doi: 10.2490/prm.20220045 Progress in Rehabilitation Medicine 2022; Vol. 7, 20220045

ORIGINAL ARTICLE

Efficacy of Low-frequency Monophasic Pulsed Microcurrent Stimulation Therapy in Undermining Pressure Injury: A Double-blind Crossover-controlled Study

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Objectives: This double-blind crossover-controlled trial aimed to verify the effect of electrical stimulation therapy on pressure injuries with undermining. **Methods**: In this trial, we compared the healing rates between a sham period and a treatment period using monophasic pulsed microcurrent therapy. The participants were randomly assigned to the sham or treatment group and received stimulation for 2 weeks. All the participants, physical therapists, and researchers were blinded to the allocation. For the main analysis, data on the effect of the intervention on changes in weekly healing and contraction rates of the wound areas, including undermining, were analyzed based on a two-period crossover study design. The intervention effect was estimated by examining the mean treatment difference for each period using Wilcoxon's signed-rank test. **Results**: The reduction of the entire wound area, including the undermining area, resulted in significantly higher healing and contraction rates in the treatment group (overall wound area reduction rate: contraction rate, P=0.008; period healing rate, P=0.002). **Conclusions**: Electrical stimulation therapy for pressure injuries, using conditions based on the findings of an in vivo culture study, was effective in reducing the wound area.

Key Words: electrical stimulation; pressure ulcer; wound care; wound healing

INTRODUCTION

Pressure injuries affect an individual's appearance and quality of life and represent an economic burden because of medical expenses.[1)] Systematic reviews have reported a high prevalence of pressure injuries in Europe, Asia, and the United States.[2)] A cross-sectional study in Japan demonstrated that pressure injuries occur in 2.03% of individuals aged over 65 years and in 4.46% of individuals aged over 80 years.[3)] Moreover, pressure injuries have been observed in various home and healthcare environments in Japan, with a prevalence of 2.13% in hospitals, 1.07% in long-term healthcare facilities, and 1.68% in the home setting where home-visit nurses provide services.[4)] Among the aging society of Japan, pressure ulcer treatment requires urgent attention. Therefore, in addition to epidemiological studies of pressure injuries, effective and efficient preventive measures and treatments are needed.

Electrical stimulation therapy is recommended for wound contraction, with the strength of evidence rated as category B in Japan.[5)] Furthermore, the "Prevention and Treatment of Pressure Ulcers/Injuries: Quick Reference Guide 2019" assigned a "Strength of Recommendation" (strength of

Received: January 13, 2022, Accepted: August 9, 2022, Published online: September 7, 2022
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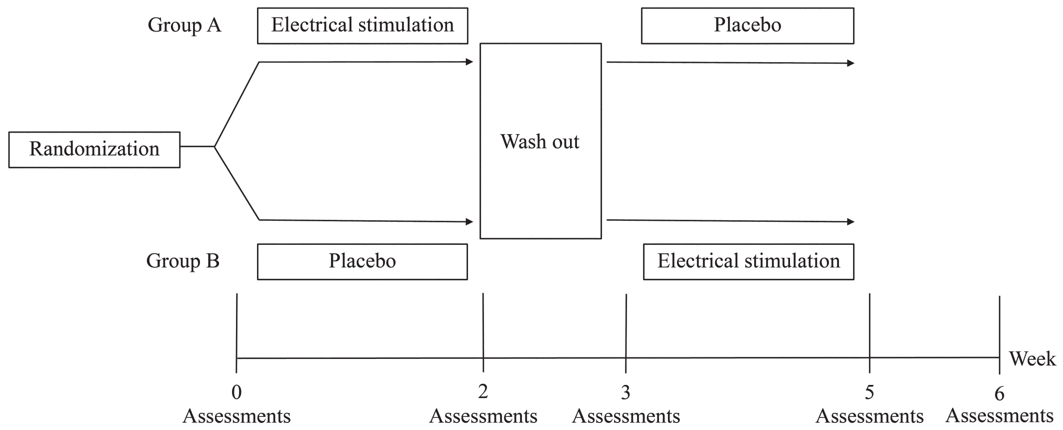

Fig. 1. Trial design and method.

evidence category A) for electrical stimulation therapy.[6] Accordingly, electrical stimulation therapy is considered an essential treatment for pressure injuries.

Several clinical studies have shown that electrical stimulation therapy has favorable therapeutic effects on pressure injuries,[7–13] and systematic reviews and meta-analyses have also confirmed the effectiveness of electrical stimulation therapy.[4–16] However, these studies had adopted varied parameters of electrical stimulation (i.e., differing waveforms, intensities, and frequencies), and the optimum parameters required to achieve good therapeutic effects were unclear.[10–19] Furthermore, several studies measured the wound surface area (WSA) but did not analyze the extent of undermining.[7–13]

Granulation tissue formation and wound contraction resulting from the migration, proliferation, and differentiation of dermal fibroblasts are necessary for chronic wound healing. Monophasic pulsed microcurrent (MPMC; intensity: 200 μA, frequency: 2 Hz, duty cycle: 50%) has been shown to promote the migration, proliferation, and differentiation of human dermal fibroblasts.[17–19] Furthermore, electrical stimulation promotes collagen synthesis from fibroblasts, proliferation, and migration, which accelerates wound healing.[20–22] Thus, we hypothesized that electrical stimulation may have a positive effect on the healing of the undermining area. Undermining formation causes delayed wound healing, and surgery is often performed for intractable undermining.[6] Surgical therapy is invasive and requires long-term bed rest, while electrical stimulation therapy is non-invasive and inexpensive. To prevent the complications associated with surgery, it is necessary to establish a non-invasive and low-cost treatment. Therefore, the purpose of this study was to analyze the therapeutic effects of different MPMC conditions, which have been shown to influence the migration, proliferation, and differentiation of human dermal fibroblasts *in vitro*, in pressure injury with undermining.

MATERIALS AND METHODS

Trial Design

A double-blind, sham-controlled, crossover trial was designed to compare the healing rate between the sham and MPMC periods. The participants were randomly assigned to a sham or MPMC period group using a blinded third-party envelope method. Given that MPMC therapy promotes healing a few days after therapy begins,[13] we designed this study such that each intervention crossed over after 2 weeks. The washout period was set to 1 week because the wound contraction effect disappeared within a few days after the end of MPMC therapy based on the findings by Honda et al.[23] All the participants, physical therapists (including those who measured the WSA and performed the statistical analysis) and researchers were blinded to the assignment, except for the physical therapist who applied the sham or MPMC stimulation. All the participants received 2 weeks of double-blinded treatment with both sham (no stimulation) and MPMC stimulation in a randomized order (**Fig. 1**).

Ethics

This study was approved by the Kobe Gakuin University Ethics Committee (HEB17-54), and all participants and/or their representatives signed a written informed consent form. Informed consent was obtained from all individual participants included in the study. This trial was registered at the UMIN Clinical Trials Registry (registration number: UMIN000029516) and was performed in accordance with

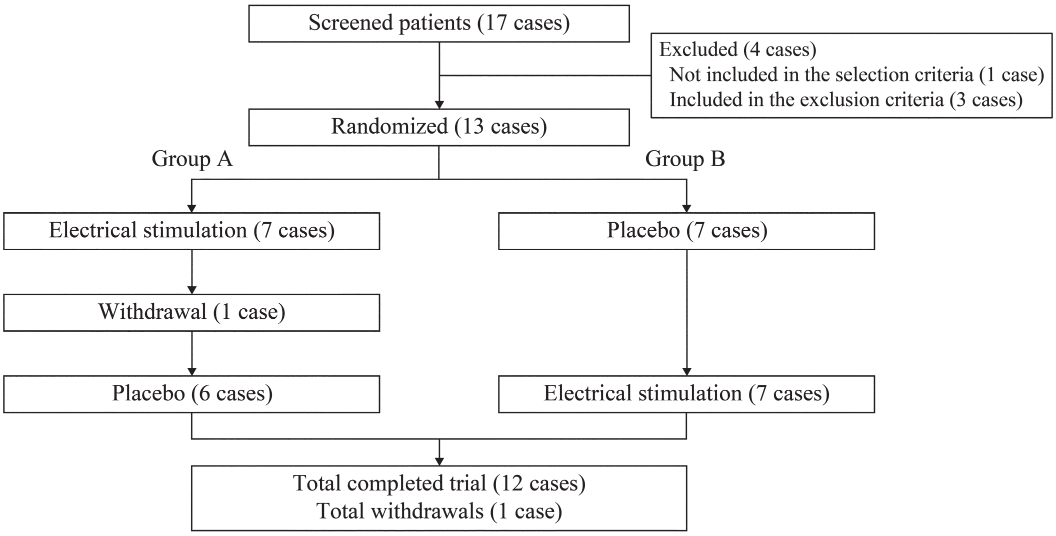

Fig. 2. Study flowchart.

the Declaration of Helsinki.

Participants

The sample size for this study was calculated from a preliminary study of 7 cases wherein the period during which electrical stimulation was not performed was the control period.[13] The preliminary study showed a significant reduction in wound size during the period of electrical stimulation therapy compared with the control period (P=0.018), with a period healing rate of 29.4%. The effect size obtained from this preliminary study (α=0.05, β=0.2) was used to calculate the sample size. We estimated that the sample size required for this study was 12 cases. Initially, 17 patients with pressure injuries who had been admitted to the hospital were screened for participation in the study. The inclusion criteria for the study were patients with pressure injuries [National Pressure Ulcer Advisory Panel (NPUAP) stage >2] who received standard care for more than 2 months but whose wounds had not healed. In contrast, we excluded (1) patients with malignant tumors; (2) patients with significant infection at the decubitus site; (3) patients with arterial or venous thrombosis or thrombophlebitis; (4) patients whose fever was not caused by the pressure injury and whose general condition was judged unstable; (5) patients with anxiety about electrical stimulation; (6) patients with osteomyelitis or pressure injury necrosis; and (7) patients with other medical conditions based on which the physician deemed them unsuitable for electrical stimulation therapy (e.g., individuals with cardiac pacemakers or other bioelectrical stimulators). Three patients were excluded because of unstable general conditions, such as fever, and 1 did not agree to participate in the study. The remaining 13 patients (aged 62–92 years) who met the inclusion criteria [had received >2 months of standard treatment for pressure injuries without healing; severity of pressure injuries: DESIGN-R score ≥15 points, NPUAP stage ≥3; and pressure injury risk assessment: Ohura and Hotta (OH) scale score was 1.5–8.5 points] were enrolled and randomized into one of two treatment groups (Group A, 7 patients; Group B, 6 patients). Group A underwent electrical stimulation therapy during the first 2-week period, and the remaining 2 weeks were the sham period. In Group B, the first 2 weeks were the sham period, and the patients received electrical stimulation therapy in the remaining 2-week period. After 1 patient in Group A developed sepsis and was excluded from the study, 12 patients (mean age 82.8 years, SD=7.7 years; 4 men, 8 women) were included in the final analysis (**Fig. 2**). Their characteristics are presented in **Table 1**.

Study Procedures

Prospective participants were first screened by wound observation. Those who closely met the inclusion criteria underwent an assessment in the hospital, where they received a full description of the study. The participants' DESIGN-R score, NPUAP stage, and OH scale score were assessed. A physician performed the medical examinations and provided standard therapy for pressure injuries. The participants who met the inclusion criteria were randomized to receive 2 weeks of either MPMC (current intensity, 170 µA; frequency, 2 Hz; duty factor, 50%; experimental period: E period) or sham stimulation (no stimulation; sham period: S period).

Table 1. Participant characteristics

Patient	Age (years)	Sex	Albumin (g/dL)	Nutrition	Underlying disease	Location of pressure injury	Duration of illness	Total DESIGN-R score
A	80	Female	3.3	Oral ingestion	Lumbar compression fracture	Sacrum	12 months	19 (D3-e3s3i0g3n0P12)
B	90	Female	3.1	Tube feeding	Cerebral infarction	Sacrum	12 months	25 (D3-e3s9i1g3n0P9)
C	80	Female	2.5	Tube feeding	Parkinson's disease	Sacrum	10 months	26 (D3-e3s-6i1G4n0P12)
D	62	Female	3.8	Oral ingestion	Diabetes	Sacrum	≥2 months	18 (D3-e3s3i0g3n0P9)
E	92	Female	2.6	Tube feeding	Pyelonephritis	Sacrum	≥5 months	18 (D3-e3s3i0g3n0P9)
F	84	Female	2.3	Tube feeding	Subarachnoid hemorrhage	Sacrum	10 months	23 (D3-e3s3i0G5N3P9)
G	89	Female	3.1	Oral ingestion	Total knee arthroplasty	Thoracic spine	≥12 months	20 (D3-e3s3i1G4n0P9)
H	80	Male	2.7	Tube feeding	Normal pressure hydrocephalus	Coccyx	20 months	15 (D3-e3s3i0g3n0P6)
I	85	Female	2.5	Tube feeding	Aspiration pneumonia	Left ilium	2 months	17 (D3-e3s6i1G4N3P0)
J	85	Male	2.0	Tube feeding	Cerebral hemorrhage	Left ilium	≥8 months	19 (D3-e3s3i0G4N3P6)
K	85	Male	3.0	Oral ingestion	Metastatic spinal cord tumor	Right greater trochanter	≥4 months	25 (D3-e3s6i0G4N3P9)
L	82	Male	2.7	Tube feeding	Hypoxic encephalopathy	Right fibula	3 months	18 (D3-e3s6i0g3n0P6)

DESIGN-R: depth, exudate, size, inflammation/infection, granulation, necrotic tissue.

The participants were scheduled for follow-up appointments, where we checked for any side effects (redness or metal allergies) from the therapy, new medications, or changes in their medical history. Subsequently, patients underwent a week of washout, followed by a second 2-week, double-blinded treatment period where the treatments were switched between the groups.

Standard Treatment

Postural changes were performed at intervals of less than 2 h. The hip joint was intermediately positioned between an internal and external rotation such that the trunk was not rotated in a 30-degree lateral position.[24,25] Air mattresses (Oscar or Revo mattresses, Molten Corporation, Hiroshima, Japan) and urethane foam mattresses (Stretch grade, Paramount, Tokyo, Japan) were used. There was no change in the pressure injury management method throughout the study period for any of the participants.

Nutritional assessment of each participant was performed by physicians and dietitians using the Mini Nutritional Assessment short-form (MNA-SF) together with details of weight, body mass index, and serum albumin levels. The MNA-SF has been validated as a nutritional assessment tool for older adults.[26] Based on these assessments, caloric requirements were calculated using the Harris–Benedict formula. The caloric intake of the participants was 1600 kcal/day for 4 individuals on oral nutrition, 1230 kcal/day for 5 on central venous nutrition, and 1000 to 1200 kcal/day for 3 on tube feeding. There were no changes in nutritional management throughout the study period for any of the participants.

The pressure wound was washed once a day with a mildly acidic detergent (Bioré U, Kao Corporation, Tokyo, Japan), and a syringe with water was used to wash the undermining area, followed by the application of ointment (Povidone-Iodine, Shionogi, Osaka, Japan). There was no change in the pressure injury treatment throughout the study.

Fig. 3. Pressure injury size assessment. Left: Overall area defining the pressure injury. Right: The pressure injury was traced using a tracing film and the film was then measured using a wound area measuring instrument.

Electrical Stimulation Therapy

An electrical stimulation device (iPES, Ito, Kawaguchi, Japan) was used for stimulation. The cathode was gold-plated with low ionization tendency; it was rod-shaped, with a length of 20 mm and a diameter of 1 mm. The indifferent electrode was an ordinary affixed electrode. When MPMC stimulation was performed, the cathode was covered with sterile gauze soaked in saline. If the wound was large enough, the electrode was inserted into the undermining area; if not, it was placed over the wound surface. The indifferent electrode (anode) was placed on the healthy skin area where the undermining area was the deepest (within 10 cm of the different electrodes). MPMC stimulation [frequency, 2 Hz; pulse width, 250 ms; stimulation intensity, 170 μA; and duty factor (DF), 50%] was administered once a day for 60 min, six times per week. For the sham stimulation, the electrodes were placed as for MPMC stimulation, and sham stimulation (0 μA) was administered for 60 min once a day.

Pressure Injury Assessment

The DESIGN-R score and pressure injury area (wound area, undermining area, and total wound area) were measured twice a week. The DESIGN-R score is evaluated by the following seven factors: depth, exudate, size, inflammation/infection, granulation tissue, necrotic tissue, and pocket (undermining). The DESIGN-R score and wound and undermined areas were assessed and measured by at least two individuals (at least two selected from dermatologists, a nurse, and a physical therapist). The undermining area was measured using a cotton swab, taking care not to damage the granulation. The area of the pressure injury was measured by tracing with a tracing film (Visitrak grid, Smith & Nephew, London, UK) and a wound area measuring instrument (Visitrak, Smith & Nephew). The total area of the wound was defined as the sum of the area of the wound and undermining areas (**Fig. 3**). The healing rate of the pressure injury area for 14 days was termed the contraction rate and was calculated as follows: contraction rate = (WSA before − WSA after)/duration (days). The percentage decrease of the pressure injury area was defined as the period healing rate and was calculated as follows: period healing rate = (WSA before − WSA after)/WSA before.

Blinding

All patients, medical personnel, and researchers were blinded except for the main investigator and principal physical therapist, who set the equipment to apply active or sham electrical stimulation therapy. Pressure injuries were evaluated by a physical therapist different from the therapist who conducted the MPMC. In addition, the operator of the MPMC therapy was instructed not to inform the participant that the stimulation had begun. When in operation, the participants could not perceive the electrical stimulation because the intensity of 200 μA was lower than the sensitivity threshold.

Statistical Analyses

Statistical analyses were performed using SPSS v. 20.1 (IBM, Armonk, NY, USA). All analyses were two-sided, and statistical significance was set at $P<0.05$. The data were checked for consistency, missing values, outliers, and normality before the analyses. Descriptive statistics are reported as percentages, medians, and means with minimum–maxi-

Table 2. Changes in wound area for each case

Patient	E period				S period			
	WSA (before; cm^2)	WSA (after; cm^2)	Contraction rate (cm^2/day)	Period healing rate (%)	WSA (before; cm^2)	WSA (after; cm^2)	Contraction rate (cm^2/day)	Period healing rate (%)
A	8.8	8.3	0.04	5.7	13.5	10.3	0.23	23.7
B	38.9	35.8	0.22	8.0	39.5	40.0	−0.04	−1.3
C	13.9	10.2	0.26	26.6	15.3	14.4	0.06	5.9
D	7.8	3.6	0.30	53.8	1.7	1.2	0.04	29.4
E	8.8	7.4	0.10	15.9	5.3	4.9	0.03	7.5
F	9.1	6.2	0.21	31.9	10.3	9.3	0.07	9.7
G	10.5	6.1	0.31	41.9	6.5	6.6	−0.01	−1.5
H	3.5	3.6	−0.01	−2.9	3.5	3.7	−0.01	−5.7
I	5.3	1.8	0.25	66.0	1.3	0.5	0.06	61.5
J	3.6	1.6	0.14	55.6	2.9	2.6	0.02	10.3
K	11.8	8.9	0.21	24.6	14.7	12.3	0.17	16.3
L	6.8	5.1	0.12	25.0	4.8	5.0	−0.01	−4.2

mum values. For the main analysis, the data were analyzed according to a two-period crossover design to evaluate the effect of the intervention on changes in weekly healing and contraction rates of the wound areas, including undermining. Wilcoxon's signed-rank test was used to evaluate the mean treatment differences between the treatments for each period (the first and second 2 weeks).

The primary outcome variable for this study was the change in weekly healing and contraction rates of the wound area, including undermining, at the end of the 2-week stimulation. In addition, the size of the effect was calculated from the results obtained by a post hoc test.

RESULTS

There were no side effects and no change in clinical findings or vital signs was observed during or after the MPMC therapy. Overall, one patient dropped out of the study because of sepsis (not related to MPMC therapy) at the end of the E period (dropout rate; 7.7%).

When the E and S periods were compared, no significant difference was observed in either the contraction rates or period healing rates in the wound area (contraction rate: P=0.170, period healing rate: P=0.410). There was no significant difference in the total DESIGN-R scores between the E and S periods. The healing and contraction rates were significantly higher with the reduction of the entire wound area, including the undermining area, than with the reduction of only the wound area (overall wound area reduction rate: contraction rate, P=0.008; period healing rate, P=0.002) (**Tables 2 and 3**). No difference in wound healing outcome was observed between different electrode insertion sites (wound surface and undermining area, data not shown). The size of the effect on the wound area by the post hoc test was 0.40 (period healing rate) and 0.43 (rate reduction rate). The effect size of the entire wound area, including the undermining area, was 0.77 (period healing rate) and 0.71 (rate reduction rate).

DISCUSSION

This study evaluated the therapeutic outcomes of electrical stimulation therapy on pressure injuries with undermining using different MPMC conditions. When the E and S periods were compared, no significant difference was detected in the DESIGN-R or wound area alone. However, regarding the overall pressure injuries with undermining, the wound healing rate was significantly improved in the E period. These results indicate that MPMC therapy promotes the healing of undermined pressure injuries. Although our study participants were not standardized in terms of age or underlying disease, all participants had pressure injuries with stagnant wound healing and non-healing after at least 2 months of standard treatment. A chronic wound is defined as a wound that fails to progress through a normal, orderly, and timely sequence of repair or in which the repair process fails to restore anatomical and functional integrity.[27] Therefore, although all 12 participants in this study presented chronic wounds, which deviated from the normal healing process,

Table 3. Statistical examination

Wilcoxon signed rank test: period healing rate (%), contraction rate (cm²/day)					
		E period (n=12)		S period (n=12)	
		Contraction rate (cm²/day)	Period healing rate (%)	Contraction rate (cm²/day)	Period healing rate (%)
Wound area	Average	0.05	26.2	0.02	17.1
	Median	0.03	23.0	0.01	16.7
	Min–Max	0–0.25	0–66.0	−0.02 to 0.06	−6.7 to 61.5
	z-value			−1.38	−0.83
	P-value			0.170	0.410
Undermining area	Average	0.16	34.5	0.01	9.0
	Median	0.13	30.6	0.01	7.8
	Min–Max	−0.01 to 0.29	−11.5 to 83.3	−0.23 to 0.16	−18.2 to 33.3
	z-value			−1.33	−2.13
	P-value			0.182	0.033*
Wound area (including undermining area)	Average	0.18	29.3	0.05	12.6
	Median	0.21	25.8	0.03	8.6
	Min–Max	−0.01 to 0.31	−2.9 to 66.0	−0.04 to 0.23	−5.7 to 61.5
	z-value			−2.67	−3.06
	P-value			0.008**	0.002**

* P<0.05; ** P<0.01

MPMC therapy effectively promoted wound contraction in 10 of the 12 cases.

More notably, this effect was confirmed for pressure injuries with undermining. Few studies have reported the effects of electrical stimulation therapy on pressure injuries with undermining. Therefore, the findings of this study are novel in that they confirmed the effect of MPMC therapy on the undermining area.

The sample size was calculated based on a pilot study, which comprised electrical stimulation therapy (intensity, 80 µA; frequency, 2 Hz; DF, 50%; six times per week) on 7 patients with pressure injuries.[13] The pilot study showed a period healing rate of 29.4% and a contraction rate of 0.26 cm^2/day, although there were study limitations that may have influenced the results. For example, the patients included those with pressure injuries without undermining, there were no control participants, and differences in wound severity were not assessed. Therefore, in this study, we used a crossover-controlled trial design, wherein we recruited patients who had pressure injuries with undermining of equal severity and introduced a control group. Although the calculated sample size was small (12 cases), the results of the post hoc test showed that the entire wound area, including the undermining area, had effect sizes of 0.77 (period healing rate) and 0.71 (rate reduction rate). However, because the calculated effect size was less than 0.8, the findings should be verified with a larger sample size in the future.

Many clinical trials have reported the effects of electrical stimulation therapy, and the treatment is strongly recommended as Grade A in the "Prevention and Treatment of Pressure Ulcers/Injuries: Quick Reference Guide 2019."[6] However, most reports have investigated high-voltage pulsed current (HVPC) treatment, and only scattered studies using MPMC therapy are currently available.[7–9,28,29] HVPC treatment has been used in many studies,[7–9,28,29] and its efficacy has been confirmed; however, adverse events such as redness and pain have been reported.[30] Low-intensity currents, as used in MPMC therapy, may have fewer side effects because they can be applied without perceived sensation and may be considered painless.[31] Although one patient dropped out of this study, the withdrawal was not attributed to MPMC therapy, and no adverse event with MPMC therapy was observed in this study.

There has been significant discussion regarding the conditions to be used for electrical stimulation, including polarity, intensity, and frequency. Polarity is an important parameter of electrical stimulation, and there have been several clinical reports describing wound polarity.[7,29,32] A recent double-blind, randomized controlled trial by Polak et al.[7] classified 61 pressure injury cases into anode HVPC, cathode HVPC, and sham HVPC groups. They reported that the area reduction rate of the cathode HVPC group was 74.1%, and the wound reduction effect was significantly higher than that in the sham HVPC group. In contrast, Karba et al.[32] reported a reduction in pressure injury following MPMC therapy when the pressure injury site was used as the anode site. From the abovementioned results, the required polarity for electrical stimulation in pressure injury healing is controversial; however, given that results from a preliminary experimental study showed that cultured fibroblasts migrated to the cathode,[33] the pressure injury was used as the site for cathode placement in this study.

There was no difference regarding the position of the electrode (on the wound surface or in the undermining area) in this study, although this may have been because of the small number of cases, which made it difficult to obtain sufficient data. There may be room for further research in the future, considering the healing promotion of undermining.

There is still no consensus on the appropriate intensity and frequency of MPMC therapy, although there have been various reports on muscle contraction and perceptual thresholds.[11,12] However, a definite intensity and frequency have been shown in fibroblast migration and proliferation experiments *in vitro*. It has been reported that the migration of fibroblasts is promoted at a stimulation intensity of 200 µA and a stimulation frequency of 2 Hz and that cells proliferate at a frequency of 1–8 Hz.[17–19] Therefore, this study was conducted using these parameters. Our findings indicate that the wound reduction and period healing rates were significantly higher during the MPMC therapy period than during the sham period. This effect may have been observed because of the stimulus conditions selected, which were based on the results of the *in vitro* fibroblast studies, and thus were considered suitable for the wound.

Given that the undermining area was reduced by electrical stimulation, we also considered that the undermining contraction was caused by granulation growth. Granulation proliferation is not only caused by migration and cell proliferation but also by collagen proliferation. HVPC and direct current stimulation have been reported to promote the proliferation of collagen.[34,35] In addition, the proliferation of myofibroblasts by electrical stimulation[36] is also considered to have affected the contraction of the undermining. Uemura et al.[37] reported that for *in vitro* cell cultures using fibroblasts, a stimulation intensity of 200 µA, frequency of 2 Hz, and DF of 10% promoted differentiation into myofibroblasts and contraction of collagen gel. However, these were *in vivo* or *in vitro* studies; thus, it is unclear whether there was a direct effect, although it cannot be denied that MPMC therapy exerted a beneficial effect on wound healing. Considering all the abovementioned findings, MPMC therapy can be considered as an effective approach to promote the healing of pressure injuries with undermining.

CONCLUSION

This study was based on the results of previous studies and cell culture experiments. The findings in this study showed that the wound contraction healing rates of a pressure injury were significantly higher in the E period than in the S period, indicating a positive effect on pressure injuries with undermining. Therefore, MPMC therapy can promote the healing of a pressure injury with undermining. A limitation of the study included the fact that it was a single-center, double-blind, crossover-controlled trial; therefore, the number of cases was small. These results should be verified using a larger sample size and at multiple centers in the future.

ACKNOWLEDGMENTS

We express our sincere gratitude for the cooperation of the staff at Housenka Hospital, the facility where this study was conducted. We also thank Editage (www.editage.com) for English language editing. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number JP16K01529).

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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