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High Level Pulsed Heat Versus Low Level Steady Heat in Subjects With Chronic Low Back Pain
December 3, 2019

Carewave Series 5 Clinical Trial: A randomized double blinded two arm study comparing pain relief in an active Series 5 device group (113 °F) versus a Series 5 lower temperature group (96.8 °F) in subjects with chronic low back pain.

Study Overview

1. This study will be conducted under Good Clinical Practice (GCP) guidelines and suitable for FDA submission in order to obtain claims such as, “provides temporary pain relief for people with chronic lower back pain.”
2. The study is designed as a randomized double blinded two arm placebo controlled trial.
3. The active arm (N=50) receives two active Series 5 heating units (Soovu Labs Inc.) that pulse heat to 45°C (113°F). The active Series 5 placebo arm (N=50) gets two identical appearing units (Soovu Labs Inc.) that produce low level of heat at 35-36°C (96.8 °F). For reference skin temperature is about 33 °C and room temperature 23 °C.
4. The study hypothesis is that in subjects with chronic low back pain, the active high level pulses heating device group will show a statistical improvement in pain scores as compared to the low level steady heat group as measured by the primary outcome measure, the Numeric Pain Scale (NPS).
5. Subjects will be told the study is examining the pain relieving effectiveness of two different levels of heat.
6. Subjects must have chronic low back pain with a pretreatment level of pain 4 or greater on a 0-10 point scale. By definition chronic low back pain is a condition that has been present for at least 6 months and must be present more days than not over the course of a week.
7. No use of pain medications during the four hour trial. However, pain medications including schedule IIIs can be taken up to 30 minutes before the start of the trial. Medications permitted during the trial include medications such as tramadol, codeine, NSAIDs, gabapentin and acetaminophen. Non-pain medications for medical indications are permitted at any time. Subjects taking schedule II opioids are excluded from the study. Schedule II opioids include oxycodone, hydromorphone, hydrocodone, fentanyl and methadone.
8. Ages 22 through 70.

9. Exclusion criteria- sciatica if present must be rated significantly less than the non -radiating component of the low back pain, pregnancy, skin lesions such as open skin or sores, scar tissue, skins grafts, old burns over the treatment area or neuropathic sensory loss over the treatment site.
10. Pre-treatment assessments include, Numeric Pain Scale (static and bending), and a pre-study questionnaire (history, treatment preferences, short form Brief Pain Inventory, and short form Magill), and a timed walking test.
11. Each treatment session lasts approximately 30 minutes with pain assessments throughout using NPS (primary outcome measure). Secondary outcome measures include measures of comfort, willingness to endorse their treatment and a timed walking test including the number of strides.
12. All subjects are followed for a 4 hour post treatment period with intermittent pain assessments (NPS).
13. At the end of the post treatment period, subjects complete a post study usability questionnaire and a blinding questionnaire.

Study arm #1- Active treatment group (two heating units)

1. Subjects randomized to this group will receive two active Series 5 heating units. The active heating units produce waves of heat of up to 45°C. All subjects will start at 45°C (113° F).
2. The treatment session is approximately 30 minutes of active treatment with heat.
3. Pain is assessed using a standardized instrument (the numerical pain score) both static and with bending/flexion.
4. Assessment times include pretreatment (T-0) after 5 minutes of treatment (T-5), after 10 minutes of treatment (T-10), after 15 minutes of treatment (T-15), and after 30 minutes of treatment (T-30).
5. Pain is also assessed after treatment ends. This assessment is done at 15, 30, 45, and 60 minutes post-treatment. After 60 minutes into the post-treatment, pain is assessed every 30 minutes up to 4 hours post-treatment.
6. Number of subjects in active treatment arm - up to 50.

Study arm #2- Low level heat treatment group (two low level heat units)

1. Subjects randomized to this group will receive two placebo Series 5 heating units. These devices look exactly like the active heating units but produce low level heat at 35-36°C (96.8 °F).
2. The treatment session is approximately 30 minutes of active placebo treatment.
3. Pain is assessed using a standardized instrument (the numerical pain score) both static and with bending/flexion.
4. Assessment times include pretreatment (T-0) after 5 minutes of treatment (T-5), after 10 minutes of treatment (T-10), after 15 minutes of treatment (T-15), and after 30 minutes of treatment (T-30).

5. Pain is also assessed after treatment ends. This assessment is done at 15, 30, 45, and 60 minutes post-treatment. After 60 minutes into the post-treatment time, pain is assessed every 30 minutes up to 4 hours post-treatment.
6. Number of subjects in placebo arm - up to 50.

Inclusion criteria

1. Chronic low back pain. By definition chronic low back pain is a condition that has been present for at least 6 months on more days than not. If there is a radiating component of the low back pain the radiating component must have a pain rating less than the non-radiating component of the low back pain.
2. Subjects must have pretreatment level of pain 4 or greater.
3. Ages 22 through 70
4. Pain medications can be used prior to the trial; however, none can be used during the approximate four hour trial. Other non-pain medications are permitted as needed.
5. Medications permitted during the trial include medications such as tramadol, codeine, NSIADs, gabapentin and acetaminophen.

Exclusion criteria

1. Sciatica or radicular pain without non-radiating low back pain, cancer, radicular pain greater than the non-radiating component of low back pain, pregnancy, skin lesions such as open skin or sores, scar tissue, skins grafts, old burns over the treatment area
2. Subjects must have a cell phone for clinic contact and follow-up.
3. Medications including oxycodone, hydromorphone, hydrocodone, fentanyl and methadone are excluded from the trial.

Primary measure: pain using Numerical Pain Scale

1. Numerical Pain Scale (see figure 1) at rest compared to the NPS after 30 minutes of treatment.

Secondary measures

1. Comfort scale and willingness to recommend treatment assessments (see figure 2). These assessments are administered after the treatment session and at end of the post-treatment period.
2. Numerical Pain Scale (see figure 1) with painful movement. Painful movement is defined as any movement that increases the amount of pain the subjects experience. This movement may include stretching, bending forward backward or sideways as well as any other movements identified by the subject.

Other measures

1. Speed walk. Time for an individual to walk a total distance of 60 feet. (Assessing walking speed in clinical research: a systematic review (J eval. Clinic Practice 2008 14(4) 552-562, or www.physio-pedia.com/10metre_Walk_test) Walk 60 feet but time only the middle 20 feet. The number of strides over the middle 20 feet will also be recorded.
2. Pain relief for up to 4 hours after treatment session ends using the Numeric Pain Scale
3. Skin observation at baseline, at the end of active 30 minute treatment and at the end of 4 hours. The subject will be asked how the skin feels and observed for any redness.

Study methods

1. Prior to initiation subjects will complete a short pre-study questionnaire about their chronic back pain (see figure 3). The questionnaire asks subjects about the history of their back pain, pain rating, and past and present treatments.
2. All subjects will be told that they are testing devices with two different temperatures and the effect of the different temperatures on low back pain. The words low temperature or higher temperature are not used. The low level temperature Series 5 device 35-36°C (96.8 °F) functions as an active placebo. All subjects will view a short presentation that explains the pain scale, double blinded trials and active versus placebo conditions to standardize the study approach.

3. At initiation of each trial, subjects will be shown the device active or placebo. The devices look identical. Subjects will be asked to indicate the area of worst pain by pointing to the spot. This will be the starting position of the device. Once treatment starts the subject can adjust the location of the device to the most effective area. The starting temperature of the active device will be 36 °C in the low temperature series 5 device and 45°C in the higher temperature series 5 device.
4. Any location change will be recorded. Subjects can also change the temperature setting anytime during the study. The change will be made by the study assistant using the phone app. This will be also be recorded. Subjects in the placebo group can also ask to change the location or temperature with the same response by the study assistant. All requests will be recorded. Series 5 devices are controlled using one of two methods, tapping on the device can turn the device on or off, or via blue tooth connection on a cell phone app. For this study we will use the blue tooth interface because it is simpler than tapping the device especially if the subject wishes to change the temperature as the devices are placed on the low back possibly making it difficult for some subjects in pain to reach the device to properly tap it.

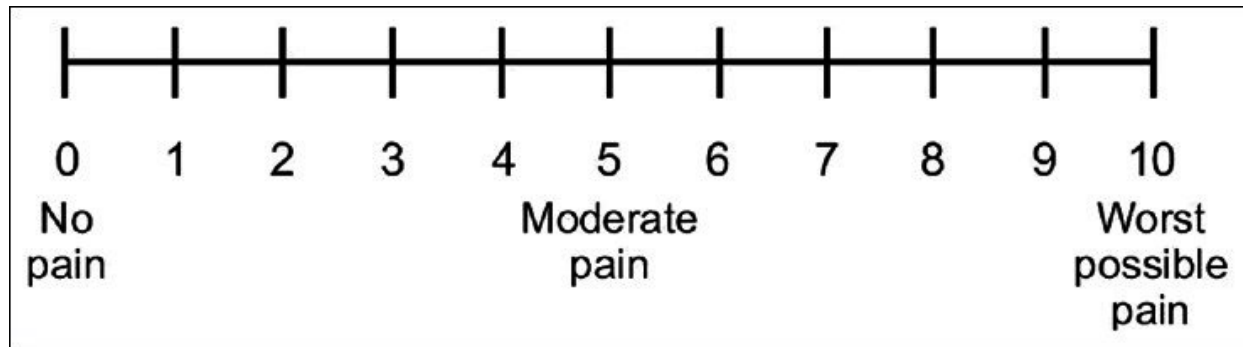
The research assistant (RA) will have a dedicated cell phone that paired with the subject's heating units and only those Series 5 devices. The RA can lower the temperature at the subject's request. The cell phone app contains an on/off switch to the paired unit, a temperature monitor and the ability to lower the temperature of the unit. For this study the temperature cannot be increased over 113 or 96.8 °F in the study units (Higher versus lower temperature series 5 units respectively). To support study blinding subjects will not have access to the cell phone app.

5. Pain will be measured both at rest and with an activity that each subject identifies as causing pain such as bending forward, backward or laterally or stretching.
6. Subjects will be required to stay for the full 4 hours post-treatment period even if their pain returns to baseline.
7. At the end of the post-treatment period subjects will complete a blinding questionnaire (see figure 4) and treatment usability questionnaire (see figure 5). The blinding questionnaire will also be administered at the end of the post-treatment period.
8. The study timeline and assessment schedule are shown on figure 7.

Data analysis of primary outcome measure

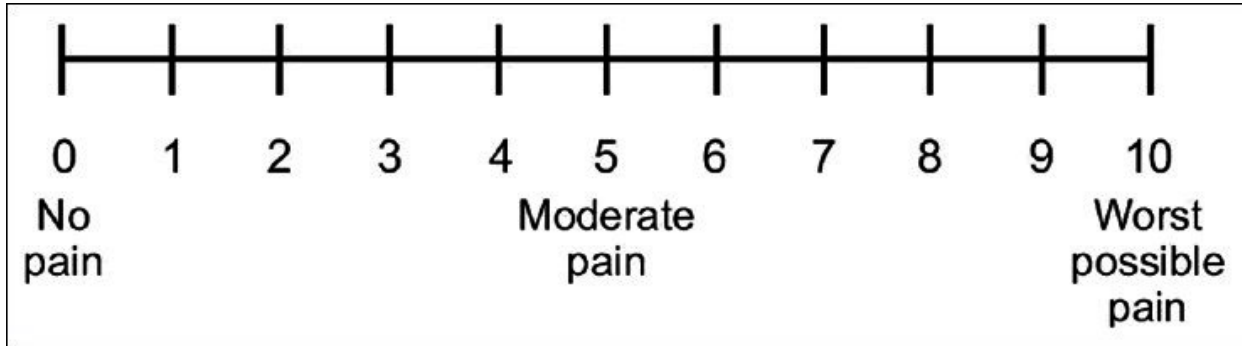
Primary analysis will consist of a two-sample t-test comparing change in numeric pain score (0 – 10 point scale) from baseline to 5, 10, 15, and 30 minute time point between the active and control arms using participants with complete observations. We will also analyse the pain level data at regular endpoints up to 4 hours post treatment. Residual change scores will be tested for departure from normality using the Shapiro-Wilk test for normality. If a statistically significant departure from normality is observed, we will use the Mann-Whitney-Wilcoxon test instead of a two-sample t-test. Secondary analysis will use two-sample t-tests to compare comfort with device (measured on a 0-10 scale) between arms and willingness to endorse treatment for others (measured on a 0-10 scale) between arms and pain with movement. Statistical tests will be conducted at the $\alpha = 0.05$ level.

Figure 1: Primary outcome measure (NPS) Static



Primary outcome measure is the Numeric Pain Scale (NPS) - Validity of four pain intensity rating scales. Pain_2011, Oct;152(10):2399-404. doi: 10.1016/j.pain.2011.07.005.

Figure 1A: Primary outcome measure (NPS) Dynamic (flexion or extension)



Primary outcome measure is the Numeric Pain Scale (NPS) - Validity of four pain intensity rating scales. Pain_2011, Oct;152(10):2399-404. doi: 10.1016/j.pain.2011.07.005.

Figure 2: Subject satisfaction measures

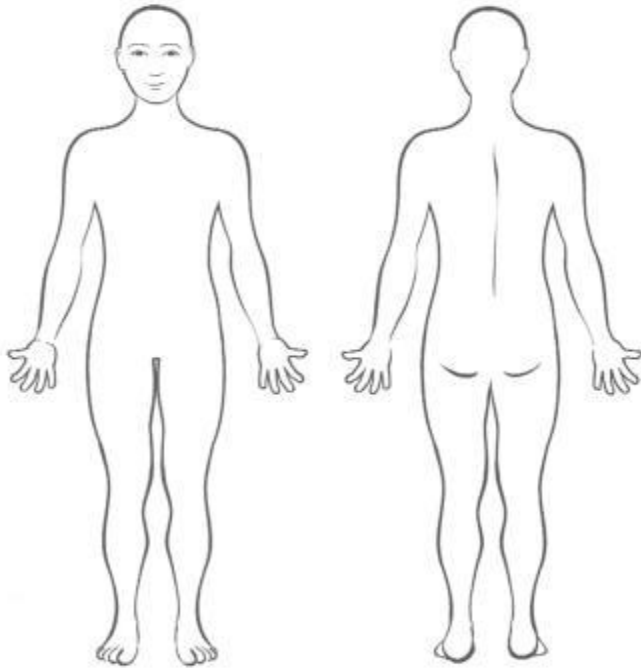
Please indicate the comfort level of your treatment by checking the appropriate box.						
Very uncomfortable	Moderately uncomfortable	Mildly uncomfortable	Comfortable	Mildly comfortable	Moderately comfortable	Very comfortable

How likely would you recommend your treatment to others by checking the appropriate box?						
Very unlikely	Moderately unlikely	Mildly unlikely	Likely	Mildly likely	Moderately likely	Very likely

Comfort and recommendation assessments.

Figure 3: Pre-study questionnaire

About how long have you had back pain? (months or years)



Please circle where your pain is located

If there is a radicular component, please indicate pain level of radicular and of non-radiating low back pain.

1. How motivated are you to do something about your chronic pain?

1. Not at All (exclude from study)
2. Slightly (exclude)
3. Somewhat
4. Very much
5. Extremely

2. What have you done in the past to treat your chronic pain? How effective was each?

3. Gender:

1. Male
2. Female

4. What is your age?

1. 22-30
2. 31-40
3. 41-50
4. 51-60
5. 61-70
6. 71+

6. What is your current employment status?

1. Employed full-time
2. Employed part-time
3. Self-employed
4. Full-time student
5. Homemaker
6. Retired
7. Unemployed
8. Prefer not to answer

7. What is the highest level of education you have achieved?

1. Some high school
2. High school graduate
3. Some college
4. Associates degree or technical degree
5. College degree
6. Graduate coursework or degree
7. Prefer not to answer

8. Overview of your household

1. Married
2. Single
3. Living with partner
4. Children in household

9. How many days a week do you typically exercise?

1. None
2. 1-2
3. 3-5
4. Every day

What treatments or medications have you tried for your low back pain? Please check the box.

Past treatments	Did not use	Used but little help	Used and helped somewhat	Used with great help
Anti-inflammatory medications like ibuprofen, naproxen				
Opioids, narcotics				
Surgery				
Physical therapy				
Massage				
Chiropractic care				
Magnetic energy devices				
Heat				
Ice				
Transcutaneous Electrical nerve Stimulation (TENS)				

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
No interference Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
No interference Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
No interference Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
No interference Completely interferes

(from BPI short form, C. Cleland)

Please circle the words that describe your pain:

Throbbing	Shooting	Stabbing	Sharp	Cramping
Gnawing	Hot	Burning	Aching	Heavy
Tender	Splitting	Tiring	Exhausting	Sickening
Fearful	Cruel			

(From the short-form McGill Pain Questionnaire, R. Melzack 1984)

Figure 4: Blinding questionnaire

Subject:


Please place a checkmark next to the item that best indicates your opinion. Only one checkmark please.	
	
I strongly believe that I received the low heat device during this study.	
I somewhat believe that I received the low heat device during this study.	
I am not sure whether I received the low heat or the higher heat device during this study.	
I somewhat believe that I received the higher heat device during this study.	
I strongly believe that I received the higher heat device during this study.	

Figure 5: Post study usability questionnaire

Please indicate the extent to which you agree or disagree with each of the following statements:

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
I prefer to use this product over a traditional heating pad					
I prefer to use this product over any other pain relief therapy I've tried					
By regularly using this product, I feel I could reduce my stress					
By regularly using this product, I feel I could better engage in life					
I found the product to be comfortable and soothing					
I would like to continue use of the product at home					

By regularly using this product,
I feel I could be more productive at work

By regularly using this product, I feel my
relationships could be better

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree

On a scale of zero to 10, how likely is it that you would recommend the product to a friend, family member, or colleague?
(0=not likely, 10=very likely)

We may extend this study to using this product at home for several months. Are you interested in being informed about participating in this study?

Yes No

Are you open to having the manufacturer of the device contact you to conduct a short market research survey (for which you'd be compensated)?

Yes No

Best email to reach you at: _____

Figure 6: Skin assessment form

Subject number date

Time of assessment T-0. T30. T240

How does the skin look?

- 1- No change
- 2- Changes in pigmentation, skin hue or tone? If so, please describe in detail.
- 3- Evidence of changes in blood flow? For example, localized edema. If so, please describe in detail.

Does the subject have pain at the site? Please note description of pain. Is there any stinging. How long has it been since the device was turned off?

Other comments?

Figure 7: Study timeline and assessment schedule

	Active treatment					Post-treatment period									
	T-0	T-5	T-10	T-15	T-30	PT-15	PT-30	PT-45	PT-60	PT-90	PT-120	PT-150	PT-180	PT-210	PT-240
Numeric pain scale at rest and movement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject satisfaction scales					X				X						
Orientation video	X														
Speed walk test	X				X										
Pre-study questionnaire	X														
Marketing questionnaire											X				
Heat and food questionnaire													X		
Blinding questionnaires							X								X
Skin assessment	X				X										X

Figure 7: Outcome measures versus study timeline.

Figure 8: Temperature and food preferences

	Strongly disagree	Mildly disagree	Mildly agree	Strongly agree
Other products I've tried that use heat to control pain have worked well for me.				
Other products I've tried that use cold to control pain have worked well for me.				
I like my coffee or tea hot				
I like my coffee or tea very hot				
I like cold drinks over hot drinks				
I tend to sweat easily				
I tend to overheat easily				
I tend to get cold easily				
I really like my shower or bath hot				
I really like my shower or bath very hot				
I have tried other pain relief products, and none worked for me.				
I like my food spicy				
I like my food very spicy				