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Clinically meaningful differences on symptoms associated chronic venous disease in response to a cooling treatment compared to placebo: A randomized clinical trial

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Abstract

Purpose—The purpose of this study was to examine the efficacy of a self-administered cooling treatment on clinically meaningful differences (CMD) in symptom changes in patients with chronic venous disease.

Design—Blinded, prospective, randomized controlled trial.

Subjects and Setting—Two hundred seventy-six community dwelling adults aged 21 years of age and above with skin changes and/or a healed venous leg ulcer (Clinical-Etiologic-Anatomic-Pathologic/CEAP 4 and 5 classification) completed the six-month active treatment period.

Methods—Participants were recruited from wound and medicine clinics, and the general population through referrals or advertisements. Participants were randomly allocated to a sham control cuff or interventional cooling cuff. Demographic and symptom-specific data were collected at baseline and months, 1, 3 and 6 with the 11-item symptom Venous Insufficiency Epidemiological QOL and Economic Study Quality of Life /Symptom (VEINES QOL/Sym) questionnaire subscale for heavy legs, aching legs, swelling, night cramps, heating or burning

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sensation, restless legs, throbbing, itching, tingling sensation (pins and needles), pain and irritability. Participants in the intervention group received a cooling gel cuff and the control group received a cotton filled cuff to place around the most affected lower leg during leg elevation. Both groups received standard of care for their chronic venous disease with compression wraps and skin hygiene. Dosing consisted of daily, 30-minute treatment for one month, twice weekly for 2 months, then thrice weekly for 3 months. To analyze and compare data, a mixed percentage clinically meaningful percentage change was used to assess CMD in symptoms between groups for treatment modality, sex and age group.

Results—All symptoms showed improvement with throbbing, aching, itching and pain demonstrating the greatest CMD in response to the cooling treatment. For throbbing and aching similar improvements were noted in response to cooling; 50% in the cooling group showed improvement whereas 60% in both groups responded favorably to pain. More than 50% of females and males reported improvements in throbbing; both males and females reported 60% improvements in pain in response to cooling. In contrast, far fewer females reported worsening of aching in the treatment group as compared to male participants (8% vs 20%). Age differences were noted for throbbing in the younger group < 65 years of age; older individuals ≥ 65 years of age saw CMD in aching in response to cooling.

Conclusions—Of the 11 symptoms, aching, throbbing, itching and pain had greater clinically meaningful improvements in response to a cooling cuff applied to lower leg skin affected by chronic venous disease. These CMD inform evidence-based practice by enhancing clinician understanding of which symptoms, or physical, physiological and behavioral outcomes in response to treatment change in a meaningful way for the patient.

Introduction

Clinically meaningful differences or changes (CMD) are defined as a change over time in symptom intensity; this change may be classified as worsening, no change, or moderate to substantially improved. These changes could be a result of disease progression or in response to a treatment; they are generally reported as a score or percentage.¹ As part of establishing CMD, the magnitude or extent of these changes is defined as a difference of at least one point on a Likert-type scale. Clinically meaningful differences inform evidence-based practice by enhancing clinicians' understanding of which symptoms, or physical, physiological and behavioral outcomes change in a manner that is meaningful for the patient.

Fisher² reported CMD for pain, disability, walking and using the stairs in a group of patients with chronic pain attending a rehabilitation program compared to the wait listed patients. In a study of patients with osteoarthritis conducted by Hayta and colleagues³, a clinically meaningful versus statistically significant blood pressure change in response to balneotherapy was used to determine safety of the intervention. In other studies, CMD in symptoms have been reported such as tic severity in Tourette Syndrome⁴, cognitive decline in Alzheimer's disease⁵, along with physical and functional impairment in individuals with heart failure.⁶ To our knowledge there are scant data on CMD in leg symptoms associated with interventions for chronic venous disease (CVD).

Chronic venous disease encompasses a variety of disorders of the venous system that affect the lower extremities of approximately 1% of the population world-wide.⁷ If left untreated, CVD can produce numerous bothersome symptoms such as leg swelling, achiness and heaviness that negatively affect physical functioning and health related quality of life. To address these symptoms, a leg cooling intervention was designed as a self-management treatment in which a gel-based cooling cuff was compared to a placebo control cotton-filled cuff applied to the lower leg skin area most severely affected by CVD. The overall purpose was to determine outcomes on skin circulation, the incidence of venous leg ulcer, and quality of life. For this portion of the study, we report findings here from the secondary aim, which was to assess CMD associated with leg symptoms. The goal was to present CMD data useful to clinicians to inform day-to-day clinical practice. Specific research questions were: (1) What were CMD in 11 symptoms associated with a cooling and placebo treatment for CVD; and, (2) were there differences within and between the two groups for sex (males, females) and age (< 65 years, ≥ 65 years).

Methods

The study was a randomized clinical trial (RCT) in which individuals were allocated to receive a cooling gel cuff treatment or placebo control cotton-filled cuff comparator placed around the lower extremity most severely affected by CVD, considered stage 4 (skin damage) or stage 5 (healed leg ulcer) according to the Clinical-Etiologic-Anatomic-Pathologic (CEAP) criteria.⁸ The study took place from January 2012 through December 2015.

Sample and setting

This patient population, including demographics and inclusion/exclusion criteria have been described in detail elsewhere.⁹ Study participants were 276 community-dwelling adults, aged ≥ 21 years with CVD, diagnosed per clinician, who were recruited from wound clinics and primary care practices in South Carolina and Georgia, and from self-referral from advertisements posted in businesses such as durable medical equipment suppliers and billboards. Individuals were excluded if they had recent leg surgery or arterial insufficiency with an ankle brachial index <0.8 or >1.3 mmHg or had cognitive impairment. For the Sample size calculation for analysis of continuous efficacy outcomes change in symptoms from baseline were based on effect sizes from previous pilot studies. With 96 participants per group, there was 85% power to detect a difference of 0.49 standard deviations between the groups assuming significance level $\alpha = 0.05$, two-sided, independent sample t-test comparison of means and equality of variance between groups. Study flow is summarized in Figure 1. The intervention was carried out by participants in their homes.

Medical University of South Carolina Institutional Review Board (ID 00008711) approved the study, which was registered with ClinicalTrials.gov (NCT01509599). Informed consent was obtained for all participants. A permuted block computer-generated randomization scheme was used to allocate individuals to the two groups.

Study Procedures

The study procedures were identical for both groups. The gel or placebo cuff was placed over the affected leg skin area during leg elevation. The cuffs were designed by Southwest Technologies, Kansas City, MO and were stored in the freezer set at 0°F until ready for use. Participants wore compression wraps (JuxtaLite, CircAid by MediUSA, San Diego, CA) during waking hours and elevated both legs on an elevated pillow during the treatment. For month 1, the treatment was performed daily for 30 minutes; the frequency was twice daily in months 2 to 3, then weekly in months 4 to 6. During the last 3 months treatment was conducted only when necessary if the skin became hot (4°F above baseline for 2 consecutive days), based on daily temperature measurement.

Demographic and symptom data were collected by trained study personnel during clinic visits at baseline and at month 6. Eleven symptoms (heavy legs, aching legs, swelling, night cramps, heating or burning sensation, restless legs, throbbing, itching, tingling sensation/pins and needles, pain, and irritability) were measured with the 11-item symptom subscale from the V Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom (VEINES QOL/Sym) questionnaire.¹⁰ The questionnaire was developed based on a list of leg symptoms that individuals with CVD deemed to be most bothersome. Items were rated based on frequency where 1 = every day, 2 = several times a week, 3 = about once a week, 4 = less than once a week, and 5 = never. Intra-class correlation coefficient, the measure of reliability or the ability of the questionnaire to detect changes over time is reported between 0.76 and 0.88 indicating good reliability.¹¹

Data Analysis

A mixed percentage change and anchor approach was used to analyze data. According to Dworkin, 10 to 20% changes from baseline reflect minimally meaningful improvements, 30% are considered at least moderate clinically meaningful and 50% are considered substantial.¹² The symptoms were rated on a 5- or 6-point Likert-type scale (anchors): a 1-point change from baseline to month 6 was considered minimally meaningful, a change of 2 points was considered moderately meaningful, and a change of 3 or more points was classified as a substantial meaningful change. Data were categorized as minimal (less than 30%), moderate (30% to less than 50%), or substantial (50% or greater) improvements or worsening of symptom severity based on a 1, 2, or > 2 point change in Likert scale for each time (baseline, end of study), respectively. Change in symptom severity was investigated by treatment modality, sex, and age group (<65 years and ≥ 65 years). Frequency distributions of the resulting categories are presented graphically.

Research studies of treatment interventions designed to improve symptoms associated with illnesses and chronic conditions often include results on whether changes are “statistically significant”. Statistical tests such as t-tests, analysis of variance (ANOVA) and descriptive statistics including means and standard deviations along with their p-values are reported to demonstrate whether differences were found between interventions and some type of comparison or control treatment on symptoms. Often missing from these studies are data about the clinical meaningfulness of the effect of the intervention on symptoms and their severity, for example, whether there were improvements or worsening of symptoms from the

perspective of the individual, an important distinction from statistically significant findings. Statistical significance lacks meaning or relevance to the individual; in other words, what is not known is whether the intervention made a clinical change in symptoms that are relevant or important to the individual receiving the treatment. Results could be statistically significant, but not clinically meaningful. Likewise, results could lack statistical significance, but be highly relevant in reducing symptoms. Based on this rationale, we did not analyze findings using inferential tests.

Results

Findings for the 11 symptoms for participants allocated to cooling or placebo treatments are summarized in Table 1. Throbbing, aching, itching and pain demonstrated the greatest CMD (improvement or no change) in response to the cooling treatment compared to the control group during the 6-month period (Figure 2). For throbbing 50% of those in the cooling group saw an improvement in (lessening of) severity with 21% showing a substantial CMD. In contrast, a little more than 30% among the control group experienced improvement, with only 8% reporting a substantial CMD.

Aching was similarly responsive to cooling with 50% in the cooling group reporting CMD improvements, however these findings were similar in the control group. More individuals reported no change in aching (35%) in response to cooling compared to 29% in the control group, indicating more individuals in the control had worsening of symptoms compared to the cooling group. For itching, approximately 47% saw no change in the cooling group compared to 43% in the control group; more individuals in the control group reported minimal CMD (18% compared to 14%) while those in the treatment group reported more moderate CMD improvements (12% compared to 9%). We included itch because this symptom has been reported to be one of the most burdensome of all symptoms with few effective remedies for its management.¹³ The influence of cooling on pain showed 36% more individuals reported no change in response to cooling compared to 25% in the control group. However, both groups experienced approximately 60% CMD improvements.

Sex

When data were analyzed by sex, more than 50% among the females in the cooling group saw a CMD improvement in throbbing severity over the course of treatment; similarly, almost 40% among the control group saw an improvement, however, about equivalent proportions reported no change (Figure 3). CMD were noted in pain with approximately 60% per group experiencing improvements; 11% of those cooling the legs compared to 6% receiving the placebo reported substantial CMD improvements. Far fewer females reported worsening of aching in the treatment group (8%) compared to 22% in the control group. For itching, 44% in the control compared to 37% in the treatment group saw CMD improvements; 53% compared to 46% in the treatment and control groups respectively experienced no change in symptoms.

Almost 50% of male participants in the cooling group reported CMD improvements in throbbing as compared to 30% in the control group (Figure 4). For aching, itching and pain, similar improvements were noted between treatment and control conditions. However, pain

showed greater CMD in the control group where 60% reported improvements compared to 45% in the cooling group.

Age

Almost 60% of participants < 65 years of age in the cooling group saw an improvement in throbbing severity over the course of treatment with 26% reporting substantial CMD improvements (Figure 5). In contrast, only about 30% among the control group experienced an improvement; about half in each group saw no change. Cooling more positively influenced aching with only 10% of individuals reporting worsening of symptoms in response to cooling compared to 20% in the control group. There were no other CMD improvements noted in itching or pain; both the treatment and control groups had similar changes, except more individuals in the treatment groups experienced no changes for aching and itching.

Individuals ≥ 65 years of age noted greater improvement in aching (50% compared to 40%) between the treatment and control groups (Figure 6). However, older individuals reported greater CMD improvements, 60% compared to 50% in the control and treatment groups respectively but 20% of the control group pain worsened compared to 10% in the treatment group.

Discussion

We report findings from this RCT of a self-administered cooling cuff treatment compared to a placebo cuff applied to the lower legs of 276 individuals with C4 and C5 CVD on CMD. We combined percentage and anchor based methods to report symptom improvement, no change, or worsening of 11 symptoms after the six-month active treatment period. Four of the 11 symptoms (aching, itching, pain and throbbing) were most positively influenced by cooling when compared to placebo, meaning, their symptoms either improved or did not worsen. We did not establish an *a priori* expectation of change but we acknowledge that the disease may have progressed symptomatically over the course of the study.

Medical management and minimally-invasive procedures to manage CVD symptoms are well-documented, as are several non-pharmacologic interventions other than compression.^{14,15} Bush and colleagues¹⁶ reported findings from a systematic review of 10 studies that evaluated oral Micronized Purified Flavonoid Fraction (MPFF) for medical management of CVD. When compared to placebo, they found sufficient evidence to support use of MPFF for reduction in CVD symptoms pain ($P = .027$), nocturnal cramps ($p = 0.002$), heaviness and swelling (both $P < .001$) and burning ($P = .006$). They did not report the effect of MPFF on itch, aching and throbbing. Neto and colleagues¹⁷ conducted a pilot study on the influence of ultra-sound guided foam sclerotherapy on symptoms in 32 patients with C4, 5, or 6 CVD. The symptoms with the highest prevalence at the start of the study were edema 53%, aching 47%, and throbbing and burning both 37%; itching was present in 31%. Statistically significant improvements after the procedure were noted for heavy legs, aching legs, swelling, burning, restless, and throbbing (all $P < .001$) but not for itch ($P = .146$). Itch has been reported to be a clinically relevant problem related to the level of CVD and is associated with higher pain ratings and lower health related quality of life. In an

observational study of 161 participants (mostly men, $n = 95$, 59%) conducted by Paul and colleagues¹³, 54.7% reported itch somewhere on their body and 45.9% reported itch on the feet/legs. This finding is similar to a report of combined data from 77,505 individuals residing in several European, Middle Eastern and Far East countries.¹⁸ Itch was reported by 42.5% individuals with C4–6.

Pain is frequently reported symptoms associated with CVD. In the data reported at the XVIIth World Meeting of the Union Internationale de Phlebologie, pain was reported in 81.1% of individuals with C4–6. Pain was present in 90.5% of all patients, regardless of stage, in a cross-sectional study conducted by Radak and colleagues¹⁹ of 2841 patients with CVD; 11.2% reported severe pain; 23.7% moderate to severe, 42.0% had moderate pain, and 22.8% had light pain. Severity of pain differed significantly ($P < .001$) according to the stages of disease with highest severity associated with C4–6. Unfortunately, we did not find any studies addressing clinical meaningfulness of symptoms in response to a specific treatment for CVD.

One of the primary aims of our RCT was to determine the influence of cooling plus standard of care on pain. We found 9.5% reported severe pain (8 – 10), 37.4% moderate pain (4 – 7) and 53.1% mild or no pain (0 – 3) measured with an 11-item numeric rating scale administered at baseline ($n=262/276$). No statistically significant differences in scores at baseline, nor differences in change from baseline to the end of study were observed between groups; however, both groups experienced statistically significant decreases in mean pain scores (-1.5 , $P < .001$; -1.7 , $P < .001$ respectively).⁽²⁰⁾

Sex and age differences were noted between the cooling and placebo groups; clinically meaningful improvements in pain and itch were noted in females, whereas males showed greater improvements in pain and throbbing. Sex differences in several symptoms were also reported in the classic Edinburgh Vein Study where 19% of 699 men and 25.3% of 867 women experienced itch ($P < .01$ for both) and this symptom increased with age in women ($P = .045$).²¹ The most common symptom among women in our study was aching (53.8%); whereas the most common symptom in men was cramps (34.0%). Pain and throbbing was not reported in that study. In a study of sex differences in itch in response to sclerotherapy, 74% of females and 50% of males experienced itch at the start of the study.²² Itch scores were 1.25 versus 0.37 for males and 1.47 versus 0.10 for females (scale of 0 to 5 with 5 being the most severe itch) before and after treatment. Statistical significance was not reported. We found that younger individuals had the greatest clinically important improvements in throbbing and aching, while older individuals showed greater improvements in aching and pain in response to cooling. There were no available studies to corroborate these findings on treatment outcomes for CMD on CVD symptoms.

Strengths and Limitations

A major strength of this study was the use of the randomized controlled trial design in which a placebo was used as a comparator to determine efficacy of the cooling intervention over a 6-month period to assess the full magnitude of outcomes on symptoms. Clinically meaningful findings add to the body of knowledge of symptom science in a way that is

useful for clinical practice by determining which symptoms were most sensitive (improvement or no change) to cooling. Additionally, these findings add an evidence-based, new component (cooling) to standard of care for CVD which does not currently exist. Limitations include having no previous studies of CMD on leg symptoms associated with CVD to include as comparisons, although there is a well-established body of literature on symptoms associated with CVD. In addition, we targeted those patients with C\$ and C5 CVD; outcomes of cooling on CMD in lower C stages are unknown.

Conclusions

Chronic venous disease is often accompanied by burdensome symptoms that may go unrecognized and undertreated. Few studies have been conducted that investigate new approaches to mitigate the myriad of these symptoms and report whether the outcomes are clinically meaningful to the patient. Analysis of CMD provides more specificity of which individual symptoms are more, not at all affected, or worsened by the treatment. This information guides clinicians on what to tell patients about study findings specific to managing their symptoms. Responses to the outcomes of treatment that are clinically meaningful are important for both researchers who study symptoms and clinicians who are charged with providing optimal patient-centered treatment. While research on symptoms that shows no statistically significant differences on certain treatment outcomes, clinically relevant differences are equally as important to study and report. These data are particular important to clinicians who are at the forefront of helping patients better manage their symptoms. Our results provide guidance to wound nurses, physicians, and other health care providers caring for individuals with CVD. We recommend instruction on the use of cooling devices such as gel packs (that do not freeze to a solid state) be applied to the affected skin for 15 to 30 minutes every other day until symptoms are lessened and then used whenever necessary. We are currently conducting additional research to compare a small gel pack applied to the affected skin on leg ulcer recurrence in patients with newly healed venous leg ulcers and reduction of symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Figure 2.

Proportions of change from baseline in 4 symptoms showing greatest clinically meaningful differences in response to the cooling treatment compared to placebo across the entire sample (N=276)

Figure 3.

Proportions of change from baseline in 4 symptoms showing greatest clinically meaningful differences in response to the cooling treatment compared to placebo among females (n = 150)

Figure 4.

Proportions of change from baseline in 4 symptoms showing greatest clinically meaningful differences in response to the cooling treatment compared to placebo among males (n=126)

Figure 5.

Proportions of change from baseline in 4 symptoms showing greatest clinically meaningful differences in response to the cooling treatment compared to placebo among individuals <65 years of age (n=166)

Figure 6.

Proportions of change from baseline in 4 symptoms showing greatest clinically meaningful differences in response to the cooling treatment compared to placebo among individuals 65 years of age (n=110)

Table 1

Percent change in symptoms per group

	Cooling	Placebo
Symptom		
Aching	51.0% ¹ 35.3% ² 13.7% ³	50.0% ¹ 29.0% ² 21.0% ³
Burning	42.2% ¹ 40.2% ² 17.6% ³	37% ¹ 48% ² 15.0% ³
Cramps	40.2% ¹ 40.2% ² 19.6% ³	28.0% ¹ 51.0% ² 21.0% ³
Heavy Legs	45.6% ¹ 35.0% ² 19.4% ³	45.5% ¹ 30.7% ² 23.8% ³
Irritable	50.0% ¹ 33.3% ² 16.7% ³	44.5% ¹ 41.6% ² 13.9% ³
Itch	35.0% ¹ 46.6% ² 18.4% ³	38.6% ¹ 42.6% ² 18.8% ³
Pain	53.4% ¹ 35.9% ² 10.7% ³	59.4% ¹ 24.8% ² 15.8% ³
Restless	30.4% ¹ 53.9% ² 15.7% ³	30.7% ¹ 50.5% ² 18.9% ³
Swelling	46.0% ¹ 39.2% ² 14.8% ³	40.0% ¹ 39.0% ² 21.0% ³
Throbbing	51.0% ¹ 33.3% ² 15.7% ³	33.7% ¹ 45.5% ² 20.8% ³

	Cooling	Placebo
Tingling	35.9% ¹	39.5% ¹
	40.8% ²	39.4% ²
	23.3% ³	21.3% ³

Improvement¹ No change², Worsening³

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