Clinical Trial/Experimental Study

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Moist exposed burn ointment for treating pressure ulcers

A multicenter randomized controlled trial

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Abstract

Background: Pressure ulcers often seriously affect the quality of life of patients. Moist Exposed Burn Ointment (MEBO) has been developed to treat patients with pressure ulcers. The present study aimed to evaluate the efficacy and safety of MEBO in the treatment of pressure ulcers in Chinese patients.

Methods: Seventy-two patients with pressure ulcers were randomly assigned to 2 groups who received a placebo or MEBO for 2 months. The primary outcomes included the wound surface area (WSA) and pressure ulcer scale for healing (PUSH) tool. The secondary outcomes included a visual analog scale (VAS), questionnaire of ulcer status, and adverse effects.

Results: Sixty-seven patients completed the study. After 2 months of treatment, the difference of mean change from the baseline was greater for MEBO (vs placebo) for WSA mean (SD) −6.0 (−8.8, −3.3), PUSH Tool −2.6 (−4.7, −1.5), and VAS score −2.9 (−4.4, −1.7). On the basis of the questionnaire, the pressure ulcers were "completely healed" (50.0% vs 16.7%) ($P < .05$) in patients after 2 months of treatment with MEBO versus placebo. No major adverse effects were found in the 2 groups.

Conclusion: We showed that MEBO is effective and well tolerated for improving wound healing in Chinese patients with pressure ulcers.

Abbreviations: GCP = good clinical practice, ITT = intention-to-treat, MEBO = Moist Exposed Burn Ointment, PUSH = pressure ulcer scale for healing tool, SAS = Statistical Analysis System package, SPSS = Statistical Package for the Social Sciences, VAS = visual analog scale, WSA = wound surface area.

Keywords: clinical trial, Moist Exposed Burn Ointment, pressure ulcers, randomized controlled trial

1. Introduction

Pressure ulcers are very common conditions for bed bound patients.[1–7] They are often caused by many factors, such as prolonged pressure on skin. These kinds of ulcers usually occur at bony of the body, such as heals, ankles, hips, and elbows.[8,9] If they are not treated adequately, these conditions can seriously affect the quality of life of the patients resulting from pain, disability, and infection.[10,11] These conditions are usually classified into 4 stages according to the pressure ulcers guidelines.[12]

It has been reported that the prevalence of pressure ulcers ranged from 8.8% to 53.2%,[13,14] and the incidence of pressure ulcers varied from 7% to 71.6%.[15,16] The annual treatment cost of pressure ulcers is large, for example, in the UK, the cost ranges from 1.4 to 2.1 billion British Pound. It is the same in amount of the total UK National Health Service expenditure on mental illness, or the total cost of community health services.[17] Thus, adequate and effective treatment is a very important issue for both patients and clinicians.

Traditional Chinese medicines, such as herbal medicinal ointments, especially Moist Exposed Burn Ointment (MEBO), and those for acupuncture and moxibustion have been administered to treat pressure ulcers in China.[1,18–20] In previous studies, MEBO was effectively used to treat burns in clinical practice.[21,22] It consists of sesame oil, β-sitosterol, berberine, and other Chinese herbal plant ingredients.[23] Further clinical and experimental studies have found that MEBO can not only have analgesic and antimicrobial effects but also can shorten the healing time for patients with burn wound.[21–33] In addition, it can also either induce debridement and epithelial repair, or can save costs of treatment for patients and their families.[22,25] Furthermore, it also has been reported that MEBO can promote the healing for the chronic ischemic and neurogenic ulcers.[26,27] However, there is currently limited evidence to evaluate the efficacy and safety of MEBO for treating pressure ulcers. Thus, in

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the present study, we assessed the efficacy and safety of MEBO for the treatment of pressure ulcers.

2. Methods and design

2.1. Objective

The present study aimed to assess the efficacy and adverse effects of MEBO for treating patients with pressure ulcers.

2.2. Study design

This study is a multicenter randomized controlled clinical trial with 2 parallel arms. The trial was conducted at the First Hospital of Harbin and Hongqi Hospital of Mudanjiang Medical College between January 1, 2014, and May 30, 2015. It was approved by the ethics review boards of the First Hospital of Harbin and Hongqi Hospital of Mudanjiang Medical College, respectively. Written informed consent was obtained from all patients before enrollment. Eligible patients were randomized in a ratio of 1:1 to the MEBO and placebo groups, and received treatment for 2 months. Outcome measures were assessed at the baseline, 1, and 2 months after randomization. Results data were analyzed by professionals blinded to the group allocation.

2.3. Eligibility

2.3.1. Inclusion criteria. Participants were included if they met the following criteria: aged 18 to 75 years; pressure ulcers were at stage III or IV according to the european pressure ulcer advisory panel/national pressure ulcer advisory panel (NPUAP) guidelines[12]; and at least 1 pressure ulcer.

2.3.2. Exclusion criteria. Patients were excluded as follows: undertaking other therapies that could affect healing, such as corticosteroids, radiation therapy, or chemotherapy for cancer; complications of peripheral vascular disease, malignant tumors, diabetes mellitus, or infection; and severe diseases, including liver, cardiac, and kidney diseases, and serious relevant complications.

2.4. Randomization and allocation concealment

Stratified randomization schedule was conducted by a statistician of the First Hospital of Harbin using the software of Statistical Analysis System (SAS) package (Version 9.1.3; SAS Institute Inc., Cary, NC). Seventy-two qualified subjects were allocated to the MEBO group or placebo group equally. The allocation concealment was blinded to the participants, investigators, outcome assessors, and data analysts.

2.5. Intervention

All patients in both groups received position change every 2 hours, and mattress that helped to protect the vulnerable skin. In addition, medications for pain control and infection prevention were also applied. As for pain control, patients were given ibuprofen 200 mg (1 tablet) each time for every 6 hours as needed. As for infection prevention, povidone iodine (Betadine solution; Chengdu Yongan Pharmaceutical Co.,Ltd., Chengdu, China) was used to clean pressure ulcers before MEBO or placebo intervention. Then, the pressure ulcers were cleansed with normal saline gauze. MEBO was smeared successively onto the wounds at a thickness of 1 mm twice daily with a sterile gloved finger. The MEBO was not removed in the first 4 days of the treatment. On the fifth day, the accumulated MEBO was removed with a finely serrated metal spatula. Then, MEBO was freshly applied twice daily. The total treatment lasted 2 months. The same application was used as for placebo.

2.6. Outcome measures

2.6.1. Primary outcomes. The primary outcomes were evaluated by the wound surface area (WSA) and pressure ulcer scale for healing (PUSH) tool. The PUSH tool[28] was developed by NPUAP as a quick, reliable tool to monitor the change in pressure ulcer status. It categorized ulcers with respect to surface area, exudate, and type of wound tissue. In addition, if a patient had more than 1 ulcer, all the ulcers were treated by the same method to eliminate the possible complicating factor of treatment interactions. However, only the largest WSA was measured and analyzed in this study.

2.6.2. Secondary outcomes. The secondary outcome was assessed using the visual analog scale (VAS) and a questionnaire of ulcer status. The pain intensity of pressure ulcers was assessed using the 10-point VAS scale (0, absence of pain; 10, the worst pain imaginable).[29,30] A questionnaire regarding the ulcer status was completed by the practitioners. At the end of 2 months, the ulcers were examined blindly and assessed as "Completely Healed," "Partially Healed," "Without Improvement," or "Worsening." The WSA was traced by a paper overlay around the ulcer borders, and measured using AutoCAD 2000 software (AutoCAD, CA). "Completely healed" was defined as an intact dermis and epidermis, and no abrasion or ulceration. "Partially healed" was defined as any decrease in ulcer size compared with the baseline ulcer tracing, but excluding complete healing. "Without improvement was defined as no change in ulcer size compared with the baseline ulcer tracing. Worsening" was defined as any increase in ulcer size compared with the baseline ulcer tracing. In addition, adverse effects were recorded to assess safety.

2.7. Statistical analyses

Data were analyzed by a statistician blinded to the group allocations using the Statistical Package for the Social Sciences (SPSS) 15.0 statistical software package (SPSS Inc., Chicago, IL). Significance was reported at $P < .05$. Data analysis of the baseline characteristics of primary and secondary outcomes was based on the intention-to-treat (ITT) principle. We used the Chi-square, *t*, and Fisher exact tests to analyze the outcome data. The required sample size of this study was estimated to be 72 subjects, 36 in each group with $\alpha = 0.5$, $\beta = 0.8$. It assumed that there was a 20% drop-out rate.

3. Results

One hundred thirty-five patients were initially recruited in this study (Fig. 1). Of these 135 participants, 51 individuals did not meet the inclusion criteria, and 12 refused to involve the present study. Therefore, 72 patients were included and then randomly divided into 2 groups in this study. All outcome data in this study were analyzed by ITT approach. Five patients withdrew from the present study because of their medicine change and lost to follow-up (Fig. 1).

Characteristics of all included participants at the baseline are summarized in Table 1. The 2 groups did not differ significantly at baseline. At the baseline, the mean age (SD) was 71.5 (20.4)

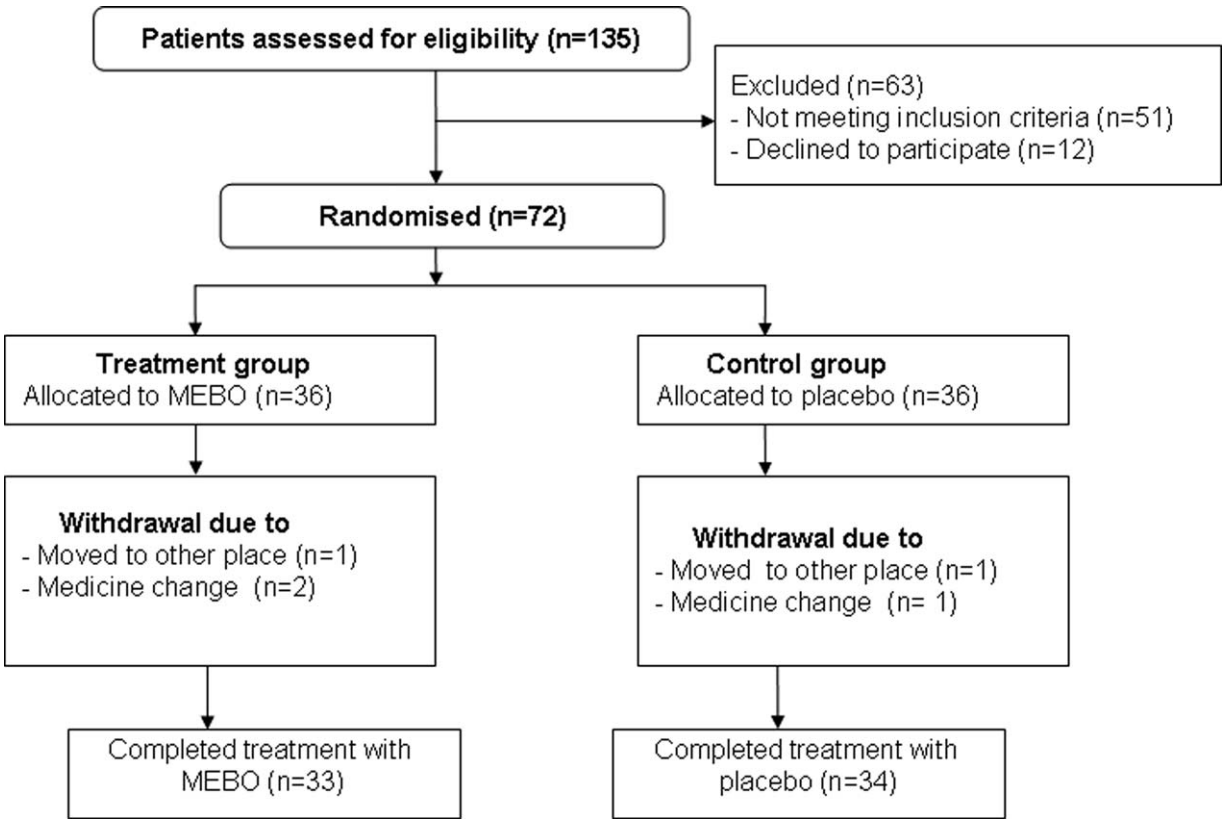

Figure 1. Flow of participants through the trial.

Table 1

Characteristics of participants at baseline.

Characteristics	Variable	MEBO (n = 36)	Placebo (n = 36)	*P*
Age, y: mean (SD)		71.5 (20.4)	69.8 (21.4)	.81
Race	Asian (Chinese)	36 (100.0%)	36 (100.0%)	1.00
Sex				
	Male	22 (61.1%)	16 (44.4%)	.32
	Female	14 (38.9%)	20 (55.6%)	.32
Weight, kg; mean (SD)				
	Male	70.1 (16.4)	68.6 (17.9)	.79
	Female	53.4 (13.1)	52.8 (12.6)	.89
Height, cm; mean (SD)				
	Male	170.5 (4.3)	169.7 (4.5)	.59
	Female	160.2 (4.1)	158.9 (3.9)	.33
BMI, kg/m^2; mean (SD)				
	Male	24.4 (6.1)	23.9 (5.7)	.80
	Female	20.9 (4.2)	20.7 (4.1)	.89
Length of hospital stay mean (SD), mo		4.5 (1.3)	4.3 (1.7)	. 69
Duration of PU, mean (SD), mo		5.1 (1.9)	5.0 (1.7)	.87
WSA, mean (SD), cm^2		18.4 (13.5)	17.9 (12.8)	.91
PUSH Tool		11.9 (1.5)	11.7 (1.5)	.69
VAS		5.9 (1.2)	6.1 (1.4)	.65
PU stage				
	III	24 (66.7%)	20 (55.6%)	.50
	IV	12 (33.3%)	16 (44.4%)	.50
Main diagnosis, n (%)				
	Dementia	16 (44.4%)	14 (38.9%)	.74
	Stroke	10 (27.8%)	12 (33.3%)	.72
	Spinal cord injury	6 (16.7%)	8 (22.2%)	.67
	Parkinson disease	4 (11.1%)	2 (5.6%)	.55
Location, n (%)				
	Sacrum	18 (50.0%)	14 (38.9%)	.50
	Heel	10 (27.8%)	14 (38.9%)	.48
	Trochanter	4 (11.1%)	6 (16.7%)	.63
	Buttock	4 (11.1%)	2 (5.5%)	.55

BMI = body mass index, MEBO = Moist Exposed Burn Ointment, n = number, PU = pressure ulcers, PUSH Tool = Pressure Ulcer Scale for Healing, SD = standard deviation, VAS = visual analogue scale, WSA = wound surface area.

Table 2

Primary and secondary outcomes at 1 and 2 months after treatment (change from baseline).

Outcome measurements	Month 1				Month 2			
	MEBO (n = 36)	Placebo (n = 36)	Difference	*P*	MEBO (n = 36)	Placebo (n = 36)	Difference	*P*
WSA, cm^2	−8.3 (−11.7, −6.5)	−3.4 (−7.5, −2.1)	−4.9 (−6.9, −3.4)	<.01	−14.6 (−17.1, −7.3)	−8.7 (−12.3, −4.6)	−6.0 (−8.8, −3.3)	<.01
PUSH Tool	−4.8 (−6.1, −3.6)	−3.1 (−5.7, −2.0)	−1.8 (−2.5, −1.3)	<.01	−7.3 (−9.8, −4.1)	−4.7 (−6.1, −2.9)	−2.6 (−4.7, −1.5)	<.01
VAS	−2.8 (−3.3, −2.3)	−1.6 (−2.3, −1.0)	−1.4 (−1.9, −0.9)	<.01	−4.5 (−5.1, −3.9)	−2.6 (3.3, −2.1)	−2.9 (−4.4, −1.7)	<.01

MEBO = Moist Exposed Burn Ointment, WSA = wound surface area, PUSH Tool = Pressure Ulcer Scale for Healing, VAS = visual analogue scale.

Table 3

Healing status of pressure ulcers after 2 months treatment in 2 groups.

Groups	Response rate, n (%)				
	Complete	Partial	Not improved	Worsened	Total
MEBO	18 (50.0%)	12 (33.3%)	6 (16.7%)	0 (0%)	36 (100%)
Placebo	6 (16.7%)	14 (38.9%)	12 (33.3%)	4 (11.1%)	36 (100%)

Difference in efficacy between the 2 groups, $P < .05$.
MEBO = Moist Exposed Burn Ointment, n = number of pressure ulcers patients.

years in the MEBO group and 69.8 (21.4) years in the placebo group. All patients in each group were Chinese. The duration of the pressure ulcers was 5.1 (1.9) and 5.0 (1.7) months in the MEBO and placebo groups, respectively. The BMI (kg/m^2) was 24.4 (6.1) for males and 20.9 (4.2) for females in the MEBO group, and 23.9 (5.7) for males and 20.7 (4.1) for females in the placebo group. The length of hospital stay was 4.5 (1.3) months in the MEBO group and 4.3 (1.7) months in the placebo group. The stages of pressure ulcers were IV [12 (33.3%) in the MEBO group and 16 (44.4%) in the placebo group] and III [24 (66.7%) vs 20 (55.6%) in the MEBO and placebo groups, respectively].

At the baseline, the mean WSA (SD), PUSH tool, and VAS were 18.4 (13.5), 11.9 (1.5), 5.9 (1.2) in the MEBO group, respectively, and 17.9 (12.8), 11.7 (1.5), 6.1 (1.4) in the placebo group, respectively. After 1 month of treatment, the difference of adjusted mean change from the baseline was −4.9 (−6.9, −3.4), −1.8 (−2.5, −1.3), and −1.4 (−1.9, −0.9), respectively, between the 2 groups ($P < .01$; Table 2). After 2 months of treatment, these changes were −6.0 (−8.8, −3.3), −2.6 (−4.7, −1.5), and −2.9 (−4.4, −1.7), respectively, between the 2 groups ($P < .01$; Table 2).

Analysis of the healing status of pressure ulcers after 2 months found that ulcers in 50.0% of patients in the MEBO group and 16.7% of those in the placebo group underwent completely healed ($P < .05$; Table 3). In addition, no patients in the 2 groups reported any major adverse effects.

4. Discussion

Pressure ulcers are widespread chronic wounds. They often inflict extensive damage to the skin, and the recovery time often exceeds 3 months, because of the chronicity.[31] The incidence of pressure ulcers will possibly grow rapidly in the future due to increased life expectancy and aging. However, although various methods are used to treat pressure ulcers, no standard therapy has previously been established.

MEBO has been widely used in China for treating wounds, especially for burn healing. Several clinical trials were conducted to evaluate the efficacy of MEBO, and determined that MEBO had a positive effect on burn wound healing.[22,24,26,27,32] The possible mechanisms of MEBO for treating wounds are that it provides a moist environment for the wound healing of pressure ulcers[33] and exhibits analgesic and antimicrobial effects.[22] In addition, MEBO can increase neovascularization in granulation tissue, and enhance vascular endothelial cell proliferation.[34] It can also increase fibroblast cells in the granulation tissue and help them migrate from the surrounding connective tissue into the wound site.[35]

To the best of our knowledge, the present study is the first multicenter randomized controlled trial to evaluate the efficacy and safety of MEBO for treating pressure ulcers in China. It was designed strictly with assessor and analyst blinding. The results demonstrated that MEBO was an effective therapy for improving pressure ulcer healing when compared with the placebo.

However, the present study has some limitations. First, all patients kept their daily medication treatment, because it was impossible to stop the medication intervention for patients with pressure ulcers. Thus, the achieved effectiveness may have been affected by the additional effects of the medication. Second, this study did not have a follow-up evaluation. Therefore, the efficacy of longer term after treatment is needed in future studies.

5. Conclusion

The results of the present study provide evidence to support the hypothesis that MEBO is an effective and safe therapy for treating pressure ulcers in Chinese patients. However, larger studies conducted over a longer treatment period are still warranted.

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