Randomized Controlled trial evaluating the Efficacy of Wrap Therapy for Wound Healing Acceleration in NPUAP Stage II and III Pressure Ulcer Patients

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Randomized Controlled trial evaluating the Efficacy of Wrap Therapy for Wound Healing Acceleration in NPUAP Stage II and III Pressure Ulcer Patients

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Abstract

Objectives: To evaluate if 'wrap therapy' using food wraps, which is widely used in Japanese clinical sites, is not inferior when compared to guideline adhesion treatments.

Design: Multi-centre, prospective, randomized, open blinded endpoint clinical trial.

Setting: Fifteen hospitals in Japan

Patients: Sixty-six elderly patients with new NPUAP Stage II or III pressure ulcers.

Interventions: Out of these 66 patients, 31 were divided into the conventional treatment guidelines group and 35 into the wrap therapy group.

Main outcome measures: The primary end point was the period until the pressure ulcers were cured. The secondary end point was a comparison of the speed of change in the Pressure Ulcer Scale for Healing (PUSH) score.

Results: Sixty-four of the 66 patients were analysed. The estimated mean period until healing was 57.5 days [95% confidence interval (CI) 45.2–69.8] in the control group as opposed to 59.8 days (95% CI 49.7–69.9) in the wrap therapy group. By the extent of pressure ulcer infiltration, the mean period until healing was 16.0 days in the control group (95% CI 8.1–23.9) as opposed to 18.8 days in the wrap therapy group (95% CI 10.3–27.2) with NPUAP Stage II ulcers, and 71.8 days (95% CI 61.4–82.3) as opposed to 63.2 days (95% CI 53.0–73.4), respectively, with Stage III ulcers. There is no statistical significance in difference in PUSH scores.

Conclusions: It might be possible to recommend wrap therapy as an effective treatment in primary care settings as an extremely simple and inexpensive dressing care.

Trial registration: UMIN Clinical Trials Registry UMIN000002658

Article Summary

Article focus

- 'Wrap therapy' is a method for localized care of pressure ulcers using polyethylene sheets, such as in food wraps, to the pressure ulcers. There are numerous case reports promoting efficiency of this therapy in Japan.
- We hypothesized non-inferiority of the efficacy of wrap therapy on adult patients with pressure ulcers classified as National Pressure Ulcer Advisory Panel (NPUAP) Stage II or III comparing with that of guideline adhesion treatment to Japanese patients.

Key messages

- The survival curves showed the inferiority of wrap therapy comparing with guideline adhesion treatment on the period until the pressure ulcers healed.
- Focusing on NPUAP Stage III pressure ulcers, wrap therapy showed tendency of faster healing than guideline adhesion treatment.

Strengths and limitations of this study

- This study is the first study revealing the efficacy of wrap therapy, that is inexpensive and simple for home care, using RCT design.
- Relatively weak statistical power and impossibility of blindness of the treatment.

INTRODUCTION

Among the health problems specific to the frail elderly, pressure ulcers[1-3]has been a major health problem, and the establishment and spread of an effective treatment method for it has been a pressing issue. After guideline publication by Agency for Health Care Policy and Research[4], there have been few standard policy announcements regarding localized treatments with high evidence levels[5,6]. The Japanese Society of Pressure Ulcers (JSPU) published its 'Evidence-Based Localized Pressure Ulcer Treatment Guidelines' in 2005, and treatments based on these have become the conventional treatments in Japan[7]. According to the guidelines, overall complex treatments aiming to debride necrotic tissue and reduce the ulcers are recommended for deep pressure ulcers. However, the recommendation grades regarding individual ointments and dressings, physical treatments, and surgical treatments are low level. Several intervention researches have been performed on specific drugs in localized treatments, but few clinical breakthrough methods have been discovered in the effects of these interventions[8-14].

'Wrap therapy' is a method for localized care of pressure ulcers through which healing can be expected based on the natural healing effects by applying polyethylene sheets, such as in food wraps, to the pressure ulcers. This method has spread following its proposal by Toriyabe Shunichi[15]. On the effectiveness of wrap therapy in treating pressure ulcers, and of their simplicity and low cost, there are numerous case reports and case series research supporting no-inferiority of wrap therapy in Japan[16-20]. On March 2010, JSPU approved wrap therapy as one of the first treatment choices in limited situations.

Our purpose is to evaluate the efficacy of wrap therapy on adult patients with pressure ulcers classified as National Pressure Ulcer Advisory Panel (NPUAP) Stage II or III on their backs using the current conventional treatment in Japan, described in the guideline published by JSPU, as a control. If this research verifies that wrap therapy is not harmful and has equivalent or better efficacy compared to conventional treatments, a low-cost treatment method can be well applied to the care of the elderly.

METHODS

Study Design and Setting

The study evaluated outcomes and analysis of the prospective randomized open blinded endpoint trial at numerous facilities. For this study, we recruited facilities by appealing to them for participation via mailing lists related to JSPU and those regarding pressure ulcer diagnosis and treatment. To assure implementation of the research work, we set the following as suitable standards for the facilities sharing the work: facilities that were able to use body pressure diffusion mats for pressure ulcer patients, facilities with experience of wrap therapy on some patients, the existence of care systems for pressure ulcer care and environments that were able to perform pressure ulcer treatments during hospitalization. Fifteen hospitals finally were identified to be eligible facilities.

Patients and randomization

For patient registration, we set the following inclusion and exclusion criteria: patients aged 50 or over with one or more NPUAP Stage II or III pressure ulcers on either their torso or trochanter, body temperature of 35.5°C min. to 37.5°C max., 600kcal or over daily intake, no critical nutritional impairment, renal failure, cirrhosis, immunosuppression, uncontrollable diabetes, or malignant tumours according to an examination performed within past four weeks. End-of-life patients whose estimated alive period were less than three months were excluded. When the patient did not possess the ability to make the autonomous decision to participate in the study, the outline and methods of the research were explained to their representing immediate family member, from whom written consent was obtained. After obtaining written consent, then uncoordinated random allocations were performed at the registration centre in the research office within 24 hours.

Interventions

Wrap therapy was defined as a method of treatment that uses food wraps and perforated polyethylene as a wound dressing. In many cases, wrap therapy follows the procedure of

thoroughly irrigating the pressure ulcers (Fig. 1-1) before directly covering the pressure ulcers with food wrap if the exudation is small, or with commercially available perforated polyethylene sheets and diapers, or with a cover sheet combined with sanitary towels if the exudation is great (Figs. 1-2 and 1-3). Irrigation and the covering process are performed every day[21].

To standardize the categories and treatment procedures of wrap therapy as much as possible, a meeting for instruction of interventions was held beforehand. A DVD of the lecture was distributed to the physicians that were unable to participate in the instruction meeting.

Patients allocated to the control group were treated using methods conforming the 'Evidence-Based Localized Pressure Ulcer Treatment Guidelines' issued by JSPU[7]. These guidelines are diagnosis and treatment guidelines created by JSPU based on current diagnosis and treatment evidence.

Outcomes evaluated

The primary endpoint was defined as the period from the start of registration until the pressure ulcers that had been the subject of observation for three months were healed. After the patient had been discharged from the hospital, continuous observation was performed as far as possible through diagnosis and treatment at home. Every wound heal was confirmed by supervising physicians. As the secondary endpoint, we measured the PUSH score for the localized status of the pressure ulcers as defined by NPUAP at two, four, six, eight, ten and 12 weeks from the start of registration[22].

To avoid the occurrence of observation bias, we established an 'outcome evaluation centre'. Digital camera images were sent from every facility to the outcome evaluation centre, and all outcomes were evaluated there. The outcome evaluation centre was blinded so as not to know the treatment group to which the subject belonged. Because it was impossible to evaluate the exudates amount using images, records were made by the observer directly.

We also recorded the total amount of ointment used in localized treatments during the observation period, and performed rough calculations with regards to cost.

Adverse Events and Role of the Patient Safety Monitoring Board

A safety evaluation committee was established comprising several specialists and non-specialists. The members were independent from the patient registration, research offices and the outcome evaluation centre. In all cases of death, worsening of the pressure ulcers during the research period, systemic deterioration or sepsis occurring within 30 days from the day of the protocol treatment, and when the connection to the pressure ulcers was undeniable, researchers sharing the research at the core facilities reported to the committee.

Statistical Analysis

We aimed to clarify our statistical hypothesis that wrap therapy was not inferior compared to conventional treatments conforming to the guidelines. The mean period until healing for the localized treatment of Stage II pressure ulcers was set as 21 days based on previous literature[9-14]. The non-inferior threshold was set at seven days according to clinical judgment. When set to a tolerable threshold difference of 7 days when one side has a 5% significance level and a test power of 90%, the required number of cases in the two cohorts was 80. Similarly, the required number of cases for Stage III pressure ulcers was 60. For the total number of target cases, 140 was set as the number of target registered patients. The analysts were blinded about which group was the wrap therapy or the conventional treatment until the analysis was finished. Intention to treat analysis was performed.

For the main endpoint comparisons, a Kaplan-Meier plotswere created and the estimated mean value until the endpoint occurrence and its 95% confidence interval (CI) were calculated. The differences in the PUSH scores were calculated from two weeks immediately after the start of observations, between two to four weeks, four to six weeks, six to eight weeks, eight to ten weeks and ten to 12 weeks, and described the speed of pressure ulcer healing over time for both groups. We used PASW Statistics 18 (SPSS, Inc) for the statistical analysis.

RESULTS

The study flow diagram is shown in Fig. 2. During the research period, a total of 66 patients participated. Of these, two could not be followed up due to early discharge or transfer to another hospital. A total of 64 participants were analysed: 29 in the conventional treatment group and 35 in the wrap therapy group. The percentage of patients whose endpoints could be pursued four weeks after registration was 95%, eight weeks after registration was 77% and 12 weeks after registration was 64%.The characteristics distribution of the patients analysed was 33 females and 29 males, and the locations of the target pressure ulcers were most common on the sacrum (56%), followed by the trochanter (13%), gluteus (6%) and the coccyx (5%).

Table 1 shows a comparison of the patients' characteristics distribution, their health at registration, the status of their pressure ulcers and the treatment method for the two groups. The mean values in the conventional treatment and wrap therapy cohorts were 12.7 versus 12.7 for the Braden Scale at registration[23].The percentages using hydrocolloids, hydrogels or polyurethane foam as pressure ulcer dressings were 76% in the control group and 3% in the intervention cohort.

Time until the Pressure Ulcers Healed

The percentage of patients in whom healing of the pressure ulcers was verified from among the samples that could be followed up at four weeks after registration were 26% of the conventional group as opposed to 21% in the wrap therapy group; at eight weeks after registration the percentages were 46% in the conventional group as opposed to 52% in the wrap therapy group (Fig. 2).

Fig. 3-1 shows the survival curves of both groups. The mean of the estimated value until healing was 57.5 days (95% CI 45.2 days; 69.8 days) for the conventional group as opposed to 59.8 days (95% CI 49.7 days; 69.9 days) for the wrap therapy group. Fig. 3-2 and Fig. 3-3describes the survival curve for the patients with NPUAP Stage II and III pressure ulcers, respectively. For Stage II pressure ulcers, the estimated mean value until healing were 16.0 days (95% CI 8.1 days; 23.9 days) for the conventional group compared to 18.8 days (95% CI

10.3 days; 27.2 days) for the wrap therapy group. Meanwhile, for Stage III pressure ulcers, the estimated mean value until healing were 71.8 days (95% CI 61.4 days; 82.3 days) for the conventional group compared to 63.2 days (95% CI 53.0 days; 73.4 days) for the wrap therapy group.

Speed of Pressure Ulcer Healing Using PUSH Scores

The mean values of the difference in the PUSH scores at registration and upon either healing or the final observation divided by the treatment period were 1.1±2.1 points in the conventional group and 0.9±1.3 points in the wrap therapy group (p= 0.73 Student's t-test). No significant difference was identified in the mean PUSH score reduction values in either cohort from immediately after the start of observations to the second week, from the second to the fourth week, from the fourth to the sixth week, from the sixth to the eighth week, from the eighth to the tenth week and from the tenth to the twelfth week (Table 2).

Adverse Events

During the total observation period, there was systemic worsening such as pneumonia, occurring immediately after the start of observation in three cases in the conventional group, and four cases in the wrap therapy group. Two cases in the conventional group died of pneumonia and one died from heart failure for a total of three deaths. In the wrap therapy group, one patient died of pneumonia and one of senescence for a total of two deaths. Regarding localized adverse events, there were problems with the covered skin (eczema, maceration, rash, etc.) in the conventional group and six cases in the wrap therapy group.

DISCUSSIONS

Statement of principal findings

'Wrap therapy' has already been introduced nationwide in Japanese clinical facilities. The main reasons for its spread in clinical settings are both that wrap therapy is a rational treatment method compared to basic wound-healing therapies, in that it is possible to maintain a lubricated environment without applying stress to the wound[24,25], and because compared to complex pressure ulcer treatments that combine various ointments and dressings, it has frequently been recognized empirically in actual clinical settings as having equal or better effects in treating pressure ulcers.

Looking only at the main outcome survival curves, and taking all the patients into consideration, almost identical results were obtained in both the wrap therapy and conventional treatment groups for the period until the pressure ulcers healed. Meanwhile, when the two treatment groups are compared using the NPUAP classification, although no clear difference between the survival curves of the two treatments were identified with shallow Stage II pressure ulcers, in the comparison between the Stage III pressure ulcer cohorts, the survival curve of the wrap therapy cohort showed that healing tended to be faster than in the conventional treatment cohort. No statistical significance, however, was presented due to insufficient statistical power. It might be possible to present results in which wrap therapy is sufficiently effective as an alternative treatment to the current conventional treatments for comparatively deep pressure ulcers such as Stage III pressure ulcers with bigger sample study. Nor was any significant difference identified between the wrap therapy and conventional treatment cohorts regarding the extent of PUSH score reduction either, and this result can also be stated to support the fact that wrap therapy is not inferior to conventional treatments. Nevertheless, initially we estimated 80 cases and 60 cases in the NPUAP classification subgroups as the non-inferior estimate, but on this occasion, the total effective sample, at 64 cases, lacked sufficient statistical power.

During the comparison of adverse events, there were concerns that skin problems caused by food wraps and perforated polyethylene used in the wrap therapy might occur, but in our research, no significant difference was identified with the results of the conventional treatments. Rashes due to adhesive plasters and tape were identified in four cases in the

conventional cohort, but none were observed in the wrap therapy cohort. This is thought to be because it is basically possible to implement wrap therapy merely by making the patient wear paper diapers without affixing tape after applying the dressing.

Strengths and weakness of the study

This research is the world's first randomized controlled trials that comparing conventional treatments and wrap therapy. The conclusions obtained will greatly influence pressure ulcer care methods in the future. Theoretical superiority of wrap therapy to conventional treatments conforming to guidelines is the simplicity and cost effectiveness of the treatment[20,26]. Conventional treatments require the use of multiple ointments and dressings of suitable size and type, and the treatment requires a certain level of specialist skills. The simplicity of treatment protocols using wrap therapy might better promote the spread of care skills. Regarding cost effectiveness, the various ointments and dressings such as hydrocolloid used in pressure ulcer treatments are often expensive, but the perforated polyethylene and diaper sheets used in wrap therapy can be supplied at less than ten cents per treatment. If the accelerated pressure ulcer healing effects of wrap therapy are the same as those of conventional treatments, the efficiency of wrap therapy is presumably extremely great when considering cost effectiveness. Larger scale additional tests strengthening the verified backing of these research results could offer new, simple and effective methods of pressure ulcer care and noticeably improve the benefits to both patients and society.

This research, on the other hand, has some limitations. The greatest concern was impossibility of blindness of the treatment. Without blindness, health staff may have biases on the treatments themselves and wound evaluations. To minimize observation bias, we attempted to eliminate bias occurring during the evaluations by combining all the outcomes in a single outcome evaluation centre as far as possible. The second limitation resulted in bias among the participating facilities. Wrap therapy is currently viewed as an alternative treatment of choice. The facilities that participated in this research currently use wrap therapy clinically under this present condition, and the possibility of wrap therapy effects being overvalued beforehand cannot be denied.

Meaning of the study

The results we found could be called the high quality evidence to date from among the evidence that supports the safety and efficacy of wrap therapy, which have been reported many times in Japanese academic conferences concerned with wound healing and treatment of the elderly. In future, as the rapid aging of the population progresses worldwide, the problem of caring for the frail elderly in Japan, which has the highest rate of population aging in the world, will become a highly compelling problem in the societies of Europe and North America. Wrap therapy may be an epoch-making method of treatment and the verification of its usefulness by clinical experiment is thought to be a major advance for the future elderly care.

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Trial registration: UMIN Clinical Trials Registry UMIN000002658. Summary protocol is available on https://upload.umin.ac.jp/cgi-bin/ctr/ctr.cgi?function=brows&action=brows&type=detail&recptno=R000003235&admin=0&language=J

Contributors: SB conducted literature review, developed the initial protocol, examined statistical analysis and drafted the manuscript. AM wrote grant application, recruited collaboration facilities, developed intervention protocol and planned research meeting and startup meeting. SO contributed to research design, reviewed and amended the research protocol including intervention protocol and contributed to enrolment of patients. KT also contributed to research design, reviewed and amended the research protocol and contributed to enrolment of patients. MS contributed to research design, reviewed and amended the research protocol. KA contributed to enrolment of patients. KK contributed to research design and enrolment of patients. KM managed an outcome evaluation centre.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Japanese Academy of Family Medicine Ethics Review Board examined and approved our research plan and informed consent process in October, 2009.

Data sharing: no additional data available

Table 1: Patient Characteristics and Health Status, and Pressure Ulcer Status at Registration (n=64)

	Conventional Treatment Cohort (n=29)	Wrap Therapy Cohort (n=35)	P value
Mean Age (years)	82±10	81±12	0.60
Sex (Female Percentage)	48	54	0.28
Nutrition Absorption Status (Each %) Oral Nutrition Enteral Alimentation: Nasally Enteral Alimentation: Gastrostoma Central Venous Nutrition	 52 0 38 10	 49 9 40 3	0.27
Use of Pressure-Resistant Diffusion Mattress (Percentage 'Yes')	93	100	0.20
Use of Diapers (Percentage 'Yes')	90	91	0.97
Depth of Target Pressure Ulcer NPUAP Class II (%) NPUAP Class III (%)	 28 72	 11 89	0.09
Pressure Ulcer Pockets (% Present)	38	34	0.28
Calories Absorbed (Each %) Over 1200kcal 800kcal to 1200kcal 600kcal to 800kcal	 45 45 10	 49 37 9	0.58
Serum Albumin (Mean ± SD)	2.8±0.5	2.9±0.5	0.61
Serum Creatinine (Mean ± SD)	0.66±0.3	0.64±0.3	0.77

Braden Scale at Registration (Mean ± SD)	12.8±3.5	12.7±2.8	0.89
PUSH Score at Registration (Mean ± SD)	10.8±2.6	10.7±2.7	0.91
Pressure Ulcer Surface Area at Registration (Mean ± SD)	14±21	15±25	0.79
Use of ointments or sprays including pharmaceuticals with tissue regeneration accelerant actions	21	14	0.006
Percentage using hydrocolloids, hydrogels, or polyurethane foam as a pressure ulcer dressing	76	3	<0.0001

Table 2: Comparison of the mean reduction in PUSH scores for both cohorts for two weeks immediately after the start of observations, between two to four weeks, four to six weeks, six to eight weeks, eight to ten weeks and ten to 12 weeks, respectively. See separate appendix.

	0 to 2W	**2W to 4W**	**4W to 6W**	**6W to 8W**	**8W to 10W**	**10W to12W**
n	54	45	34	25	18	11
Control: Mean [95% CI]	1.8 [1.0-2.6]	0.4 [0.0-0.9]	0.7 [0.1-1.3]	0.8 [0.1-1.5]	0.3 [-0.1-0.7]	1.0 [0.1-1.9]
Wrapp therapy: Mean [95% CI]	1.8 [1.0-2.6]	0.4 [-0.2-1.0]	0.1 [-0.4-0.6]	0.3 [-0.2-0.8]	0.4 [-0.2-1.0]	0.5 [-0.1-1.1]
P value*	0.77	0.44	0.24	0.43	0.79	0.54

* tested by Mann-Whiteney U test

Fig. 1-1

Fig. 1-2

Fig. 1-3

Figure 2. Study flow diagram

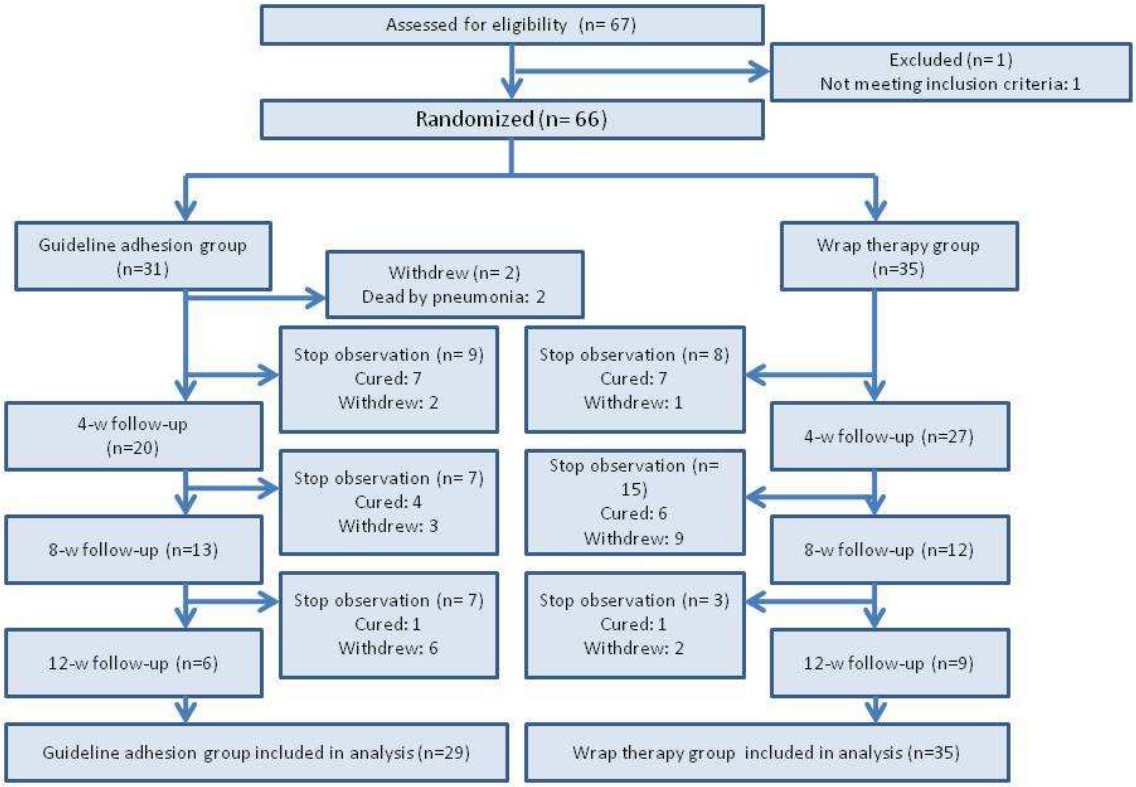


Fig. 3

Fig. 3-1: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - All Cases

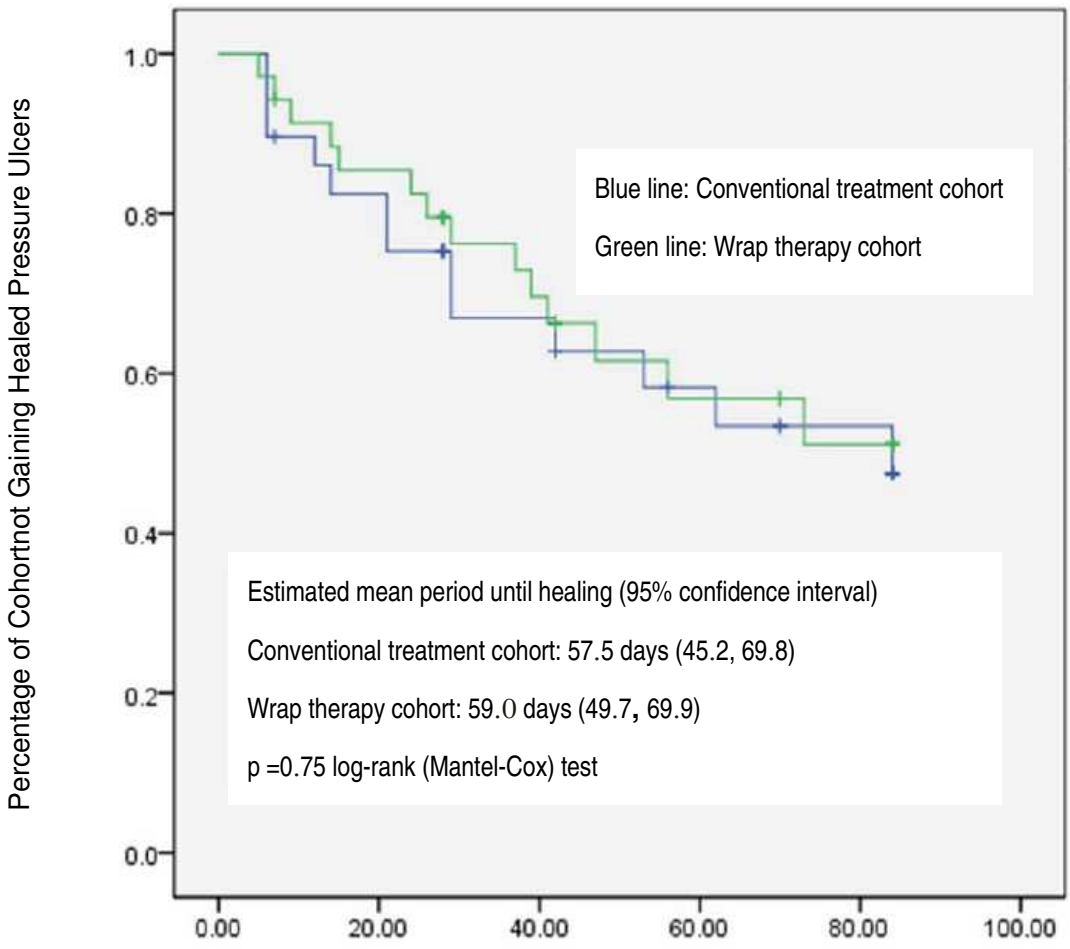


Fig. 3-2: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - NPUAP Class II Pressure Ulcers Cohort

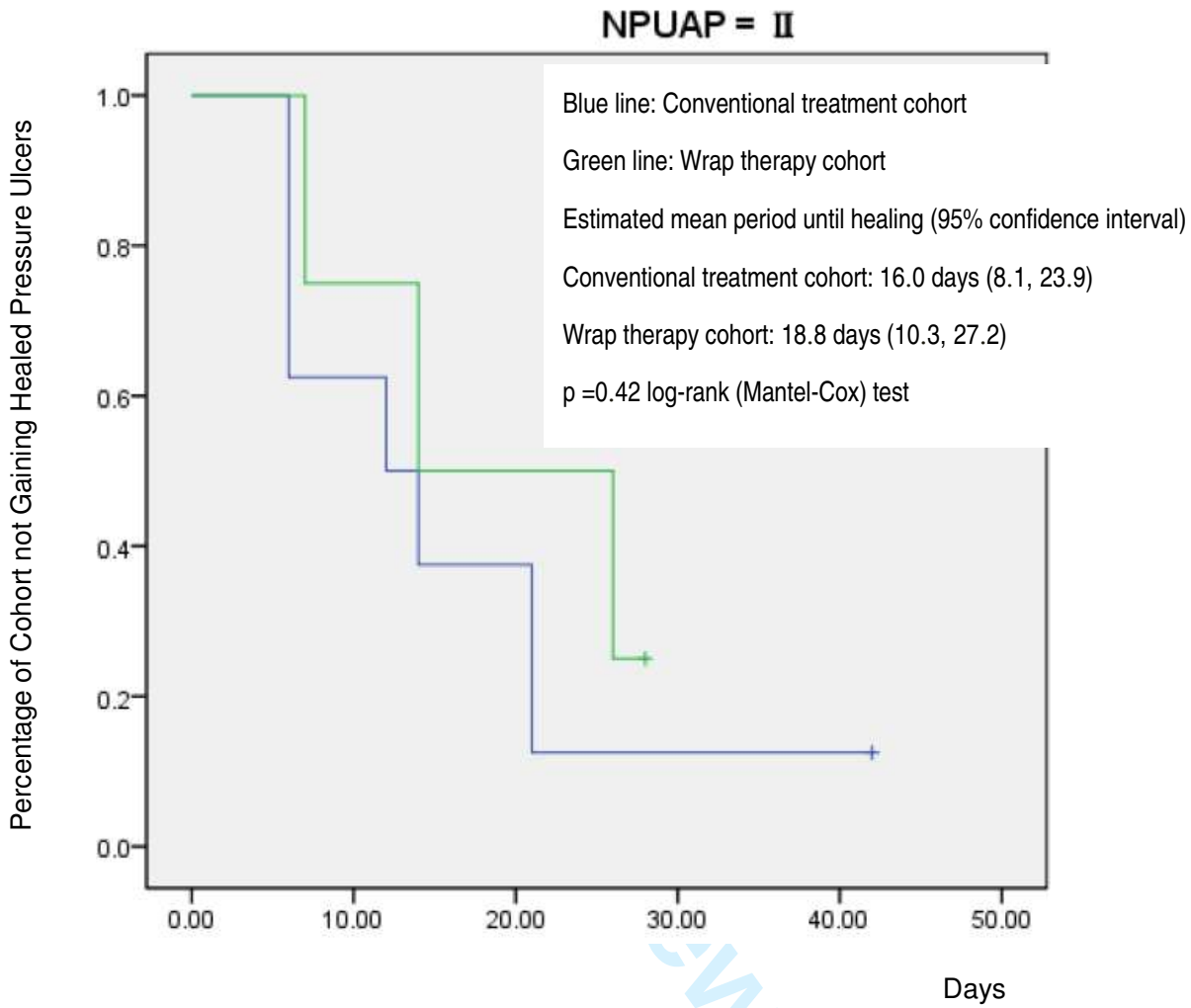
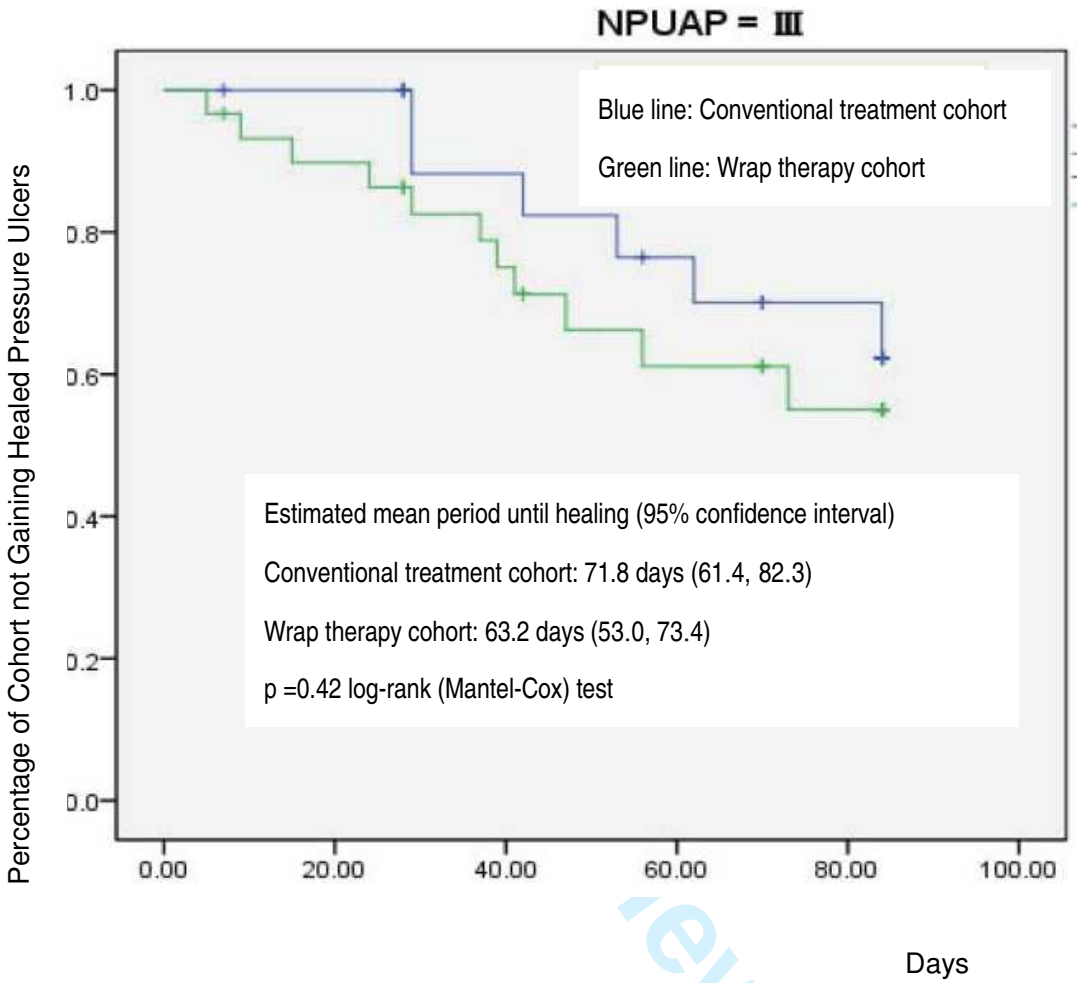


Fig. 3-3: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - NPUAP Class III Pressure Ulcers Cohort



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	18
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	4

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7, 13-14
	13b	For each group, losses and exclusions after randomisation, together with reasons	7, 18
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7, 8
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13-14
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	18
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7-8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7-8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9-10
Other information			
Registration	23	Registration number and name of trial registry	11
Protocol	24	Where the full trial protocol can be accessed, if available	11
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Randomized Controlled trial evaluating the Efficacy of Wrap Therapy for Wound Healing Acceleration in NPUAP Stage II and III Pressure Ulcer Patients

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Randomized Controlled trial evaluating the Efficacy of Wrap Therapy for Wound Healing Acceleration in NPUAP Stage II and III Pressure Ulcer Patients

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Abstract

Objectives: To evaluate if 'wrap therapy' using food wraps, which is widely used in Japanese clinical sites, is not inferior when compared to guideline adhesion treatments.

Design: Multi-centre, prospective, randomized, open blinded endpoint clinical trial.

Setting: Fifteen hospitals in Japan

Patients: Sixty-six elderly patients with new NPUAP Stage II or III pressure ulcers.

Interventions: Out of these 66 patients, 31 were divided into the conventional treatment guidelines group and 35 into the wrap therapy group.

Main outcome measures: The primary end point was the period until the pressure ulcers were cured. The secondary end point was a comparison of the speed of change in the Pressure Ulcer Scale for Healing (PUSH) score.

Results: Sixty-four of the 66 patients were analysed. The estimated mean period until healing was 57.5 days [95% confidence interval (CI) 45.2–69.8] in the control group as opposed to 59.8 days (95% CI 49.7–69.9) in the wrap therapy group. By the extent of pressure ulcer infiltration, the mean period until healing was 16.0 days in the control group (95% CI 8.1–23.9) as opposed to 18.8 days in the wrap therapy group (95% CI 10.3–27.2) with NPUAP Stage II ulcers, and 71.8 days (95% CI 61.4–82.3) as opposed to 63.2 days (95% CI 53.0–73.4), respectively, with Stage III ulcers. There is no statistical significance in difference in PUSH scores.

Conclusions: It might be possible to consider wrap therapy as an alternative choice in primary care settings as a simple and inexpensive dressing care.

Trial registration: UMIN Clinical Trials Registry UMIN000002658

Article Summary

Article focus

- 'Wrap therapy' is a method for localized care of pressure ulcers using polyethylene sheets, such as in food wraps, to the pressure ulcers. There are numerous case reports promoting efficiency of this therapy in Japan.
- We hypothesized non-inferiority of the efficacy of wrap therapy on adult patients with pressure ulcers classified as National Pressure Ulcer Advisory Panel (NPUAP) Stage II or III comparing with that of guideline adhesion treatment to Japanese patients.

Key messages

- The survival curves did not showed the inferiority of wrap therapy comparing with guideline adhesion treatment on the period until the pressure ulcers healed.
- The result of this study imply clinical utility of wrap therapy which have been reported many times in Japanese academic conferences concerned with wound healing and treatment of the elderly. Bigger sample trials are necessary to confirm this implication as rigorous clinical evidence.

Strengths and limitations of this study

- This study is the first study revealing the efficacy of wrap therapy, that is inexpensive and simple for home care, using RCT design.
- Relatively weak statistical power and impossibility of blindness of the treatment.

INTRODUCTION

Among the health problems specific to the frail elderly, pressure ulcers[1-3]has been a major health problem, and the establishment and spread of an effective treatment method for it has been a pressing issue. After guideline publication by Agency for Health Care Policy and Research[4], there have been few standard policy announcements regarding localized treatments with high evidence levels[5,6]. The Japanese Society of Pressure Ulcers (JSPU) published its 'Evidence-Based Localized Pressure Ulcer Treatment Guidelines' in 2005, and treatments based on these have become the conventional treatments in Japan[7]. According to the guidelines, overall complex treatments aiming to debride necrotic tissue and reduce the ulcers are recommended for deep pressure ulcers. However, the recommendation grades regarding individual ointments and dressings, physical treatments, and surgical treatments are low level. Several intervention researches have been performed on specific drugs in localized treatments, but few clinical breakthrough methods have been discovered in the effects of these interventions[8-14].

'Wrap therapy' is a method for localized care of pressure ulcers through which healing can be expected based on the natural healing effects by applying polyethylene sheets, such as in food wraps, to the pressure ulcers. This method has spread following its proposal by Toriyabe Shunichi[15]. On the effectiveness of wrap therapy in treating pressure ulcers, and of their simplicity and low cost, there are numerous case reports and case series research supporting no-inferiority of wrap therapy in Japan[16-20]. On March 2010, JSPU approved wrap therapy as one of the first treatment choices in limited situations.

Our purpose is to evaluate the efficacy of wrap therapy on adult patients with pressure ulcers classified as National Pressure Ulcer Advisory Panel (NPUAP) Stage II or III on their backs using the current conventional treatment in Japan, described in the guideline published by JSPU, as a control. If this research verifies that wrap therapy is not harmful and has equivalent or better efficacy compared to conventional treatments, a low-cost treatment method can be well applied to the care of the elderly.

METHODS

Study Design and Setting

The study evaluated outcomes and analysis of the prospective randomized open blinded endpoint trial at numerous facilities. For this study, we recruited facilities by appealing to them for participation via mailing lists related to JSPU and those regarding pressure ulcer diagnosis and treatment. To assure implementation of the research work, we set the following as suitable standards for the facilities sharing the work: facilities that were able to use body pressure diffusion mats for pressure ulcer patients, facilities with experience of wrap therapy on some patients, the existence of care systems for pressure ulcer care and environments that were able to perform pressure ulcer treatments during hospitalization. Fifteen hospitals finally were identified to be eligible facilities.

Patients and randomization

For patient registration, we set the following inclusion and exclusion criteria: patients aged 50 or over with one or more NPUAP Stage II or III pressure ulcers on either their torso or trochanter, body temperature of 35.5°C min. to 37.5°C max., 600kcal or over daily intake, no critical nutritional impairment, renal failure, cirrhosis, immunosuppression, uncontrollable diabetes, or malignant tumours according to an examination performed within past four weeks. End-of-life patients whose estimated alive period were less than three months were excluded. When the patient did not possess the ability to make the autonomous decision to participate in the study, the outline and methods of the research were explained to their representing immediate family member, from whom written consent was obtained. After obtaining written consent, then uncoordinated random allocations were performed at the registration centre in the research office within 24 hours.

Prospective, Randomized, Open, Blinded-Endpoint design was applied for this study because blinding two different interventions was impossible in clinical setting. We adopted non-stratified pure random allocation for randomization of the enrolled patients. If health staff obtained informed consent from eligible patients, then they send fax to the allocation centre located at Higashi-Washinomiya Hospital with basic information including location and stage of pressure ulcers. The allocation centre finally decided eligibility and inform

registration confirmation and allocation results to the facilities by fax within 48 hours of the reception.

Interventions

Wrap therapy was defined as a method of treatment that uses food wraps and perforated polyethylene as a wound dressing. In many cases, wrap therapy follows the procedure of thoroughly irrigating the pressure ulcers (Fig. 1-1) before directly covering the pressure ulcers with food wrap if the exudation is small, or with commercially available perforated polyethylene sheets and diapers, or with a cover sheet combined with sanitary towels if the exudation is great (Figs. 1-2 and 1-3). Irrigation and the covering process are performed every day[21].

To standardize the categories and treatment procedures of wrap therapy as much as possible, a meeting for instruction of interventions was held beforehand. A DVD of the lecture was distributed to the physicians that were unable to participate in the instruction meeting.

Patients allocated to the control group were treated using methods conforming the 'Evidence-Based Localized Pressure Ulcer Treatment Guidelines' issued by JSPU[7]. These guidelines are diagnosis and treatment guidelines created by JSPU based on current diagnosis and treatment evidence.

Outcomes evaluated

The primary endpoint was defined as the period from the start of registration until the pressure ulcers that had been the subject of observation for three months were healed. After the patient had been discharged from the hospital, continuous observation was performed as far as possible through diagnosis and treatment at home. Every wound heal was confirmed by supervising physicians. As the secondary endpoint, we measured the PUSH score for the localized status of the pressure ulcers as defined by NPUAP at two, four, six, eight, ten and 12 weeks from the start of registration[22].

Method for blinded end point evaluation

To avoid the occurrence of observation bias, we established an 'outcome evaluation centre'. Digital camera images were sent from every facility to the outcome evaluation centre, and all outcomes were evaluated there. The outcome evaluation centre was blinded so as not to know the treatment group to which the subject belonged. Because it was impossible to evaluate the exudates amount using images, records were made by the observer directly. In case the outcome evaluation centre found some problems that excuse the leakages of blindness, then that was reported to the administration office immediately.

We also recorded the total amount of ointment used in localized treatments during the observation period, and performed rough calculations with regards to cost.

Adverse Events and Role of the Patient Safety Monitoring Board

A safety evaluation committee was established comprising several specialists and non-specialists. The members were independent from the patient registration, research offices and the outcome evaluation centre. In all cases of death, worsening of the pressure ulcers during the research period, systemic deterioration or sepsis occurring within 30 days from the day of the protocol treatment, and when the connection to the pressure ulcers was undeniable, researchers sharing the research at the core facilities reported to the committee.

Statistical Analysis

We aimed to clarify our statistical hypothesis that wrap therapy was not inferior compared to conventional treatments conforming to the guidelines. The mean period until healing for the localized treatment of Stage II pressure ulcers was set as 21 days based on previous literature[9-14]. The non-inferior threshold was set at seven days according to clinical judgment. When set to a tolerable threshold difference of 7 days when one side has a 5% significance level and a test power of 90%, the required number of cases in the two cohorts was 80. Similarly, the required number of cases for Stage III pressure ulcers was 60. For the total number of target cases, 140 was set as the number of target registered patients. The analysts were blinded about which group was the wrap therapy or the conventional treatment until

the analysis was finished. Intention to treat analysis was performed.

For the main endpoint comparisons, a Kaplan-Meier plots were created and the estimated mean value until the endpoint occurrence and its 95% confidence interval (CI) were calculated. The differences in the PUSH scores were calculated from two weeks immediately after the start of observations, between two to four weeks, four to six weeks, six to eight weeks, eight to ten weeks and ten to 12 weeks, and described the speed of pressure ulcer healing over time for both groups. We used PASW Statistics 18 (SPSS, Inc) for the statistical analysis.

RESULTS

We started recruitments in October, 2009 and followed until May, 2010. The study flow diagram is shown in Fig. 2. During the research period, a total of 66 patients participated. Of these, two could not be followed up due to early discharge or transfer to another hospital. A total of 64 participants were analysed: 29 in the conventional treatment group and 35 in the wrap therapy group. The percentage of patients whose endpoints could be pursued four weeks after registration was 95%, eight weeks after registration was 77% and 12 weeks after registration was 64%.The characteristics distribution of the patients analysed was 33 females and 29 males, and the locations of the target pressure ulcers were most common on the sacrum (56%), followed by the trochanter (13%), gluteus (6%) and the coccyx (5%).

Table 1 shows a comparison of the patients' characteristics distribution, their health at registration, the status of their pressure ulcers and the treatment method for the two groups. The mean values in the conventional treatment and wrap therapy cohorts were 12.7 versus 12.7 for the Braden Scale at registration[23].The percentages using hydrocolloids, hydrogels or polyurethane foam as pressure ulcer dressings were 76% in the control group and 3% in the intervention cohort.

Time until the Pressure Ulcers Healed

The percentage of patients in whom healing of the pressure ulcers was verified from among the samples that could be followed up at four weeks after registration were 26% of the conventional group as opposed to 21% in the wrap therapy group; at eight weeks after

registration the percentages were 46% in the conventional group as opposed to 52% in the wrap therapy group.

Fig. 3-1 shows the survival curves of both groups. The mean of the estimated value until healing was 57.5 days (95% CI 45.2 days; 69.8 days) for the conventional group as opposed to 59.8 days (95% CI 49.7 days; 69.9 days) for the wrap therapy group. Fig. 3-2 and Fig. 3-3 describes the survival curve for the patients with NPUAP Stage II and III pressure ulcers, respectively. For Stage II pressure ulcers, the estimated mean value until healing were 16.0 days (95% CI 8.1 days; 23.9 days) for the conventional group compared to 18.8 days (95% CI 10.3 days; 27.2 days) for the wrap therapy group. Meanwhile, for Stage III pressure ulcers, the estimated mean value until healing were 71.8 days (95% CI 61.4 days; 82.3 days) for the conventional group compared to 63.2 days (95% CI 53.0 days; 73.4 days) for the wrap therapy group.

Speed of Pressure Ulcer Healing Using PUSH Scores

The mean values of the difference in the PUSH scores at registration and upon either healing or the final observation divided by the treatment period were 1.1±2.1 points in the conventional group and 0.9±1.3 points in the wrap therapy group (p= 0.73 Student's t-test). No significant difference was identified in the mean PUSH score reduction values in either cohort from immediately after the start of observations to the second week, from the second to the fourth week, from the fourth to the sixth week, from the sixth to the eighth week, from the eighth to the tenth week and from the tenth to the twelfth week (Table 2).

Adverse Events

During the total observation period, there was systemic worsening such as pneumonia, occurring immediately after the start of observation in three cases in the conventional group, and four cases in the wrap therapy group. Two cases in the conventional group died of pneumonia and one died from heart failure for a total of three deaths. In the wrap therapy group, one patient died of pneumonia and one of senescence for a total of two deaths. Regarding localized adverse events, there were problems with the covered skin (eczema, maceration, rash, etc.) in the conventional group and six cases in the wrap therapy group.

DISCUSSIONS

Statement of principal findings

'Wrap therapy' has already been introduced nationwide in Japanese clinical facilities. The main reasons for its spread in clinical settings are both that wrap therapy is a rational treatment method compared to basic wound-healing therapies, in that it is possible to maintain a lubricated environment without applying stress to the wound[24,25], and because compared to complex pressure ulcer treatments that combine various ointments and dressings, it has frequently been recognized empirically in actual clinical settings as having equal or better effects in treating pressure ulcers.

Looking only at the main outcome survival curves, and taking all the patients into consideration, almost identical results were obtained in both the wrap therapy and conventional treatment groups for the period until the pressure ulcers healed. Meanwhile, when the two treatment groups are compared using the NPUAP classification, although no clear difference between the survival curves of the two treatments were identified with shallow Stage II pressure ulcers, in the comparison between the Stage III pressure ulcer cohorts, the survival curve of the wrap therapy cohort showed that healing tended to be faster than in the conventional treatment cohort. No statistical significance, however, was presented in this study. We can't state so far that wrap therapy should be chosen as the first recommended therapy to shorten the healing time of pressure ulcer. Further study with bigger sample is needed to ensure these visual differences in survival curves. Nor was any significant difference identified between the wrap therapy and conventional treatment cohorts regarding the extent of PUSH score reduction either, and this result can also be stated to support the fact that wrap therapy is not inferior to conventional treatments. Nevertheless, initially we estimated 80 cases and 60 cases in the NPUAP classification subgroups as the non-inferior estimate, but on this occasion, the total effective sample, at 64 cases, lacked sufficient statistical power.

During the comparison of adverse events, there were concerns that skin problems caused by food wraps and perforated polyethylene used in the wrap therapy might occur, but in our research, no significant difference was identified with the results of the conventional treatments. Rashes due to adhesive plasters and tape were identified in four cases in the

conventional cohort, but none were observed in the wrap therapy cohort. This is thought to be because it is basically possible to implement wrap therapy merely by making the patient wear paper diapers without affixing tape after applying the dressing.

Strengths and weakness of the study

This research is the world's first randomized controlled trials that comparing conventional treatments and wrap therapy. Theoretical superiority of wrap therapy to conventional treatments conforming to guidelines is the simplicity and cost effectiveness of the treatment[20,26]. Conventional treatments require the use of multiple ointments and dressings of suitable size and type, and the treatment requires a certain level of specialist skills. The simplicity of treatment protocols using wrap therapy might better promote the spread of care skills. Regarding cost effectiveness, the various ointments and dressings such as hydrocolloid used in pressure ulcer treatments are often expensive, but the perforated polyethylene and diaper sheets used in wrap therapy can be supplied at less than ten cents per treatment. If the accelerated pressure ulcer healing effects of wrap therapy are the same as those of conventional treatments, the efficiency of wrap therapy is presumably extremely great when considering cost effectiveness. Larger scale additional tests strengthening the verified backing of these research results could offer new, simple and effective methods of pressure ulcer care and noticeably improve the benefits to both patients and society.

This research, on the other hand, has some limitations. The greatest concern was impossibility of blindness of the treatment. Without blindness, health staff may have biases on the treatments themselves and wound evaluations. To minimize observation bias, we attempted to eliminate bias occurring during the evaluations by combining all the outcomes in a single outcome evaluation centre as far as possible. The second limitation resulted in bias among the participating facilities. Wrap therapy is currently viewed as an alternative treatment of choice. The facilities that participated in this research currently use wrap therapy clinically under this present condition, and the possibility of wrap therapy effects being overvalued beforehand cannot be denied.

Practical applications

When we consider clinical application of wrap therapy, we should pay some attentions. First, because wrap therapy is simple and inexpensive method, it may be accepted for practical application in home care and primary care setting. Many primary care physicians and nurse practitioners are not familiar with complex protocols using new-coming modern dressings, which have additional advantages for quality of life for patients, and wrap therapy may be a useful application as an initial intervention for pressure ulcers. If wrap therapy is not effective, then using other modern dressings should be considered. Second, this attractive method has ethical concerns. Wrap therapy is not be approved as a formal medical intervention which is covered social health insurance in Japan. Because this therapy uses food wrapping sheet without sterilization, approval as an insured health intervention by Japanese Ministry of Health, Labour and Welfare is difficult. All devises for wrap therapy are so far prepared by health providers as voluntary actions. Even this therapy is useful for home-care setting, it should be examined under supervision of well-trained health professionals.

Meaning of the study

Even though our conclusions failed empirical statement of effectiveness of wrap therapy directly, the results would not deny actual situations in current Japanese clinical settings. In future, as the rapid aging of the population progresses worldwide, the problem of caring for the frail elderly in Japan, which has the highest rate of population aging in the world, will become a highly compelling problem in the societies of Europe and North America. Wrap therapy may be an epoch-making method of treatment and the verification of its usefulness by clinical experiment is thought to be a major advance for the future elderly care.

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Trial registration: UMIN Clinical Trials Registry UMIN000002658. Summary protocol is available on https://upload.umin.ac.jp/cgi-bin/ctr/ctr.cgi?function=brows&action=brows&type=detail&recptno=R000003235&admin=0&language=J

Contributors: SB conducted literature review, developed the initial protocol, examined statistical analysis and drafted the manuscript. AM wrote grant application, recruited collaboration facilities, developed intervention protocol and planned research meeting and startup meeting. SO contributed to research design, reviewed and amended the research protocol including intervention protocol and contributed to enrolment of patients. KT also contributed to research design, reviewed and amended the research protocol and contributed to enrolment of patients. MS contributed to basic concept of research design, reviewed and amended the research protocol. KA contributed to enrolment of patients and acquisition of data. KK contributed to research design and enrolment of patients. KM managed an outcome evaluation centre. All authors meet ICMJE authorship criteria for inclusion.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Japanese Academy of Family Medicine Ethics Review Board examined and approved our research plan and informed consent process in October, 2009.

Data sharing: no additional data available

Table 1: Patient Characteristics and Health Status, and Pressure Ulcer Status at Registration (n=64)

	Conventional Treatment Cohort (n=29)	Wrap Therapy Cohort (n=35)	P value
Mean Age (years)	82±10	81±12	0.60
Sex (Female Percentage)	48	54	0.28
Nutrition Absorption Status (Each %)	52	49	0.27
Oral Nutrition	0	9	
Enteral Alimentation: Nasally	38	40	
Enteral Alimentation: Gastrostoma	10	3	
Central Venous Nutrition			
Use of Pressure-Resistant Diffusion Mattress (Percentage 'Yes')	93	100	0.20
Use of Diapers (Percentage 'Yes')	90	91	0.97
Depth of Target Pressure Ulcer			
NPUAP Class II (%)	28	11	0.09
NPUAP Class III (%)	72	89	
Pressure Ulcer Pockets (% Present)	38	34	0.28
Calories Absorbed (Each %)			
Over 1200kcal	45	49	0.58
800kcal to 1200kcal	45	37	
600kcal to 800kcal	10	9	
Serum Albumin (Mean ± SD)	2.8±0.5	2.9±0.5	0.61
Serum Creatinine (Mean ± SD)	0.66±0.3	0.64±0.3	0.77
Braden Scale at Registration	12.8±3.5	12.7±2.8	0.89

(Mean ± SD)			
PUSH Score at Registration (Mean ± SD)	10.8±2.6	10.7±2.7	0.91
Pressure Ulcer Surface Area at Registration (Mean ± SD)	14±21	15±25	0.79
Use of ointments or sprays including pharmaceuticals with tissue regeneration accelerant actions	21	14	0.006
Percentage using hydrocolloids, hydrogels, or polyurethane foam as a pressure ulcer dressing	76	3	<0.0001

We used Student t-test for comparison of mean values of the two groups. Chi-square test was adopted for comparisons of frequency.

Table 2: Comparison of the mean reduction in PUSH scores for both cohorts for two weeks immediately after the start of observations, between two to four weeks, four to six weeks, six to eight weeks, eight to ten weeks and ten to 12 weeks, respectively. See separate appendix.

	0 to 2W	2W to 4W	4W to 6W	6W to 8W	8W to 10W	10W to12W
n	54	45	34	25	18	11
Control: Mean [95% CI]	1.8 [1.0-2.6]	0.4 [0.0-0.9]	0.7 [0.1-1.3]	0.8 [0.1-1.5]	0.3 [-0.1-0.7]	1.0 [0.1-1.9]
Wrapp therapy: Mean [95% CI]	1.8 [1.0-2.6]	0.4 [-0.2-1.0]	0.1 [-0.4-0.6]	0.3 [-0.2-0.8]	0.4 [-0.2-1.0]	0.5 [-0.1-1.1]
P value*	0.77	0.44	0.24	0.43	0.79	0.54

* tested by Mann-Whitney U test

Figure 2. Study flow diagram

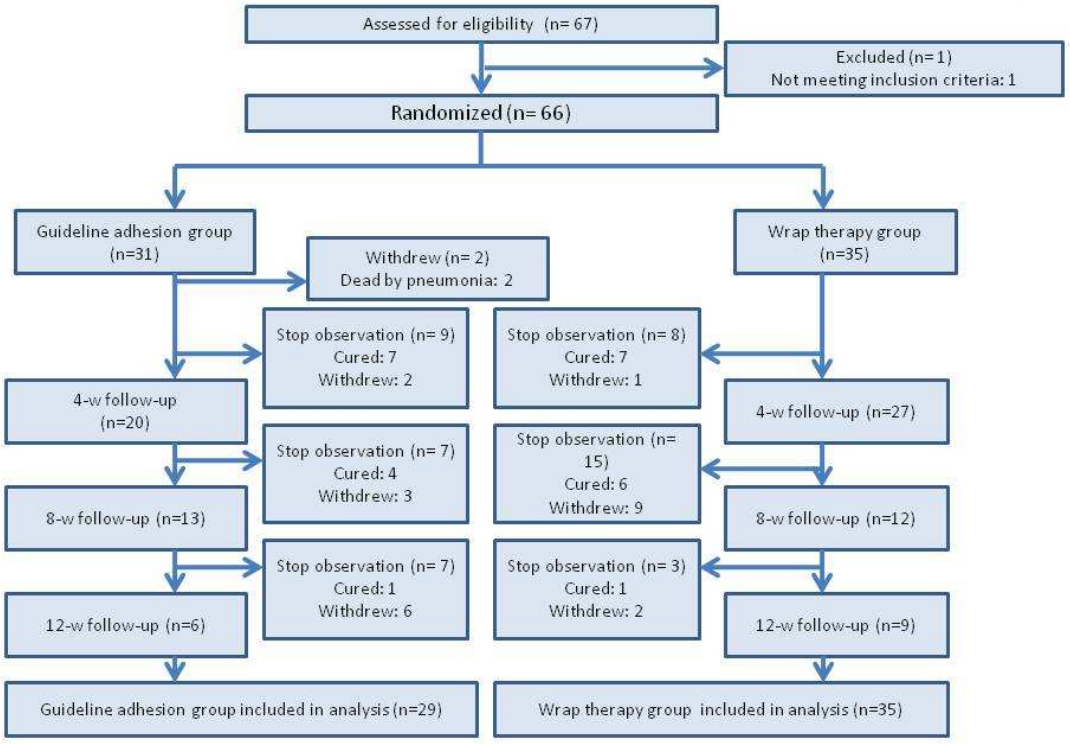
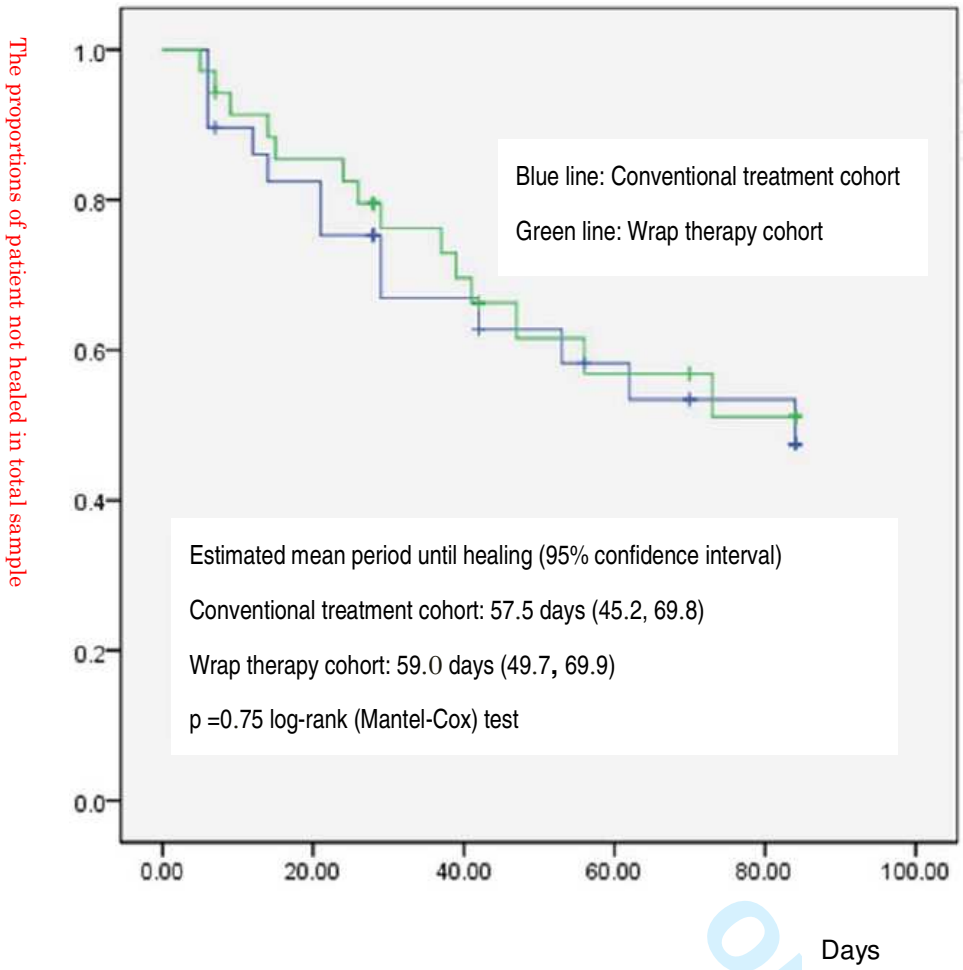


Fig. 3

Fig. 3-1: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - All Cases



Y axis means the proportion of patients that has not been confirmed healing of pressure ulcers. The distribution curves represent the results of an intention-to-treat survival analysis involving all patients in Fig. 3-1, NPUAP stage II patients in Fig. 3-2 and NPUAP stage III patients in Fig. 3-3.

Fig. 3-2: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - NPUAP Class II Pressure Ulcers Cohort

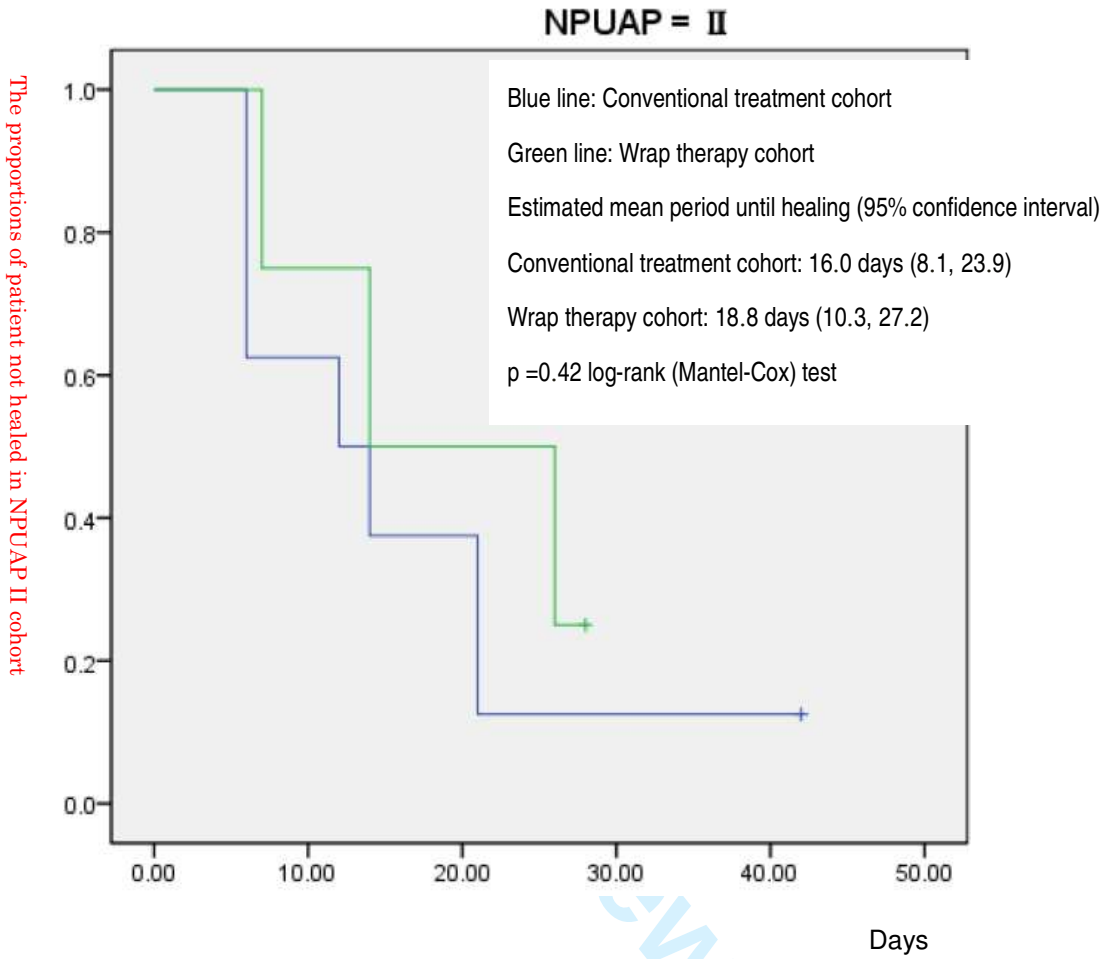
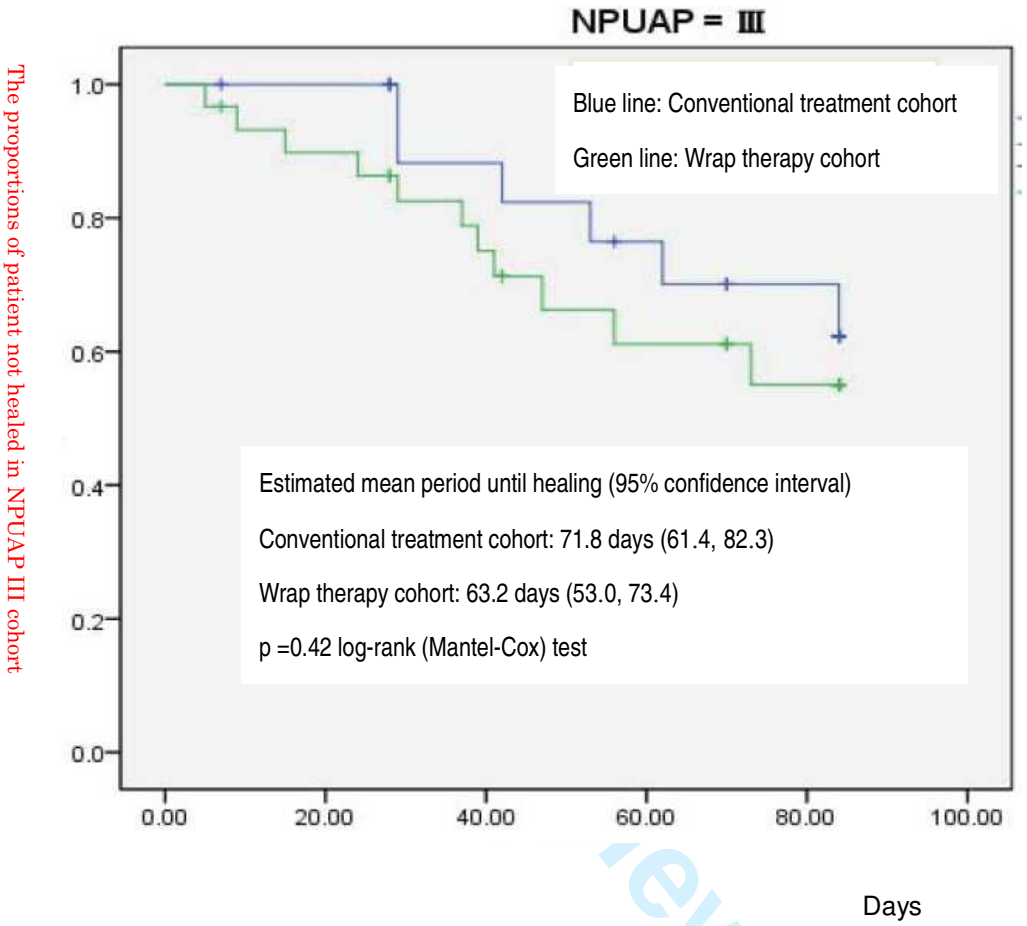


Fig. 3-3: Comparison of Survival Curves Using the Period until Pressure Ulcers Healing as the Endpoint - NPUAP Class III Pressure Ulcers Cohort



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CONSORT Statement 2006 - Checklist for Non-inferiority and Equivalence Trials

Items to include when reporting a non-inferiority or equivalence randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned"), *specifying that the trial is a non-inferiority or equivalence trial.*	1-2
INTRODUCTION Background	2	Scientific background and explanation of rationale, *including the rationale for using a non-inferiority or equivalence design.*	4
METHODS Participants	3	Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected.	5
Interventions	4	Precise details of the interventions intended for each group *detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered.	5-6
Objectives	5	Specific objectives and hypotheses, *including the hypothesis concerning non-inferiority or equivalence.*	4
Outcomes	6	Clearly defined primary and secondary outcome measures *detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	6
Sample size	7	How sample size was determined *detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules (*and whether related to a non-inferiority or equivalence hypothesis*).	7
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	5
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	5
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	5
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	7
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), *specifying whether a one or two-sided confidence interval approach was used.* Methods for additional analyses, such as subgroup analyses and adjusted analyses.	7-8
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	20
Recruitment	14	Dates defining the periods of recruitment and follow-up.	8
Baseline data	15	Baseline demographic and clinical characteristics of each group.	8
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was *"intention-to-treat" and/or alternative analyses were conducted.* State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	8

Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). *For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*	8,9,15-17,21
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	9,22,23
Adverse events	19	All important adverse events or side effects in each intervention group.	9
DISCUSSION Interpretation	20	Interpretation of the results, taking into account the *non-inferiority or equivalence hypothesis and any other* study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	10-11
Generalizability	21	Generalizability (external validity) of the trial findings.	12
Overall evidence	22	General interpretation of the results in the context of current evidence.	12

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Fig. 1-1

Fig. 1-2

Fig. 1-3