J Wound Ostomy Continence Nurs. 2018;00(0):1-6.
Published by Lippincott Williams & Wilkins

Polyhexanide Versus Metronidazole for Odor Management in Malignant (Fungating) Wounds

A Double-Blinded, Randomized, Clinical Trial

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ABSTRACT

PURPOSE: The aim of this study was to compare the effects of 0.2% polyhexamethylene biguanide (PHMB) to 0.8% metronidazole on malignant wound (MW) odor, health-related quality of life (HRQOL), and pain upon application.

DESIGN: A double-blinded, randomized, clinical trial.

SUBJECTS AND SETTING: Twenty-four patients with malodorous MWs hospitalized in a referral cancer center in Sao Paulo, Brazil, participated in the trial.

METHODS: Participants were randomly allocated to treatment with 0.8% metronidazole solution (control group) or 0.2% PHMB (experimental group). Study outcomes were measured at baseline (day 0), 4 days, and 8 days. The primary end point was the odor that was measured in terms of its intensity, quality, and impact on participants during the study period. Health-related quality of life was measured with the Ferrans and Powers Quality of Life Index–Wounds Version (FPQLI-WV) on day 0 and on the day when odor was completely eliminated as per evaluation by the investigators. Pain intensity related to application of the control and experimental solutions was measured as a secondary outcome using a scale of 0 to 10.

RESULTS: Twenty patients (83.3%) were classified as having "no wound odor" at 4 days, and 100% achieved no wound odor by day 8 ($P < .001$). Odor control in patients with MW significantly influenced their general HRQOL ($P = .002$). We found no difference in odor elimination, or HRQOL, when patients managed with PHMB were compared to those managed with metronidazole. There were no statistically significant differences over time in pain measurement between the 2 groups.

CONCLUSIONS: Both PHMB and metronidazole significantly reduced odor in malodorous MWs within 4 days. Neither solution was found to be more effective than the other in the magnitude of odor reduction or its effect on condition-specific HRQOL.

KEY WORDS: Fungating wounds, Local anti-infective agents, Metronidazole, Polymeric polyhexanide biguanide, Skin neoplasms, Wounds and injuries.

INTRODUCTION

Malignant wounds (MWs), sometimes referred to as fungating, ulcerating cancerous, or malignant cutaneous wounds, occur when a malignancy infiltrates the skin and surrounding blood and lymphatic vessels via direct invasion from a primary lesion or via metastasis from a distant primary tumor. Metastatic MWs are most commonly associated with cancer of the breast and head and neck. Malignant wounds are caused by rapid proliferative growth and hypergranulation producing an unmistakable fungoid, cauliflower-like appearance. While the exact prevalence remains elusive, the estimated incidence ranges between 0.6% and 9.0%; they usually occur in patients with advanced stages of cancer receiving palliative or end-of-life care.[1] Bleeding, foul odor, pain, profuse exudate, and local infection are frequent and distressing aspects of MWs.[2-5] In a survey study of 269 nurses exploring difficulties associated with the care of MWs,[6] 48% identified management of odor as a challenge, followed by pain control (46%), containment of exudate (30%), bleeding (27%), and problems with the periwound skin (27%). Care of patients with MW focuses on comprehensive symptom management to promote health-related quality of life (HRQOL) rather than comfort; wound healing is often unattainable.

Although the exact mechanisms are unknown, various factors responsible for the abnormal blood supply in MWs include (1) direct mechanical compression of blood vessels by the tumor, (2) inflammatory response damaging endothelial cells and autoregulation of vasodilation, and (3) increased blood viscosity associated with cancer resulting in thrombosis of local capillaries. In addition, tumor growth and increased metabolic demand may outstrip the blood supply, leading to tissue necrosis.[7,8] These necrotic areas enable rapid proliferation of aerobic and anaerobic bacteria, creating a pungent, foul, and nauseating odor.[9-11] Approximately 70% of MWs associated with malodor harbor at least one obligate anaerobic

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The authors have no funding or conflicts of interest to disclose.

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DOI: 10.1097/WON.0000000000000460

species, such as *Clostridium*, that do not require oxygen for their metabolism and growth. Volatile metabolic end products of anaerobic bacteria such as dimethyl trisulfide create the distressing malodors often associated with these wounds.[12] In a previous study of patients with breast cancer, the risk of wound odor increases with more than 10^5/g of bacterial counts and/or with 1 or more anaerobic bacteria in the MWs.[13]

An international survey of 4 countries and 1444 health professionals from 36 countries found that health care providers and patients ranked odor management as one of the most challenging aspects in the care of patients with MW (83% and 85%, respectively).[14] To explore the lived experience of living with MWs, Alexander[15] reported findings from a phenomenological study of patients with malodorous MWs, along with their caregivers and nurses. Patients repeatedly described the "bad smell" in wounds as a primary source of their misery. Although participants also described intense pain, the need to address pain was "overshadowed" by the distress and suffering associated with malodor from MWs. Professional caregivers openly acknowledged their personal reactions that involved the feelings of revulsion and disgust. One of the nurses described the odor as a long-lasting foul smell that stayed on the skin and clung to clothing like cigarette smoke.[15] Despite the magnitude of psychosocial distress associated with MW malodor, Santos and colleagues[16] reviewed the literature and concluded that little evidence is available to validate the effectiveness of various topical antimicrobials for odor control.

Assuming that odor stems from increased bacteria bioburden, topical antimicrobial agents have been recommended as first-line interventions to alleviate malodor; metronidazole is the most commonly prescribed agent.[1,17] Adderley and Holt[18] conducted a systematic review of topical metronidazole for MW malodor. They identified an early study of 11 patients with malignant fungating wounds randomly allocated to receive either 0.8% metronidazole gel or placebo gel daily for 6 days.[19] Participants randomized to the metronidazole group reported a reduction in odor from 7.8/10 (SD = 0.8) on a visual analog scale on day 0 (D0) to 5.0 on day 6 (SD = 2.1). Unfortunately, the study lacked sufficient power to achieve statistically significant differences over time. In a prospective, randomized, experimental study, Lian and colleagues[20] compared metronidazole powder (400 mg in 50 cm^2) to a topical green tea compress in 30 cancer patients with malodorous fungating wounds over a period of 7 days. All participants experienced improvement in odor control by day 7, but differences between the 2 groups were not statistically significant.[20] Watanabe and colleagues[21] reported findings from a multicenter clinical trial of 21 breast cancer patients treated with a 0.75% metronidazole gel. The metronidazole gel treatment successfully achieved deodorization in 20 of 21 or 95.25% of the participants within 14 days. More recently, George and colleagues[22] published a 10-year retrospective study of topical, oral, and maintenance metronidazole for management of MW odor. Since metronidazole has become part of their routine practice for MW care, the proportion of patients with odor problem has reduced from 12.5% to 1.5% visits per patient over a 10-year period. Despite these encouraging results, emerging resistance to metronidazole has raised various diagnostic and therapeutic dilemmas. Rotimi and colleagues[23] demonstrated that *Bacteroides*, an anaerobic gram-negative bacterial species, can acquire resistance to metronidazole after a single dose even in the absence of prior therapy or exposure.

Topical antiseptics such as quaternary ammonium compounds, biguanide compounds, and triclosan have also been used for management of MW malodor.[24-28] Polyhexamethyl biguanide (PHMB), also known as polyhexanide and polyaminopropyl biguanide, is a common antiseptic agent used in contact lens cleaning solutions, mouthwash, skin disinfectant solutions, and wound dressings. It has a board antimicrobial activity against gram-negative and gram-positive fungi, spores, yeasts, and viruses.[24] The risk of cytotoxicity and bacterial resistance in relation to PHMB use is relatively low. It is approved for topical use on skin, wounds, and mucous membranes but may not be appropriate when cartilage is exposed.[25] There is evidence that PHMB may increase the rate of healing and reduction in colonization/infection in traumatic wounds, venous leg ulcers, and burns when compared with iodine and silver.[26,27] To and colleagues[28] reviewed evidence pertaining to topical PHMB and its effectiveness for the treatment of chronic wounds. Six studies met inclusion criteria including 4 studies with wound healing as their primary outcomes. Two evaluated changes in wound surface area and 2 evaluated wound bed evolution. In 5 studies, participants randomly assigned to PHMB topical agents showed significant improvement in bacterial control compared to control groups. Five studies reported pain reduction from the use of PHMB agents. While PHMB may appear to be an effective antimicrobial agent, the specific advantage of topical PHMB for odor management has not been explored. This study aimed to compare the effectiveness of metronidazole and PHMB in controlling MW malodor.

METHODS

This double-blinded, randomized study was conducted in a 450-bed AC Camargo Cancer Center in Sao Paolo, Brazil, from July 2013 to July 2015. All participants were older than 18 years; inpatients at the cancer center, diagnosed with MWs (regardless of location, etiology, and tumor staging, as well as whether in treatment or in palliative care), and able to provide consent. Patients receiving systemic antimicrobial therapy and those with concerns about bleeding in wounds were excluded. Study procedures were reviewed and approved by the Ethics Committee of the Fundação Antonio Prudente (CAAE: 04127512.9.0000.5392). The study was registered at ClinicalTrial.gov (NCT02394821). Funding was provided by the Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP (2013/01179-4). All participants or their legal representative provided written consent for study participation.

Sample Size

The sample size was estimated based on expected changes in mean odor score as the primary outcome indicator. Independent-samples *t* tests were used to compare the difference of means between the 2 groups. Effect size *d* was estimated to be 1.7 based on study results from a previous randomized controlled trial by Bower and colleagues,[19] who reported mean odor reduction from 7.8 (SD = 0.8) at baseline to 5 (SD = 2.1) at the end of the study. Considering $\alpha = .05$, power = 0.9, effect size = 1.7, 2-tailed test, and 20% attrition, the sample size was estimated to be 24 participants (12 in each group) using G-power.

Study Measures and Instruments

The main outcomes of this study were changes in odor intensity, quality, and its impact on HRQOL. Wound pain during dressing changes was measured as a secondary outcome.

After careful review of the literature, we were not able to find any validated instrument that met the needs of our study. We therefore developed an instrument to evaluate odor intensity, odor quality, and its impact on individuals. The instrument was not subjected to psychometric evaluation of its validity and reliability. The instrument was pretested, and revisions were made based on feedback of participants. During the study, nursing staff were asked to indicate the initial moment when odor was perceived. The choices were as follows: no odor (0); odor detected only after removing the bandage (1); odor perceived when approaching the patient (2); odor noted upon entering the room (3); and odor detected before entering the room (4). The quality of the odor was classified as follows: no odor (0); odor perceived but not offensive (1); odor perceived and a little offensive (2); odor perceived and moderately offensive (3); and odor perceived and extremely offensive (4).

Participants indicated the impact of odor by selecting 1 or more of the following 5 reactions/experiences: (1) aware of the odor; (2) worried that others will be aware of the odor; (3) reluctant to socialize because of the odor; (4) odor negatively affects appetite; and (5) nauseated by the smell. The odor impact was then scored according to the number of reactions selected by the patient: a score of 0 when all listed descriptions were selected; 1 indicating when 4 descriptions selected; 2 for 3 selected descriptions; 3 for 2 selected descriptions; 4 for 1 selected description; and 5 when none of the descriptions were selected.

Pain was measured based on the frequency of discomfort experiences and intensity. Participants were asked to indicate if pain or discomfort was experienced during wound dressing change including removal of the dressing, exposure of the wound to air, cleaning, disposal of dressing, and reapplication of dressings. Frequency was scored according to the number of situations that was selected by the participant, from 0 representing discomfort that was experienced in all situations to score of 1 representing discomfort that was experienced in only one situation. Participants were also asked to rate the intensity of the pain before and after application of the solution on a scale from 0 (no pain) to 10 (the most severe pain).

Health-related quality of life was measured by the Ferrans and Powers Quality of Life Index–Wounds Version (FPQLI-WV).[29] This instrument was designed to measure condition-specific HRQOL in people with skin lesions of any etiology. The total score of the instrument varies from 0 to 30, corresponding to worst and best HRQOL, respectively. A cumulative score was calculated. In addition, subscales scores are calculated for Health and Functioning (HF), Socioeconomic (S), Psychological and Spiritual (PS), and Family (Fa) subscales. The HF subscale included items that queried wound pain, time to wound healing, drainage/odor from the wound, and self-care ability. Items on the S subscale queried emotional support received from friends and people other than family, neighborhood, education, and financial needs. The PS subscale comprised items querying faith in God, peace of mind, happiness in general, personal appearance, and self-esteem. The fifth subscale, Fa subscale, consisted of items querying family health and perceived emotional support from the individual's spouse, lover, or partner.

Wound Assessment

Malignant wounds were classified into 4 categories; category 1 indicated intact skin, whereas category 1N indicated superficial wound or intact skin with a punctate opening that allows drainage of exudate. Category 2 was assigned to an open wound involving the dermis and epidermis, with superficial ulcerations. Category 3 described a full-thickness wound involving the dermis, epidermis, and subcutaneous tissue, with considerable depth. Category 4 indicated a wound that invaded into deep anatomical structures; the exact depth and area were difficult to describe due to extensive tunneling and undermining.[4]

Intervention

A metronidazole 0.8% topical solution was compounded by the hospital pharmacy and its effectiveness was compared to a PHMB 0.1% solution (Prontosan, B. Braun, São Gonçalo, RJ, Brazil) that was available commercially. Both solutions were dispensed in identical containers from pharmacy to ensure patients, nurses, and the research team were blinded to treatment that was randomly assigned to the participants.

Study Procedures

Patients with MW who were admitted to inpatient units were initially approached by the nursing staff on the unit. Those who agreed to hear more about the study were contacted by the principal investigator (D.L.V-C.) to determine study eligibility. Those who met inclusion and exclusion criteria were invited to sign the informed consent form and were then randomly allocated to one of the groups by a computerized program.

Blinding to intervention was achieved by using identical bottles for 2: the treatment and control solutions to conceal group allocation. Only the principal investigator was aware of which topical therapy was used for each participant. At every change of wound dressing, 3 professionals were present to collect data: (1) one member from the research team was responsible for collecting the data and filling the survey, (2) unit nurse, and (3) another physician or nurse (not in charge of daily patient attendance or care). Wound dressings were changed at least twice daily by the unit nurse and at baseline (D0), day 4 (D4), and day 8 (D8). The 3 evaluators assessed the variables on the first dressing change of the day. During each dressing change, a staff nurse removed the old dressing, cleansed the wound by irrigation with saline, followed by irrigation with 300 mL of either PHMB or metronidazole solution (according to the experimental group). The staff nurse then applied a thin layer of gauze over the wound that was moistened with the same (antiseptic) solution, keeping it on the bed. A calcium alginate or surgical compress was applied as a secondary dressing. The solution for odor management was considered effective when it was classified as "no odor" by the 3 evaluators on the odor intensity and odor quality scales. The FPQLI-WV was applied on D0 and on the day when the participant's was classified as "no odor" by the 3 evaluators.

Data Analysis

Demographic information of the participants was summarized using descriptive statistics. Data were analyzed using Friedman's analysis of variance test to evaluate changes in odor and pain over time between the 2 treatment groups. The Mann-Whitney test was used to compare HRQOL scores between groups. Data were analyzed using the Statistical Package for Social Sciences software package (SPSS, Chicago, Illinois).

RESULTS

One hundred thirty-one patients with MW were approached; 29 agreed to study participation, and 24 completed the study (Figure). Three discontinued due to bleeding from the wound, and 5 transferred from the unit and were lost to follow-up.

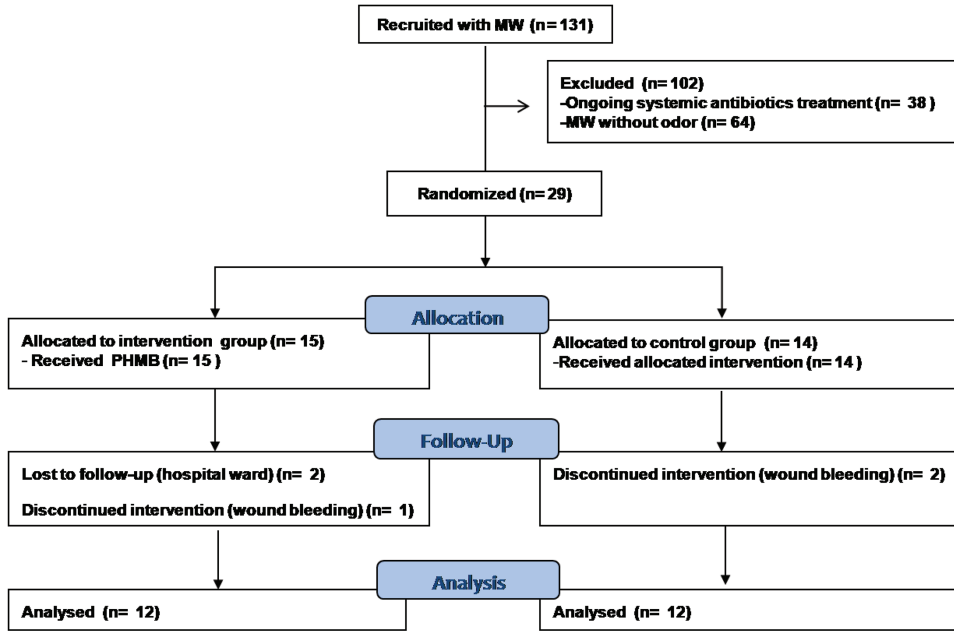

Figure. Study design according to CONSORT diagram. MW, malignant wound; PHMB, polyhexamethylene biguanide.

Table 1 summarizes demographic and pertinent clinical characteristics of participants; analysis revealed no statistically significant differences in demographic or pertinent clinical characteristics based on group allocation.

The MWs were predominantly located on the lower limbs (n = 12; 50.0%), followed by the head and neck (n = 6; 25.0%), breast (n = 3; 12.5%), penis (n = 2; 8.3%), and hypochondrium (upper abdomen, inferior to the thorax, and underneath the lower rib cage) (n = 1; 4.2%). The most frequent primary tumor was a melanoma (n = 9; 37.5%), followed by squamous cell carcinoma (n = 6; 25.0%), other types of carcinoma (n = 4; 16.7%), sarcomas (n = 2; 8.3%), adenocarcinomas (n = 2; 8.3%), and lymphoma (n = 1; 4.2%).

The majority of participants experienced 3 of 5 reactions described on the odor impact assessment scale, validating the clinical relevance of odor to this patient population. At baseline (D0), odor was detected by all staff members upon approaching the patients. Of the 24 participants, 20 (83.3%) achieved odor control at D4 and the remaining 4 at D8 (16.6%). There were no significant differences between the performance of PHMB versus metronidazole at any stage of the study. Table 2 shows a significant difference in intensity, quality, and impact of the odor when comparing D0 and D4 in both groups ($P < .001$). The study evaluators and the participants described the odor as little to moderately offensive at baseline and not offensive on D4. Analysis revealed a statistically significant difference between D0 and D4 in the both treatment groups ($P < .001$).

Condition-specific HRQOL based on cumulative scores on the FPQLI-WV improved marginally overtime from 13 to 14 out of 30 during the study (effect size = 0.912). However, analysis indicated statistically significant improvements in the HF ($P = .025$; effect size = 0.142) and Fa subscales ($P = .020$; effect size = 0.996) from D0 to D8. The PS subscale showed the highest magnitude of change in both groups between D0 and D4 ($P < .00$; effect size = 0.528). We found no significant differences between patients who received treatment of topical metronidazole compared to PHMB for their wounds (Table 3).

As noted earlier, pain was assessed during dressing changes. We found no statistically significant differences over time and no differences between the 2 groups (Table 4).

TABLE 1.
Clinical and Demographic Variables

Items	Group 1 n (%)	Group 2, n (%)	*P*[a]
Sex			
Female	5 (41.7)	9 (75.0)	.214
Male	7 (58.3)	3 (25.0)	
Medical history			
Primary	7 (58.3)	10 (83.3)	.371
Local recurrence	5 (41.7)	2 (16.7)	
Staging			
Category 3	8 (66.7)	9 (75.0)	1.000
Category 4	4 (33.3)	3 (25.0)	
Items	**Mean (SD)**	**Mean (SD)**	***P*[b]**
Age	63.33 (18.54)	61.42 (11.67)	.765
Wound evolution, mo	23.17 (21.17)	22.50 (20.39)	.969

[a]Fisher's exact test.
[b]Student's *t* test.

DISCUSSION

An MW is a source of distress to patients who are suffering from cancer, reminding them of the disintegration of their bodies.[2,9,15] While there are many symptoms linked to MWs, odor is often underestimated and undertreated. Odor is associated with the smell of death, dirtiness, and disgust; patients feel embarrassed and ashamed of their bodies. We found that topical application of 0.8% metronidazole and 0.2% PHMB significantly reduced odor over a period of 4 days. We also found that neither topical therapy was superior to the other based on odor reduction, impact on condition-specific HRQOL, or pain upon application. This finding has several

TABLE 2.
Intensity, Quality, and Impact of Wound Odor

Items	Group	Day 0, Mean (SD)	Day 4, Mean (SD)	*P*[a]
Odor rating				
Researcher B	1	2.67 (0.98)	0.33 (0.65)	<.001
	2	2.58 (0.51)	0.08 (0.29)	
Nurse	1	2.42 (1.00)	0.25 (0.62)	<.001
	2	2.58 (0.79)	0.08 (0.29)	
Other	1	2.67 (0.89)	0.33 (0.65)	<.001
	2	2.83 (0.58)	0.00 (0.00)	
Odor quality				
Researcher B	1	2.83 (1.03)	0.33 (0.89)	<.001
	2	3.17 (0.72)	0.17 (0.58)	
Nurse	1	2.83 (0.94)	0.50 (1.00)	<.001
	2	2.92 (0.67)	0.08 (0.29)	
Other	1	3.33 (0.98)	0.50 (0.90)	<.001
	2	3.50 (0.80)	0.00 (0.00)	
Patient	1	2.83 (1.03)	0.58 (1.08)	<.001
	2	3.17 (0.94)	0.17 (0.58)	
Odor impact				
Patient	1	2.25 (1.14)	0.42 (0.79)	<.001
	2	2.58 (1.44)	0.83 (1.75)	

[a]Fisher's exact test.

clinical implications. While odor may be controlled by the use of topical or systemic antibiotics such as metronidazole, the medication is prescribed by a health care professional, making it less ready and accessible to patients than antiseptic solutions.

We found that the topical antiseptic PHMB was as effective in malodor management as metronidazole. Topical use of antiseptic is desirable for its lower cost, low risk of bacterial resistance, and easy accessibility without a prescription. Antiseptic can be used by nurses and patients whenever odor is present, without causing any discomfort or pain. Metronidazole is susceptible to emergence of bacterial resistance as demonstrated by Rotimi and colleagues.[23] In contrast, PHMB is an antiseptic that is not susceptible to the same resistance mechanisms

TABLE 3.
Cumulative and Subscale Scores From the Ferrans and Powers Quality of Life Index

Variable	Group	Day 0, Mean (SD)	Day 4, Mean (SD)	*P*[a]
Quality-of-Life Index	1	13.00 (2.42)	14.21 (2.11)	.002
	2	13.04 (1.48)	14.22 (1.27)	
Health/Function	1	12.69 (3.05)	12.93 (2.76)	.025
	2	12.93 (1.90)	13.04 (1.76)	
Socioeconomic	1	16.21 (2.14)	16.21 (2.14)	…
	2	16.58 (1.75)	16.58 (1.75)	
Psychological/Spiritual	1	13.58 (3.38)	15.00 (2.13)	<.001
	2	13.74 (2.45)	15.21 (1.51)	
Family	1	5.89 (2.82)	13.16 (2.50)	.020
	2	4.86 (1.51)	12.26 (1.31)	

[a]Fisher's exact test.

TABLE 4.
Mean Pain Scores on Application of the Solution and During Dressing Change

Items	Group	Day 0, Mean (SD)	Day 4, Mean (SD)	*P*[a]
Pain				
Patient	1	2.00 (3.22)	2.08 (3.37)	…
	2	1.58 (2.84)	1.58 (2.84)	…
Discomfort in dressing change				
Patient	1	2.08 (1.31)	2.08 (1.31)	…
	2	1.92 (1.24)	1.92 (1.24)	…

as are the antibiotics, is less expensive than metronidazole, and accessible without a prescription.

The vast majority of patients in our study (83.3%) found that odor was completely eliminated by D4 of treatment. This time frame to achieve odor control is different from those in other studies. Castro and Santos[30] completed a systematic review and found that reduction in odor occurred in as little as 24 hours after topical application of metronidazole with complete odor elimination in 48 hours.

STRENGTHS AND LIMITATIONS

This double-blinded, randomized, clinical trial is the first to evaluate the efficacy of PHMB versus metronidazole, the most commonly used topical treatment of MW with odor. Unlike several other studies,[15,31-33] we used a validated instrument to evaluate condition-specific HRQOL and found significant differences in several dimensions that paralleled reductions in wound odor. Limitations of the study include use of a single facility for subject recruitment and data collection. In addition, the study is limited by its small sample size, considering the number of diagnoses and wound locations. Results may not be generalizable to all patients with MWs. Furthermore, dressings were changed daily to allow daily cleansing and reapplication of dressings; this practice may not be feasible for patient in the community. The lack of a validated tool to measure odor may introduce bias, affecting the quality of assessment.

IMPLICATIONS FOR NURSING PRACTICE

The currently recommended topical therapy for MW malodor control is the antibiotic metronidazole.[1,7,18] This finding has implications for nursing practice, and particularly for first-line or specialty practice nurses who may not be able to directly order the prescribed medication metronidazole. Because these nurses are not able to prescribe antibiotics, the antiseptic PHMB provides an excellent alternative to this approach that is immediately accessible to patients in a variety of settings including the home, is not prone to development of bacterial resistance, and may be less costly than metronidazole.

CONCLUSIONS

Findings from this clinical trial indicate that PHMB is noninferior to metronidazole for reduction in odor associated with MW. In addition, we found that several dimensions of condition-specific HRQOL improved as odor control was achieved. Given it classification as an antiseptic and its performance in this trial, we recommend PHMB for malodor control in patients with MW.

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