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Abstract
Objective
To determine the effect of noncontact normothermic wound therapy (NNWT) versus standard wound care on chronic full-thickness pressure ulcers.

Design
Prospective, randomized, controlled trial

Setting
Veterans administration medical center and 7 long-term-care facilities

Patients
40 inpatients with 43 Stage III and IV pressure ulcers

Interventions
A sterile noncontact wound dressing was applied to 21 wounds for 24 hours per day, 7 days per week. Each day after the wound was irrigated and the noncontact dressing was changed, a heating element in the dressing was activated for 3 1-hour periods for 12 weeks or until wound closure. Twenty-two control wounds were treated with standard, moisture-retentive dressings 24 hours per day, 7 days per week for 12 weeks or until wound closure.

Main Outcome Measure
Measurement of wound surface area

Main Results
Healing rate for the NNWT group was significantly greater than for the control group (0.52 cm^2 per week and 0.23 cm^2 per week, respectively;P <.02). A clinically significant increase was seen among the NNWT group in the incidence of closure among wounds that completed the entire 12-week protocol compared with controls (11 of 14 or 79% and 8 of 16 or 50%, respectively; not significant). The mean slope of the individual regression analyses for the NNWT group was significantly different from the mean slope for the control group (−0.07 and −0.033, respectively;P <.05). Large wounds in the NNWT group demonstrated a significantly greater healing rate than large wounds in the control group (P <.05).

Conclusion

Wounds treated with NNWT healed significantly faster than wounds in the control group. The healing rate was greatest for larger wounds treated with NNWT.

The primary response of human skin to locally applied external heat is an increase in capillary perfusion. [1] This occurs, along with augmented transport of oxygen and anabolic substrates, via the arterioles [2]; removal of catabolic waste products occurs via the venules. Millard [3] found that the rate of blood flow in the lower extremity in human skin varied directly with skin temperature. Ikeda et al [4] reported a 50% increase in subcutaneous oxygen tension above baseline in human thigh skin exposed to 38°C, 42°C, or 46°C for 2 hours. In addition, the elevation of oxygen tension was sustained following treatment at all 3 temperatures for 3 hours, despite the termination of externally applied heat.

Rabkin and Hunt [5] first reported the beneficial effect of local heat application to open wounds in hospitalized patients. In their study, local heat application was associated with a 3-fold increase in capillary flow and a mean increase in subcutaneous oxygen tension of 39.5 mm Hg. [5] Subcutaneous oxygen tension was correlated not only with an increase in perfusion, but with resistance to infection, occurring through oxidative killing by neutrophils of pathogens that colonize wounds. [6,7] This reported resistance to infection counters long-standing belief that increases in tissue moisture and temperature beneath occlusive dressings favor proliferation of bacteria and other infectious organisms. [8] In addition, Lee et al [9] demonstrated a significant reduction in the growth of *Staphylococcus aureus* following treatment of infected dermal flaps with a noncontact radiant heat dressing in an ovine model.

Elevation of tissue oxygen tension secondary to tissue warming has also been reported to accelerate wound healing by impacting collagen deposition [10] and scar tensile strength. [11] Other investigators have reported that chronic wound fluid taken from venous leg ulcers inhibits proliferation [12–14] and growth [15] of newborn dermal fibroblasts, in part, by modulating cell cycle-regulatory proteins, a response shown to be temperature sensitive. [16,17] Other data indicate that thermal wound therapy contributes to healing of chronic venous ulcers by counteracting the effects of chronic wound fluid on cell cycleregulatory proteins. [18] Warming chronic wound fluid to 38°C in vitro has been shown to reduce its inhibitory activity on newborn fibroblasts and to enhance the growth of adult fibroblasts. [12] A related study reported that in vitro warming of human dermal fibroblasts produced a 30% increase in cell counts compared with control plates. [17] The same investigators reported that metabolic activity in the warmed cells was 47% to 90% higher than in the control cells. Other investigators have recently demonstrated significant increases in proliferation of endothelial cells exposed to radiant heat at 38°C and 42°C in vitro. [19] They suggested that warming these cells in vivo may enhance formation of granulation tissue in wounds that heal by secondary intention.

Several other clinical studies have reported positive outcomes following warming of chronic wounds with noncontact radiant heat. [20–24] In 2 of these studies, venous leg ulcers warmed with noncontact radiant heat progressed toward healing at a significantly greater closure rate when compared with control wounds. [20,21] Three other studies compared warming therapy with standard wound care on

healing of Stage III and IV pressure ulcers (PrUs). [22–24] In a 6-week randomized trial of 50 patients, Price et al [22] reported an accelerated healing rate among PrUs treated with warming therapy versus standard care alone. The difference in time to closure was clinically significant at 75% wound closure (P <.057) and statistically significant at 50% wound closure (P <.039) and 25% wound closure (P <.01). In a 4-week nonrandomized trial, Kloth et al [23] found that 15 PrUs treated with warming therapy plus standard care underwent a statistically significant reduction in mean surface area of 61%; 6 control PrUs that received standard care alone underwent a statistically insignificant reduction in mean surface area of 19%. In an 8-week randomized study, Whitney et al [24] evaluated the linear healing rate of wound edges in 15 patients whose PrUs were treated with warming therapy and 14 whose PrUs received standard care only. The researchers reported significantly faster healing in the group treated with heat (P <.01).

Collectively, the responses to cell and tissue warming reported in basic science studies and the outcomes of clinical trials suggest that externally applied local heat may accelerate the healing rate of recalcitrant PrUs faster than standard care alone.

Pressure Ulcers And NNWT

Pressure ulcers frequently occur in individuals with diagnoses that cause a significant reduction in mobility, including those with Alzheimer's disease or dementia, femoral neck fracture, spinal cord injuries, cerebral vascular infarctions, head trauma, multiple sclerosis, and Parkinson's and other diseases of the central nervous system. [25] In 1989, the National Pressure Ulcer Advisory Panel (NPUAP) set a national goal for the ensuing decade to decrease the incidence of PrUs by 50%. [26] To determine whether this goal was achieved, the NPUAP disseminated the results of a comprehensive literature review of PrU prevalence and incidence data published during the last decade. [27] This publication cites upper limits of 29% for prevalence and 40% for incidence for Stage I to IV PrUs. These rates reflect evidence of the clinical dilemma PrUs create in terms of patient quality of life, morbidity, mortality, cost of treatment, and length of stay in a health care facility. [28,29] Mean adjusted hospital costs associated with PrUs that developed during hospitalization have been reported to increase approximately 2.7 times, from $13,924 to $37,288. [29] In the same report, mean lengths of stay increased approximately 2.4 times, from 12.8 days to 30.4 days. In the United States, the estimated national cost of treating PrUs exceeds $1.3 billion annually [30]; therefore, there is a great need for interventions that significantly decrease the time to close these chronic wounds.

To determine the effect of NNWT alone versus standard wound care alone on full-thickness PrUs, a 12-week study was undertaken. NNWT (Warm-Up; Augustine Medical, Inc, Eden Prairie, MN) is designed to transmit constant, radiant heat at 38°C to wound and periwound tissues. NNWT utilizes a noncontact sterile wound cover and warming unit that maintains 100% relative humidity in the wound and restores periwound and wound temperatures toward normothermia. [15]

Methods

The study was conducted in Milwaukee, WI, at the Zablocki Veterans Administration Medical Center and 7 long-term-care facilities. Institutional review board (IRB) approval was obtained from the Office of Research and Sponsored Programs at Marquette University, from the Veterans Administration Medical Center, and from the 7 IRB committees responsible for overseeing human research at the

participating long-term-care facilities. Informed consents were obtained from all patients or their designated representatives.

Patients were excluded if they had poorly controlled diabetes, a terminal illness, wound undermining greater than 1.0 cm, clinical signs of infection, more than 50% of the wound bed covered with necrotic tissue after debridement, or an allergy to adhesives. Fifty-three patients with 56 Stage III and IV PrUs were recruited. Of these 56 wounds, 13 were omitted from the study prior to completing 3 weeks of the protocol. Ten subjects were omitted due to death or deterioration in their general medical condition unrelated to treatment and 3 were nonadherent with the protocol.

Of the remaining 43 wounds, 6 control wounds and 7 wounds treated with NNWT completed between 3 and 11 weeks of treatment. These 13 subjects with 1 wound each were adherent with the protocol and remained in adequate health to complete at least 3 weeks of study participation. However, each of these 13 subjects was discontinued prior to completing 12 weeks due to health deterioration or nonadherence to the protocol. Therefore, data for 40 subjects with 43 wounds who completed 3 or more weeks of the study were analyzed based on the intent-to-treat paradigm. [31]

Pressure ulcers were assigned by a random number generator to receive either NNWT or standard care. In the event a subject presented with multiple PrUs, each ulcer was independently randomized. This process yielded a total of 21 PrUs treated with NNWT alone and 22 PrUs that received standard care alone.

Facility wound care teams provided the same level of care to subjects in both groups. Subjects whose wounds were treated with NNWT wore the sterile, noncontact wound dressing (cover) 24 hours per day, 7 days per week, for 12 weeks or until wound closure. The radiant heat element was inserted into the wound cover and activated for 3 separate 1-hour periods per day, with at least 2 hours between warming sessions. The noncontact wound cover was changed daily, during which time the wound was irrigated with normal saline. Wounds in the control group were treated with standard care that included removing the moisture-retentive dressing daily, irrigating the wound with normal saline, and applying a fresh dressing. Because wound dressing formularies varied at each facility, the dressings used for standard care of control wounds were limited to moisture-retentive dressings: hydro-fibers, alginates, hydrogels, hydrocolloids, saline-moistened gauze, and saline-impregnated gauze. Only these dressings were used on control wounds; all products containing enzymes, pastes, and other impregnated dressings were prohibited.

To prevent possible wound trauma by pressure, subjects in both groups who were confined to recumbent or sitting positions were repositioned onto anatomic surfaces with intact skin, according to a standard 2-hour turning schedule, 24 hours per day. In addition, subjects were maintained on dynamic powered (alternating pressure) replacement mattresses [32] while in recumbent positions. Three subjects had their wounds debrided to less than 50% necrotic tissue prior to study enrollment. Wounds with eschar were not enrolled.

Upon entry of each subject into the study and weekly thereafter, a single investigator recorded digital images of each wound, with a manual tracing as a back-up. All images were downloaded into a wound measurement software program (VeV MD; Vista Medical, Ltd, Winnipeg, Manitoba, Canada). This stereophotogrammetry technique allows for measuring wound size in 2 and 3 dimensions and has

been shown to have accurate test-retest and interrater reliability between 0.96 and 0.99 for surface area, circumference, depth, and volume. [33,34] Two trained investigators independently performed 2 on-screen tracings of the previously downloaded digital images. The highest and lowest values calculated from the 4 tracings were eliminated and the remaining 2 values were averaged and used for inclusion in the analysis. Wound data are presented as surface area in square centimeters (cm^2).

Differences in subject age, ulcer size, and ulcer age upon entry into the study were determined by the Student *t* test or the Mann-Whitney test, as appropriate. To determine whether there was a difference in healing time between wounds in the control and NNWT groups, a linear regression analysis was performed on all of the data points, representing weekly measurements of wound surface area for each subject (3 to 12 data points) to obtain a slope and an intercept. Slopes from each subject were pooled for statistical analysis and group means were compared by the Student *t* test. Data were analyzed using a lognormal regression model (Cox model) with wound age as a covariate. Significance was set at $P < .05$. The Cox regression analysis uses a hazard to estimate risk. Specifically, a covariate regression analysis was used with time-dependent covariates adjusted as appropriate.

Results

Patient demographics are summarized in Table 1. Randomization of subjects to 2 groups did not produce statistically significant differences in group mean ages (77.9 ± 4.0 versus 78.1 ± 3.0 years). Subjects in the 2 treatment groups were evenly distributed between the Veterans hospital and the long-term-care facilities, eliminating an effect of subject location. Wound demographics are presented in Table 2. The mean duration of PrUs was greater for the control group than the NNWT group (151.0 ± 36 versus 106.3 ± 22 days). This difference did not reach statistical significance ($P = .30$). Eight of 22 (36%) control wounds closed and 10 of 21 (48%) NNWT-treated wounds closed. As mentioned in the methods section, 13 wounds failed to complete 12 weeks of the study without closing. When these 13 wounds are not considered with respect to the incidence of wound closure, 8 of 16 (50%) of controls closed and almost all, 11 of 14 (79%), of the NNWT-treated wounds closed.

	Control Group (Standard Wound Care)	Normothermic Noncontact Wound Therapy (NNWT) Group
Number (n)	22	21
Age	77.9 ± 4.0	78.1 ± 3.0
Gender		
Male	7	9
Female	15	12
Diagnosis		
Neurological disease or injury	8	9
Diabetes	0	2
Orthopedic conditions	3	2
Vascular conditions	5	2
General medical conditions	6	6
Facility Type		
Veterans administration medical center	6	6
Long-term-care facility	16	15

Table 1: PATIENT DEMOGRAPHICS

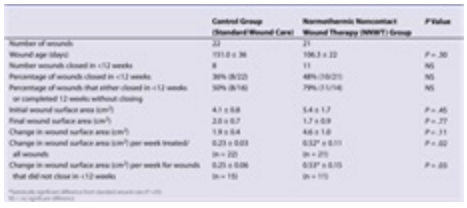

Table 2: WOUND DEMOGRAPHICS

No significant differences in initial wound surface area (4.1 ± 0.8 versus 5.4 ± 1.7 cm^2) were detected between the control group and the NNWT group, respectively. The control wounds underwent a mean surface area reduction of 50%, while the NNWT-treated wounds decreased by 69% (*P* = .11).

When the actual length of time for which all wounds were treated is considered, the rate of healing in the NNWT group was significantly greater, 0.52 cm^2 per week for the NNWT group versus 0.23 cm^2 per week (*P* = .02) for the control group. To determine whether factors unrelated to treatment may have influenced wound closure, wounds were subdivided based on whether they closed or remained open in less than 12 weeks. Among all wounds that did not close, virtually the same significant difference in mean area closed per week was again found, favoring treatment with NNWT, 0.53 cm^2 per week for NNWT-treated wounds versus 0.25 cm^2 per week for controls (*P* = .03).

The mean slope of individual regression analyses for the NNWT group was significantly different from the mean slope of the control group, –0.07 versus –0.033;*P* <.05; (Figure 1). This translates into a significant reduction in healing time for the NNWT group and in an extrapolated mean closure time of 78 days for the NNWT group and 180 days for the control group (Figure 2).

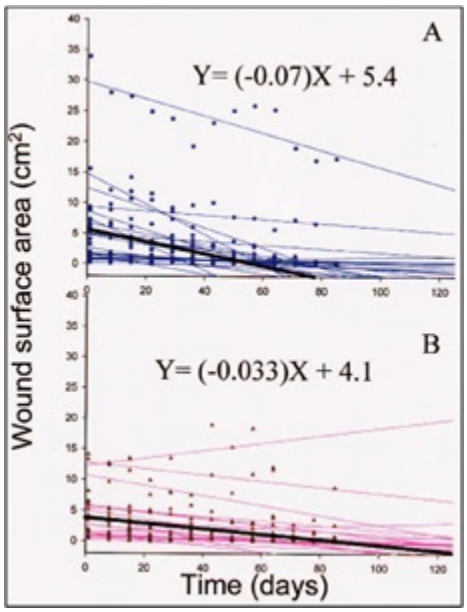

Figure 1.: MEAN OF THE SLOPES FROM INDIVIDUAL REGRESSION ANALYSES The graphs show individual linear regression lines (color) and the group regression line (black) with equations for NNWT-treated wounds (A) and control wounds (B).

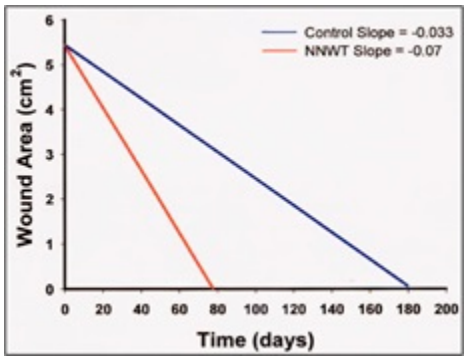

Figure 2.: PROJECTED TIME TO CLOSURE FOR AN NNWT-TREATED AND A CONTROL WOUND The projected times to closure based on calculated group slope and wound of identical size.

When wounds were subdivided based on initial surface area, the larger PrUs (>5 cm^2) in the NNWT group demonstrated a significantly greater healing rate than larger PrUs in the control group (Figure 3).

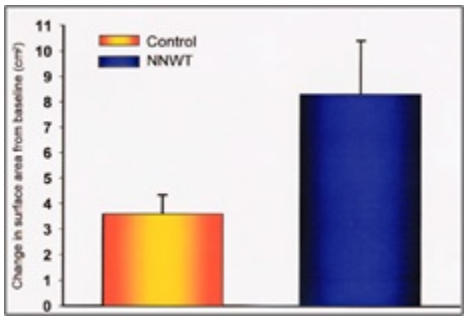

Figure 3.: CHANGE IN SURFACE AREA OF LARGER (>5 cm2) WOUNDS The NNWT-treated large wounds demonstrated significantly greater closure than controls.

DISCUSSION

This prospective randomized trial compared the effect of NNWT alone versus standard care alone on wound healing in 43 Stage III and IV PrUs. Pressure ulcers treated for up to 12 weeks with NNWT had a weekly wound closure rate that was more than 50% faster than the closure rate in the control group. These results are further supported by the results from the regression analyses; that is, wounds treated with NNWT healed faster during the 12-week protocol. This is demonstrated by the use of a logarithmic, rather than a linear, regression model. The lognormal model resulted in the best fit, particularly for the NNWT group, compared with a linear or curvilinear regression model (P <.05).

The control group had a greater percentage of older PrUs; however, statistical significance between groups with respect to wound age was not found. The trend in the control group for the age of PrUs to be older is a consequence of 1 wound having an age of 627 days. Based on this difference, one could argue that the NNWT-treated wounds benefited from being newer. Although this difference was not statistically significant, wound age and healing rate were analyzed as covariates. When wound age was

used as a covariate, the rate of healing with NNWT was still significantly increased when compared with wounds in the control group (P <.03).

The results of this study are consistent with those reported in other published studies. A 6-week randomized trial reported accelerated healing rates of Stage III and IV PrUs treated with NNWT versus controls treated with standard care. [22] A 4-week trial in which Stage III and IV PrUs were treated with standard care plus NNWT demonstrated a significantly greater reduction in wound surface area compared with wounds treated with standard care alone. [23] That study, as well as the present data, demonstrates a jump-starting of wound healing by NNWT.

NNWT may augment the healing rate of recalcitrant wounds via several mechanisms. NNWT provides active warming while maintaining a local moist environment within a dressing that makes no contact with the wound; therefore, cells are not disturbed when the dressing is removed. Delivery of radiant heat at 38°C restores the wound temperature closer to core body temperature. Mean increases in periwound skin temperatures of 1.88°C and 1.86°C from baseline, inside and at the outside edge of the noncontact dressing, respectively, have previously been demonstrated without adverse effects. [23] The temperature findings in the present study agree with those of Ikeda et al [4] and Whitney et al. [24] In a previous study, 5 wounds treated with an unheated NNWT cover (24 hours per day for 4 weeks) closed to a greater extent [35] than 6 control wounds treated with standard care [23] but less extensively than 15 wounds treated with a heated NNWT cover. [23] Therefore, elevating wound and periwound temperature toward normothermia (37 ± 1°C) appears to be a major contributing factor by which NNWT accelerates wound healing. Other mechanisms contribute to wound healing and may occur secondary to NNWT, including increases in perfusion, [1,3,5] oxygen tension, [2,4,5] resistance to infection, [6,7,9] collagen deposition, [10] scar tensile strength, [11] and counteraction of the effects of chronic wound fluid on cell cycle-regulatory proteins. [18]

This study investigated the effect of NNWT on healing of Stage III and IV PrUs in mostly elderly, frail patients who were recruited from 1 hospital and 7 long-term-care facilities. It was difficult to control the type of dressing used for the wounds in the control group. Given that no dressing is universally agreed on for “standard wound care,” clinicians were offered a choice of 6 dressing types that differ in composition but share the ability to maintain a moist wound environment. The decision to use a select list of moisture-retentive dressings on subjects in the control group allowed the 7 research sites to choose from the listed dressings that were available at their location. In addition, the study was limited by a relatively small sample size; however, the study groups were comparable in patient age, baseline wound size, and wound ages.

This study attempted to evaluate the efficacy of NNWT under imprecise, real-world clinical circumstances. Considerable improvement in efficacy could be addressed in a longer, comprehensive, multisite, randomized controlled trial designed to enroll hundreds of patients and assign them to groups that receive active NNWT, inactive NNWT, and a noncontact wound dressing only.

SUMMARY

This study demonstrates the efficacious use of radiant heat transmitted within a sterile semiocclusive dressing designed to maintain wound moisture and humidity. It is the first long-term randomized clinical trial to study NNWT on PrUs. The results from this trial are consistent with previously published

reports of shorter treatment protocols that enrolled patients with pressure [21] and venous ulcers. [20] Several clinical studies have utilized protocols in which heat has been administered at 38°C for between 1 and 4 hours daily, from 5 to 7 days per week, for 2 to 8 weeks. [20–24] No adverse effects were observed in the present study or previously published studies from such a device when the heating element emitted temperatures ranging from 38°C to 46°C. [4,20–24] Like other clinical trials, [22–24] the present study shows a significant treatment effect of NNWT on healing chronic Stage III and IV PrUs. Further, this study demonstrates a significant jump-starting of healing in PrUs greater than 5 cm^2 surface area. This positive outcome suggests that examining the use of NNWT in larger wounds with more than 1 cm of undermining merits further investigation.

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