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Clinical study

Impact of daily cooling treatment on skin inflammation in patients with chronic venous disease

Teresa J. Kelechi [a,*], **Martina Mueller** [a], **Dana E. King** [b], **Mohan Madisetti** [a], **Margie Prentice** [a]

[a] *Medical University of South Carolina, College of Nursing, 99 Jonathan Lucas Street MSC 160, Charleston, SC 29425, USA*
[b] *West Virginia University, Department of Family Medicine, Robert C. Byrd Health Sciences Center, P.O. Box 9152, Morgantown, WV 26506, USA*

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Skin temperature;
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Abstract People with chronic venous disease are at high risk for developing venous leg ulcers. Inflammation is posited as a pathological factor for this chronic condition as evidenced by persistently elevated skin temperature. As part of a larger trial to test the effects of a cooling regimen on leg ulcer prevention, the objective of this preliminary study was to evaluate the first 30 days of intense daily cooling. Compared to a placebo control cuff, a gel cuff applied to the most severely affected lower leg skin for 30 min daily showed no statistically significant differences between temperatures taken in the home at baseline compared to those measured at the 1 month follow up visit. There were also no differences in temperatures noted between the two groups, although the temperatures in the treatment group were lower 30 min after treatment, an indication of adherence. There was no discernable decrease or increase in temperature at a given time point during the 30 day treatment period compared to the control group. It may be better to have patients monitor skin temperature on a daily basis and then apply the cuff as necessary, rather than requiring daily cooling based on baseline measurement. This "prn" approach may provide a sufficient cooling milieu to prevent escalation of inflammation and thwart ulcer occurrence or recurrence.

Clinical trials registration #NCT01509599.

* Corresponding author. Tel.: +1 843 792 4602; fax: +1 843 792 2104.
E-mail address: kelechtj@musc.edu (T.J. Kelechi).

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Introduction

Leg ulcers are a serious problem for individuals with chronic venous disease (CVeD). Over 70% of all lower extremity leg ulcers are of venous origin and almost 1/3 become chronic [1]. While there is no consensus on the primary etiology of chronic leg ulcers, one theory posits an aberrant inflammatory state as a causative factor [2]. Early in the disease process, venous hypertension increases the size and permeability of dermal venules and arterioles that lead to extravasation, or leakage of fluid and electrolytes, plasma proteins, and macromolecules such as fibrinogen into the dermis, the second layer of the skin [3]. The extravasated fluid and macromolecules initiate a cascade of inflammatory reactions, including leukocyte activation that increases metabolic activity in the affected areas of skin [4]. Over time, inflammation causes varying degrees of injury to the vessels, tissues and skin, and lengthens the healing process [5,6]. When the inflammatory process itself becomes prolonged, skin damage, such as venous eczema (redness and itching), hyperpigmentation (brown discoloration), lipodermatosclerosis (hardening), and slow-to-heal or non-healing venous leg ulcers (VLUs) arise [6].

Our previous studies have described skin temperature elevation and patterns of temperature variability of CVeD-inflamed skin, measured with validated infrared- and thermistor-type thermometers at the gaiter area of affected lower legs [7]. We found that skin temperature was elevated by ~1–2 °C compared to unaffected contralateral skin and the lower leg skin of healthy controls [8]. In another study, we hypothesized there would be discernable hour-to-hour or day-to-day skin temperature variations of affected skin compared to unaffected skin [9]; however no pattern was observed. These findings suggest that normal "rise and fall" fluctuations or variability in the skin's thermoregulatory response to external stimuli (e.g., bathing) and internal mechanism (e.g., exercise) is altered. We concluded that skin temperature remains consistently elevated, however, a sudden spike in this "flat lined" temperature pattern over a 24-h period is predictive of venous ulceration [10]. The persistently elevated temperatures and lack of variability suggest inflammation may play a key role in the disease process, postulated to be responsible for the skin damage that results in chronic ulcers [11]. Thus, directly cooling the inflamed skin may provide a therapeutic option to ameliorate the negative sequelae of prolonged inflammation [12]. The data reported here are skin temperature measured on the first 30 days of an intensive cooling regimen targeting chronically inflamed lower leg skin.

Materials and methods

To investigate the variability in skin temperature in response to cryotherapy, a repeated measures design compared skin temperatures of affected (treatment leg) skin in 99 subjects randomized to the treatment group that used a cooling gel cuff and the control group that used a placebo cotton cuff applied to the lower leg.

Subjects

Individuals ages 21 and above with a diagnosis of CVeD were recruited from four study sites in Georgia and South Carolina, USA. The study protocol was approved by the Medical University of South Carolina's Institutional Review Board. All subjects signed informed consent prior to being screened, were assigned to either the cooling treatment or control placebo group via stratified permuted block randomization, and received $175 for participation. Inclusion criteria were: CEAP Classification for Chronic Venous Disease [13] stages C4 (skin damage) or 5 (healed venous leg ulcer within past two weeks up to two years). Since arterial circulation might influence the effect of cooling on skin blood flow, only subjects with ankle brachial index (ABI) of 0.8–1.3 mmHg, were included. Subjects without intact temperature sensory discrimination (measured with TipTherm® [Axon, Duesseldorf]) and pressure perception (measured with a monofilament) were excluded due to concern that the presence of neuropathy or the inability to sense changes in temperature could increase risk of harm, such as frostbite. This risk was deemed minimal.

All subjects agreed to follow the cooling treatment protocol (30 min a day), wear a compression wrap (JuxtaLite, CircAid by medi, San Diego, CA) on the treatment leg during waking hours, elevate both legs while performing the treatment, measure daily leg skin temperatures with a long handled infrared dermal thermometer before and after the treatments and then 12 h later, record temperatures on specially designed logs, and attend a follow-up clinic visit at the end of the first month.

Procedures

At the baseline clinic visit, subjects were given study instructions and materials, and viewed a short instructional DVD about study procedures.