas in the povidone iodine group about 52.9% showed cure. A failure rate of 2.9% was noted in the superoxidized solution group as against 14.7% in the povidone iodine group. Paola et al. reported that the microbiological success was significantly higher in the superoxidized solution treated group compared to the povidone iodine treated group.[16] Similar results were obtained in an open label study conducted by Landsman et al. where a higher rate of clinical success (93.3%) was obtained in patients treated with superoxidized solution.[5]

Hence, superoxidized solution represents a novel alternative to currently available antiseptics which is nontoxic and has effective antimicrobial properties.[16] This study showed that superoxidized solution produces a significant and early reduction in wound size, microbial growth, pain, periwound edema and erythema, significant and early appearance of granulation tissue and re-epithelialization and a significant reduction in the mean duration of treatment compared to povidone iodine. Thus, superoxidized solution is a safe, efficacious, and potential agent for management of lower limb ulcers.

CONCLUSION

Superoxidized solution, when compared to povidone iodine, was found to significantly reduce the signs of inflammation, achieve better microbiological clearance and accelerate wound healing, eventually resulting in better patient satisfaction and lower cost.

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