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ORIGINAL RESEARCH

A COMPARISON OF TOPICAL MENTHOL TO ICE ON PAIN, EVOKED TETANIC AND VOLUNTARY FORCE DURING DELAYED ONSET MUSCLE SORENESS

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ABSTRACT

Purpose/Background: Pain can adversely affect muscle functioning by inhibiting muscle contractions. Delayed onset muscle soreness was used as a tool to ascertain whether a topical menthol-based analgesic or ice was more effective at reducing pain and permitting greater muscular voluntary and evoked force.

Methods: Sixteen subjects were randomized to receive either a topical gel containing 3.5% menthol or topical application of ice to the non-dominant elbow flexors two days following the performance of an exercise designed to induce muscle soreness. Two days later, DOMS discomfort was treated with a menthol based analgesic or ice. Maximum voluntary contractions and evoked tetanic contractions of the non-dominant elbow flexors were measured at baseline prior to inducing muscle soreness (T1), two days following inducing DOMS after 20 (T2), 25 (T3) and 35 (T4) minutes of either menthol gel or ice therapy. Pain perception using a 10-point visual analog scale was also measured at these four data collection points. Treatment analysis included a 2 way repeated measures ANOVA (2×4).

Results: Delayed onset muscle soreness decreased ($p = 0.04$) voluntary force 17.1% at T2 with no treatment effect. Tetanic force was 116.9% higher ($p < 0.05$) with the topical analgesic than ice. Pain perception at T2 was significantly ($p = 0.02$) less with the topical analgesic versus ice.

Conclusions: Compared to ice, the topical menthol-based analgesic decreased perceived discomfort to a greater extent and permitted greater tetanic forces to be produced.

Key Words: analgesia, cryotherapy, delayed onset muscle soreness, menthol, self-reported pain

Level of Evidence: Level 2b

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INTRODUCTION

Delayed onset muscle soreness (DOMS) is a common consequence of unaccustomed exercise or overtraining especially with the inclusion of extensive eccentric contractions.[1] DOMS is commonly observed with athletes, weight lifters, and is frequently observed among recreational athletes.[1] The presence of DOMS inhibits muscle activity or motor performance for up to several days following the initiating event.[2] One of the major symptoms of DOMS is pain[1] which can cause inhibition of force production of the involved muscle.[1,3]

Various methods of ice application including cold water immersion have been used to treat DOMS with inconclusive results.[4] Isabell et al[5] found no clinically significant effect of ice massage on DOMS. Connolly et al[4] countered in their review that cold water immersion has been shown to be effective in providing some relief of DOMS. Although ice is commonly used to alleviate pain[6] the evidence for its effectiveness for relieving DOMS is contradictory.

Topically applied gels, which contain menthol, are also used as analgesics.[7-9] Topically applied menthol gels result in a cooling sensation and are reported to act as a counterirritant to reduce the sensation of pain.[9] Menthol generates feelings of cold via the transient receptor potential family of ion channels or (TRP's). TRP's are found throughout the body, but TRPM8 are found mainly within thermosensitive neurons, which in addition to responding to reductions in temperature are also particularly sensitive to menthol.[10-15] TRPM8 serves as a neuronal sensor of cold temperatures and is essential for receiving input regarding innocuous cool and noxious cold sensations.[16,17] Utilization of calcium imaging techniques has demonstrated that upon the application of menthol to cloned TRPM8 cells, a heavy intracellular influx of calcium ions caused neural depolarization due to the opening of non-selective calcium permeable cation channels.[10-15] This increase in sensitization of the thermosensitive neurons is what leads to the perceptions of coolness with topical menthol application. Stimulation of these thermosensitive neurons is also associated with an analgesic effect. Afferent thermosensitive neurons which are stimulated by moderate cooling or the application of menthol have been found to have an inhibitory effect on the nociceptive afferent neurons and on the dorsal-horn neurons which conduct pain impulses to the thalamus.[18] This analgesic effect of menthol was demonstrated in vitro by Haeseler et al[19] when studying the effect of an electrical stimulus applied to human skeletal muscle tissue after the tissue was exposed to menthol. At various menthol application strengths, inactivated sodium channels were measured to determine the effect on depolarization. It was demonstrated that the menthol blocked the alpha subunit of voltage gated sodium channels, therefore causing hyperpolarization of the nervous membrane and a block in the signal of pain transduction. This study demonstrated that the application of menthol could have an analgesic effect through exerting an inhibitory gate control over nociceptive inputs. There are no studies, to date, which have compared the analgesic effects of topical applications of ice with menthol-based gel on DOMS symptoms.

Therefore, the purpose of this study was to compare applications of topical menthol with ice on pain, maximum voluntary contraction and evoked tetanic force during DOMS. It was hypothesized that the menthol based topical analgesic would be more effective than ice in alleviating DOMS-related symptoms (pain and force reductions). Thus menthol's analgesic effect on pain would improve strength output.

METHODS

Participants

Sixteen (Menthol [Biofreeze®] group: 24.2 $\pm$ 2.1 yrs, 181.6 $\pm$ 4.5 cm, 76.1 $\pm$ 10.3 kg; Ice group: 22.8 $\pm$ 1.8 yrs, 178.3 $\pm$ 3.9 cm, 73.9 $\pm$ 7.5 kg) healthy, physically active subjects (performed regular physical activity a minimum of tice per week) including 12 males and 4 females from Memorial University of Newfoundland were randomized to receive either a topical gel containing 3.5% menthol or a topical application of ice (using an ice bag) to their non-dominant elbow flexors two days following performing an exercise designed to induce DOMS in this muscle group. No participant had any previous history of cardiopulmonary, neurological, cognitive problems, sensory deficits, cold intolerance, or hypersensitivity. The upper limbs were visually checked to ensure the absence of any skin wounds, lesions and rashes. All subjects were given verbal information on the procedure of study as well as a brief overview of the purpose of the research. A Physical

Activity Readiness Questionnaire (PAR-Q)[20] was given to every subject to ensure the subjects' health status was sufficient to participate in physical activity. Using a random allocation method, subjects were divided into two groups; menthol based topical analgesic and ice intervention groups. All subjects read and signed a written informed consent document before participation that was approved by The Human Investigation Committee of Memorial University of Newfoundland.

Delayed Onset Muscle Soreness (DOMS) Exercise Intervention

Following completion of the informed consent process, the PAR-Q and being assigned to an experimental group all subjects were instructed to sit with their upper arm supported on an inclined padded bench and hold a free weight dumbbell to provide the resistance in their non-dominant hand. The lower arm and dumbbell hung freely over the edge of the bench. The one repetition maximum (1 RM) was determined for the elbow flexors of non-dominant arm (the left arm for all subjects in this experiment)[21] using the procedure described by Robbins et al.[22,23] According to this procedure an additional 10% was added to the 1 RM resistance, in order to successfully induce DOMS. Initially, the investigators helped raise the resistance to full elbow flexion with minimal assistance from the subject. The subject then performed an eccentric contraction to return the weight to starting position[2] over a 5s duration. Each subject performed ten sets of 10 repetitions of this eccentric exercise of the non-dominant arm. If a subject was not able to control the lowering of the weight over the 5s duration the resistance was reduced by 2.5 kg to ensure the completion of 10 sets. A one-minute recovery period was provided between each set. DOMS was induced in this study as an experimental tool to induce musculotendinous pain.

Menthol Based Topical Analgesic and Ice Treatment Interventions

The treatment interventions were applied approximately 48 hours or two days following the DOMS inducing session. For the menthol gel group, 2ml of Biofreeze®, a gel containing 3.5% menthol was applied topically over the belly of the biceps brachii. The mode of application did not involve substantial force, pressure or rubbing and thus any reflex activation would not have been expected. This dose of Biofreeze®, was based upon the estimate that the average skin surface area over the biceps brachii was approximately 400 cm^2 and the recommended dosage of Biofreeze® of 1 ml per 200 cm^2.[24] Twenty minutes (T2) following the application of the menthol gel each participant completed an assessment of their MVC, evoked tetanic force and perceptions of pain. These assessments were repeated at 25 (T3) and 35 (T4) minutes following the application of the menthol gel. Whereas the effect of menthol-induced reduced vascular conductance has been reported to endure for at least 20 min,[24,25] the subjective cooling effect has been reported to last up to 70 min in some subjects (mean 32 min).[9]

The protocol for application of the ice was similar to that of the menthol gel. Subjects who were randomized into this group underwent the same baseline assessment of their MVC evoked tetanic force and their perceptions of pain (T1) prior to inducement of DOMS. Then these individuals reported to the laboratory approximately 48 hours (or 2 days) following the DOMs inducement protocol. At this time .5kg of crushed ice in a plastic bag was placed over the non-dominant biceps brachii for 20 minutes and then removed.[26,27] Assessments of MVC, evoked tetanic force and their perceptions of pain were repeated immediately following the removal of the ice (T2), and at 25 (T3) and 35 (T4) minutes following initial application of the ice.

One researcher performed all the intervention applications, while another researcher was blinded to the group allocation during testing. Anonymous codes were assigned for analysis so that only the third researcher who did not perform the data analysis was cognizant of group allocation.

Dependent Variables

Measurements of voluntary (elbow flexor isometric MVC) and evoked (tetanic force) contractile properties were randomly allocated. While subjects sat upright in a chair, the left shoulder and elbow were flexed at 90° with the forearm vertical and fully supinated. The upper arm was fastened to the chair via an adjustable strap to avoid movement during voluntary force measurements. Both forearm and wrist of the testing arm were rested on a padded support and secured to a

strap attached to a high tension wire to a Wheatstone bridge configuration strain gauge (Omega Engineering Inc., LCCA 250, Don Mills, Ontario, Canada), amplified (Biopac Systems Inc., Holliston, Massachusetts; DA 100 and analog to digital converter MP100WSW) and monitored on computer (Dell Inspiron 6000, St. John's, Newfoundland, Canada). All data were stored on a computer at a sampling rate of 2000 Hz. Data were recorded and analyzed with a commercially designed software program (AcqKnowledge III, Biopac Systems Inc., Holliston, Massachusetts).

To assess peripheral (muscle) force changes associated with DOMS and the treatment interventions, bipolar surface stimulating electrodes were secured to the proximal anterior portion of the forearm flexors and deltoid-biceps brachii intersection. Similar to previous research from this laboratory[30] stimulating electrodes, 4–5 cm in width were constructed in the laboratory from aluminum foil, paper coated with conduction gel (Signa Creme, Parker Laboratories, Fairfield, New Jersey) and immersed in water. The electrodes length was sufficient to wrap the width of the muscle belly. The electrodes were placed in approximately the same position for each subject. Tetanic stimulation was evoked with electrodes connected to a high-voltage stimulator (Digitimer Stimulator Model DS7H + Hertfordshire, UK). A stimulation frequency of 50 Hz was maintained for a duration of 3 s with a pulse duration set at 50 μs. Stimulation was started with voltage at 100 V and amperage at 200 mA and progressively increased by 200 mA until 1 ampere was reached. If the subject could tolerate greater force then voltage was increased incrementally by 50 V. The purpose of the tetanic stimulation was to determine the maximum evoked force output that could be tolerated (pain perception) by the individuals.

Maximum Voluntary Contraction (MVC) Force

All subjects performed 2–3 MVCs trials. Verbal instructions were given to each subject to maximally contract the elbow flexors as hard and fast as possible. During the contraction, verbal motivation and visual feedback was provided by the investigator to promote a maximal response. The isometric contraction lasted for 4-5 s. Subjects were given a rest period of at least 2 min between each MVC. Peak force was measured as the greatest difference between the pre-MVC or resting value (approximately 1s prior to contraction) and the greatest force amplitude. If there was a >5% difference between the first 2 MVC trials, the subject was asked to perform a third trial, and the highest MVC force was recorded.

Visual Analogue Scale

A soreness rating scale was used with a visual analogue scale (VAS) to collect the soreness perception levels prior to testing.[2,28] Since the subject's were maximally exerting and physically restricted during the MVCs and with the treatment applications, subjects were instructed to verbally report the perception of soreness levels to the researchers who would record the response on the 10-point, 100 mm VAS scale. VAS has been reported to be a valid indicator of pain with excellent consistency.[29]

Statistical Analysis

Treatment analysis included a 2 way repeated measures ANOVA (2 × 4)(GB-STAT for MS Windows, version 7.0, Dynamic Microsystems Inc., Silver Spring, MD) with factors including treatment intervention (menthol based topical analgesic and ice) and time (T1-T4). The effect of DOMS on voluntary and evoked forces was analyzed with repeated measures ANOVA. Differences were considered significant when p values were below an alpha level of 0.05. A post hoc Bonferroni- Dunn's procedure was used to detect specific significant differences. Effect sizes (ES = mean change / standard deviation of the sample scores) and confidence intervals were also calculated and reported.[31] Cohen applied qualitative descriptors for the effect sizes with ratios of <0.41, 0.41-0.7, and >0.7 indicating small, moderate and large changes respectively. Data were reported as mean ± SD.

RESULTS

A post-hoc analysis of the statistical power (for a two-sided test) calculated for an alpha of 0.05 ranged from 0.2 for MVC force measures (insignificant findings) to 0.84, 0.97 and 0.98 for tetanic force, VAS scores at rest and VAS scores during the MVC respectively. There were no significant differences between groups for any baseline (T1) measures.

Voluntary Muscle Force and Activation

There was no significant main effect or interactions for the treatment interventions. There was a significant

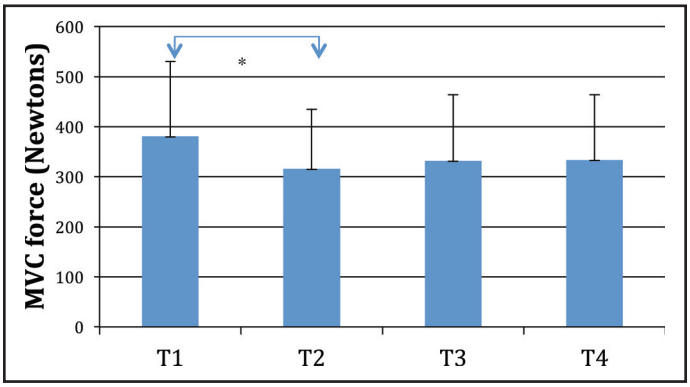

Figure 1: *Figure illustrates a main effect for time associated with changes in maximum voluntary contraction (MVC) force of the non-dominant elbow flexors. The asterisk indicates a significant (p = 0.04) difference between T1 (pre-test) and T2 (2 days following DOMS and 20 min following intervention application) MVC force. Columns and bars represent means ± standard deviation (SD).*

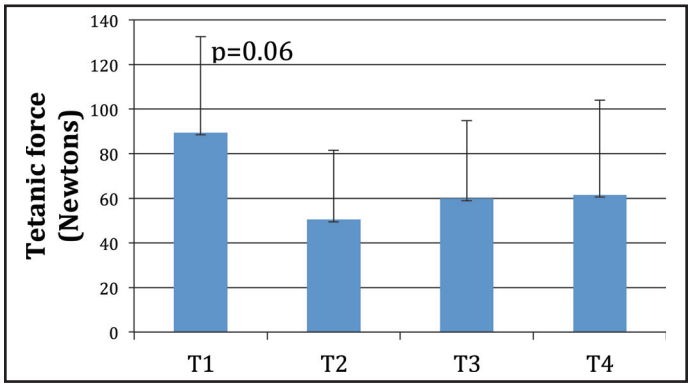

Figure 2: *Figure illustrates a tendency (p = 0.06) with a large effect size (ES = 1.2) for a main effect for time (data collapsed over treatments) associated with evoked tetanic force of the non-dominant (DOMS-induced) elbow flexors. Columns and bars represent means ± standard deviation (SD).*

(p = 0.04; ES = 0.54) main effect for time, with a DOMS-induced decrease in MVC force of 17.1% from T1 to T2 (Figure 1). There were no significant MVC force differences between T2, T3 and T4 (Table 1).

Evoked Muscle Force

There was a tendency with a large effect size (p = 0.06; ES = 1.2) for tetanic force to decrease over time with 43.4%, 35.1%, and 31.2% decreases of T2, T3 and T4 respectively, compared to T1 (Figure 2). Tetanic force changes illustrated a significant main effect for the treatments (p < 0.05; ES = 1.1) with the menthol based topical analgesic allowing 116.9% greater tetanic force (89.4 N ± 60.7) output than the ice treatment (41.2 ± 43.6). Although not statistically significantly different (p = 0.17), tetanic forces following the ice treatment at T2, T3 and T4 were 56.5%, 78.7% and 66.1% lower than tetanic forces following the respective times with the Biofreeze treatment (Table 1).

Pain Scales

There was no significant difference in pain perception pre-treatment. Although there was no significant

Table 1. *Treatment by time interactions. The first series of numbers represents mean ± standard deviations whereas the subsequent numbers below represent the 95% confidence interval (CI).*

MVC force	T1	T2 ES=0.54*	T3	T4
Menthol	393.05 ± 127.6 CI: 307.6-478.5	359.3 ± 101.9 CI: 291.1-427.5	359.9 ± 116.5 CI: 281.9-437.9	375.4 ± 106.9 CI: 303.8-447.1
Ice	367.9 ± 180.4 CI: 247.2-488.6	271.96 ± 137.1 CI: 180.1-363.7	303.8 ± 148.6 CI: 204.4-403.1	291.3 ± 153.6 CI: 188.5-394.1
Tetanic force	T1 ES=1.2~	T2	T3	T4
Menthol	96.6 ± 88.5 CI: 37.1-158.1	70.4 ± 37.1 CI: 45.6-95.3	98.8 ± 56.6 CI: 60.9-136.7	91.8 ± 62.4 CI: 50.1-154.3
Ice	82.2 ± 67.7 CI: 36.9-127.5	30.6 ± 25.5 CI: 13.5-47.6	21.03 ± 141.1 CI: 11.6-30.5	31.1 ± 23.3 CI: 15.6-54.4

ES= Effect size; A single asterisk (*) represents a main effect for time with MVC force decreasing significantly (p=0.04) from T2 to T1. A swirl (~) represents a tendency (p=0.06) for time with tetanic force at T1 to be significantly greater than T2, T3 and T4 (combined over treatments).

group by time interaction, soreness perception associated with the MVC showed trends with large effect size for both treatment and time. The soreness associated with a MVC following ice application (3.9 ± 0.5) tended to be 33% greater ($p = 0.08$; ES = 1.8) than following the topical analgesic application (3.0 ± 0.4). Soreness associated with a MVC had a tendency with a small effect size ($p = 0.1$; ES = 0.12) to decline over time with 13.1% and 17.7% less soreness respectively, perceived at T3 (3.3 ± 0.98) and T4 (3.1 ± 1.2) compared to T1 (3.8 ± 1.02). There was a significant ($p = 0.025$; ES = 1.2) difference in soreness perception with the VAS scale between the application of ice and the menthol based topical analgesic. Soreness perception was 63.1% less with application of the topical analgesic (1.1 ± 0.4) compared to the ice (3.1 ± 1.7).

DISCUSSION

The most important results of this study suggest that a menthol based topical analgesic was more effective than ice for relieving soreness associated with DOMS while at rest or during muscle contractions. The topical analgesic also permitted greater evoked tetanic forces to be produced as compared to ice.

Menthol and ice are widely used as topical analgesics. Ice is reported to be effective in reducing pain with soft tissue injuries[32,33] and has also been widely used in relieving the symptoms of DOMS.[4,34] It is suggested that the cold temperature significantly reduces the pain perceived due to DOMS.[34] However, other studies report that ice massage[5,35] have minimal effects on reducing DOMS symptoms. Although ice is commonly used to alleviate pain,[6] there is conflicting evidence regarding its effectiveness for relieving DOMS. In the present study ice was less effective than a menthol based topical analgesic for relieving DOMS symptoms. The menthol based topical analgesic showed both large magnitudes of change over the testing periods as well as achieving minimal clinical importance. A number of studies[36-38] have indicated that a change of 10-13 mm on a VAS scale of 100 mm represents the minimal clinically significant difference. The present study anchored numbers from 0-10 with a distance of 10 mm between each numeral. The VAS score with the menthol based topical analgesic of 1.1 was substantially lower than the score associated with the ice treatment (3.1) illustrating a clinically significant difference in pain perception.

Menthol has been reported to be effective in relieving pain with mild to moderate muscle strains.[39] Topical application of a menthol gel along with the chiropractic adjustment showed significant reduction in low back pain.[40] Yosipovitch et al.[9] reported that while menthol has a high skin irritating effect it did not differ from alcohol in reducing itch and pain sensations. However, Galeotti et al.[7] indicated that menthol's analgesic properties are mediated through a selective activation of opioid receptors. The feeling of coolness experienced when applying menthol is achieved by sensitization of the thermosensitive neurons that also possess analgesic properties.[7] Using mice, Galeotti et al.[7] reported an increase in heat pain threshold. Furthermore, menthol has been shown to activate temperature-activated transient receptor potential (TRP) ion channels such as TRPM8,[41] TRPV3 and inhibits TRPA1 providing a rationale for its use as an analgesic.[8] Stimulation of these thermosensitive neurons is also associated with an analgesic effect. Afferent thermosensitive neurons are stimulated by the application of menthol, have an inhibitory effect on the nociceptive afferent neurons and dorsal-horn neurons, which conduct pain impulses to the thalamus.[18]

Another possible mechanism for the analgesic effect of menthol may be related to the inflammation or swelling associated with DOMS.[4] Olive et al.[24] reported a significant reduction in vascular conductance within 60s of menthol application, which was maintained for at least 10 minutes. Similarly animal studies have shown a reduced pressor response to exercise (decreased blood pressure) reducing blood flow to the application area.[42,43] Unfortunately the extent of swelling was not measured in the present study and thus the effect of the menthol gel on DOMS-induced inflammation cannot be verified or quantified in this study. Hence, the mechanisms underlying the lower soreness scores on the VAS cannot be specified in the present study but may be attributed to one or a combination of inflammation reduction, counterirritant activation and inhibition of specific thermosensitive ion channels, or opioid receptors.

The menthol based topical analgesic permitted greater evoked tetanic forces following DOMS than ice. Unfortunately, VAS for pain was not employed during the tetanic contractions. However, all participants in this

study and the many previous studies from this laboratory have all commented on the substantially greater discomfort experienced during evoked tetanic versus voluntary contractions. Electrical stimulation of muscle through the skin can activate cutaneous pain receptors,[44] with greater magnitudes of pain experienced with increasing frequency of stimulation.[45] Furthermore the stimulator provides synchronous muscle activation[45] rather than a typical physiological asynchronous stimulation[46] resulting in a cramp-like sensation. This cramp-like contraction can also stimulate mechanical nociceptors contributing to the pain sensation.[44] Hence in the present study, the milder discomfort associated with a voluntary contraction did not allow subjects to differentiate between the topical analgesic and ice but the greater discomfort or pain of the tetanic cramp-like contraction was ameliorated to a greater degree by the menthol based topical analgesic. Thus the menthol based topical analgesic provided greater pain tolerance allowing higher evoked contraction forces to be produced. In terms of injury rehabilitation, the menthol-based analgesic would allow higher contraction forces to be elicited with functional electrical stimulation training.

The greatest limitation of the present study is related to the individual responses to pain. Behm and St-Pierre[47] reported a correlation 0.1 between pain and muscle activation. The high variability with some of the data in the present study also reflects the very different responses of each individual to pain. Thus, predictably there was no significant correlation between pain and changes in force. A further limitation could have been that the treatments could have distinctive time courses. The present study utilized early and delayed testing times for the treatments in order to identify if one treatment was more likely to have a greater effect soon after or later after application.

CONCLUSIONS

The results of the present study indicate that a menthol based topical analgesic was more effective than ice for decreasing DOMS-induced symptoms of pain and increasing evoked tetanic force. Hence, a menthol based analgesic would be recommended for reducing DOMS-induced symptoms for at least 35 minutes after the application. While patients with injuries were not employed in this study, the greater tetanic force with the menthol analgesic might suggest that more intense or aggressive muscle stimulation therapy during rehabilitation might be possible with such a therapeutic agent. Finally DOMS was used as a model to induce pain in the present study. The results may also apply to other musculoskeletal pain afflictions; however further research should investigate injured populations (e.g. strains, sprains). Furthermore, previous research[24] indicates that the effects of menthol-based gels may work within a minute of application making them more time efficient than ice.

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