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Research

Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial

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KEY WORDS

Osteoarthritis
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ABSTRACT

Objective: Does short-term cryotherapy improve pain, function and quality of life in people with knee osteoarthritis (OA)? **Design**: Randomised controlled trial with concealed allocation, blinded assessment of some outcomes, and intention-to-treat analysis. **Participants**: People living in the community with knee OA. **Interventions**: The experimental group received cryotherapy, delivered as packs of crushed ice applied to the knee with mild compression. The control group received the same regimen but with sham packs filled with sand. The interventions were applied once a day for 4 consecutive days. **Outcome measures**: Participants were assessed at baseline and on the day after the 4-day intervention period. The primary outcome was pain intensity according to a visual analogue scale. Secondary outcomes were baseline to post-intervention changes according to the Western Ontario and McMaster Universities Osteoarthritis, Knee injury and Osteoarthritis Outcome; Timed Up and Go test; and 30-Second Chair to Stand test. **Results**: Sixty participants were randomised into the experimental group (n = 30) or the control group (n = 30). Twenty-nine participants from each group completed the trial. The mean between-group difference in change in pain severity was −0.8 cm (95% CI −1.6 to 0.1), where negative values favour the experimental group. This result did not reach the nominated smallest worthwhile effect of 1.75 cm. The secondary outcomes had less-precise estimates, with confidence intervals that spanned worthwhile, trivial and mildly harmful effects. **Conclusion**: Short-term cryotherapy was not superior to a sham intervention in terms of relieving pain or improving function and quality of life in people with knee OA. Although cryotherapy is considered to be a widely used resource in clinical practice, this study does not suggest that it has an important short-term effect, when compared with a sham control, as a non-pharmacological treatment for people with knee osteoarthritis. **Registration**: NCT02725047. **[Dantas LO, Breda CC, da Silva Serrao PRM, Aburquerque-Sendín F, Serafim Jorge AE, Cunha JE, Barbosa GM, Durigan JLQ, Salvini TdF (2019) Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial. *Journal of Physiotherapy* 65:215–221]**

Introduction

Knee osteoarthritis (OA) is a prevalent and costly chronic musculoskeletal condition associated with pain and disability.[1] Clinical guidelines recommend a combination of non-pharmacological treatments[2] – including patient education, exercise and some other physiotherapy interventions – together with pharmacological treatments[3] to improve pain and symptoms.

Cryotherapy is a non-pharmacological intervention that is widely used in various rheumatic joint diseases[4,5] for its effects on pain, inflammation and oedema.[6] It is considered to be relatively safe, inexpensive, and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or in conjunction with other therapies,[5] and seems to be well accepted by people with knee OA.[7,8]

Some international knee OA guidelines recommend cryotherapy as a treatment option,[9,10] but others have found insufficient evidence to recommend it.[11–13] Recent and relevant systematic reviews conclude that further trials are needed to evaluate the isolated effects of cryotherapy on pain, function and quality of life in people with knee OA.[14–16] The most recent of these reviews[16] identified five randomised trials, almost all of which scored only 4 out of 10 on the

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PEDro scale. When the authors applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to the evidence, they concluded that the review identified only low-level evidence regarding cryotherapy for pain management, knee stiffness, knee range of motion and physical function.[16]

Some consistent methodological limitations among the existing studies were: unconcealed allocation, lack of blinding, poor baseline comparability of the groups, lack of confirmation of OA grade of the participants, and analysis not according to the principle of intention to treat.[16] Future studies should therefore seek to achieve these methodological criteria, where possible. In this way, the generated information is likely to contribute to strategies for targeted knee OA rehabilitation, and improve pain management and overall quality of life of people with knee OA.[5,14,16]

The aim of this study was to determine the effects of short-term cryotherapy in people with knee OA. We hypothesised that cryotherapy would relieve pain and improve function and quality of life when compared with a sham intervention.

Therefore, the study question for this randomised trial was:

Does short-term cryotherapy improve pain, function and quality of life in people with knee osteoarthritis?

Methods

Design

This study was a randomised sham-controlled trial carried out over a period of 6 consecutive days. A baseline assessment was performed on the first day, followed by 4 days of intervention and a post-intervention assessment on the final (sixth) day. Each participant was assessed in the same period of the day (morning or afternoon) in a physiotherapy research laboratory by the same assessor. To reduce bias, both the therapist responsible for applying the intervention and the outcomes assessor followed standardised scripts to give explanations regarding the general objective of the study.[17] Moreover, the therapist responsible for the intervention participated in a 10-hour training module before the start of the study, which consisted of scientific information and clinical training regarding cryotherapy effects and application for people with knee OA. Intervention adherence, medication intake and adverse events were tracked with a 4-day assessment diary given to the participants at the baseline assessment. All the participants were told to not practise any kind of physical exercises/activities during the intervention week.

Participants were randomly allocated into two groups of 30: an experimental group that received cryotherapy, and a control group that received a sham intervention. Random allocations were determined by a computer-generated random numbers program and matched for gender (15 men and 15 women in each group). Allocation was concealed by placing the random allocations in opaque sealed envelopes that were locked in a central location. Each participant's random allocation was revealed just before the intervention was commenced.[17]

Verbal and written explanations of the objectives and methodology of the study were provided to the patients, and those who were willing to participate signed a written informed consent form approved by the local ethics committee. The study was reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for Randomised Trials of Nonpharmacologic Treatments[18] and the Template for Intervention Description and Replication checklist (TIDieR).[19]

Participants

Participants were recruited through public announcements and waiting lists from local orthopaedic and rheumatology outpatient clinics. People who expressed interest in participating in the study underwent lateral, anteroposterior and axial radiography of both knees to determine whether they had knee OA based on the clinical and radiographic criteria of the American College of Rheumatology.[20] Participants were required to have a symptomatic and radiographic grade (Kellgren-Lawrence scale) of ≥ 2 (at least mild radiographic OA) in at least one knee compartment.[17] To be included in the study prospective participants also needed to: be aged between 40 and 75 years; be engaged in $<$ 45 minutes/week in accumulated physical activity of at least moderate intensity;[21] have a body mass index ≤ 35 kg/m^2; and have pain intensity in the previous week of ≥ 4 cm on a 10-cm visual analogue scale.[17] Exclusion criteria were: physiotherapy in the previous 3 months; intra-articular knee injections in the previous 6 months; medical restrictions such as cardiorespiratory, neurological or any other rheumatology dysfunctions; previous hip, knee or ankle surgery; and any other chronic condition that leads to pain.

Intervention

Experimental group

The experimental intervention consisted of four cryotherapy sessions performed by a trained physiotherapist over 4 consecutive days. Cryotherapy was only applied to the more-affected knee, in an air-conditioned room controlled at 21 °C ($\pm$ 2). The therapist explained that the intervention consisted of cryotherapy applied to the more-affected knee for 20 minutes. Participants were positioned in dorsal decubitus with both legs extended and relaxed. To protect the skin from possible frostbite, the entire knee surface was covered with a moist surgical gauze (45 $\times$ 50 $\times$ 0.01 cm). Next, two plastic bags (24 $\times$ 34 $\times$ 0.08 cm), each containing 1 kg of crushed ice, were placed on the knee, covering the anterior, posterior, medial and lateral surfaces. A comfortable, non-painful compression was applied over the ice packs by wrapping an elastic bandage around them, and the therapy was left in situ for 20 uninterrupted minutes. The main purposes of compression were to maintain the ice packs in position on the knee[22] and to enhance the effects of the cryotherapy.[23] To allow participants to mimic the usual clinical setting treatment, they were provided all the necessary materials (plastic bags, elastic bandage and surgical gauze) to use cryotherapy at home whenever they felt in pain or discomfort. Moreover, they received a booklet with illustrated pictures and all the instructions needed for cryotherapy application.

Control group

For the control intervention, the bags were filled with 1 kg of dry sand instead of ice. The sand bags were applied according to the same regimen in the same locations. The therapist's explanation about the intervention was changed to mention 'application of sand packs' instead of 'cryotherapy application'. The sand packs were applied with the same gauze underneath and the same bandage for compression. Participants in the control group were provided with the sand bags and other materials for application at home whenever they felt in pain or discomfort. The booklet was modified to refer to the application of sand bags.

Outcome measures

All the outcomes were measured by the same blinded assessor before and after intervention. Table 1 describes the main outcome measures included in this study and the recommended estimate of the minimum clinically important difference for each outcome measure. Pain intensity, knee subjective and objective physical function, and quality of life were measured.

Primary outcome

The primary outcome was pain intensity assessed using a visual analogue scale. This self-reported pain score is a valid and reliable measure among people with OA.[24] The visual analogue scale was administered at baseline and on the final assessment day.

Table 1
Detailed description of the study's outcome measures.

Outcome measure	Description of the test	Scoring	Minimum clinically important difference
Visual analogue scale	The scale is placed in front of the patient who is asked to rate their pain intensity in the previous week.[24]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[33]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the previous 72 hrs. It contains 24 questions in three domains: pain, stiffness and physical function.	Each question is scored from 0 to 4. The maximum score is 96. High scores indicate worse status.	An improvement of 12% from baseline is recommended in OA research.[34]
Knee Injury and Osteoarthritis Outcome Score	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the previous week, by measuring quality of life and knee function. It contains 42 questions in five domains: pain; other symptoms; function in daily life; sports-related function and recreation; and knee-related quality of life.	The answers are standardised and scored from 0 to 4. The total score is 168. High scores indicate worse status.	A difference of 8 to 10 in the total score is recommended in OA research.[35]
Timed Up and Go test	This test assesses: balance moving from sitting to standing, stability in walking, and gait course changes without using compensatory strategies. The participant is asked to stand up from a chair, walk 3 m, turn around, return and sit back in the chair.	Total time to complete the test.	A reduction of 0.8 to 1.4 s is recommended in OA research.[36]
30-Second Chair to Stand test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 s.	Total number of repetitions within 30 s.	An increase of 2 to 3 repetitions is recommended in OA research.[36]

OA = osteoarthritis.

Secondary outcomes

The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire was used to assess knee function and associated problems. The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to assess knee function and quality of life. Two objective physical functional tests were also used: the Timed Up and Go test and 30-Second Chair to Stand test.

To collect preliminary data to support future randomised controlled trials, pressure pain thresholds (algometry) and knee skin temperature (thermography) were measured. The data from these outcomes are presented in Appendix 1 on the eAddenda.

Data analysis

A blinded biostatistician performed all analyses using commercial software[a]. The Kolmogorov-Smirnov test was applied to evaluate data distribution and all variables showed $p > 0.05$. A two-factor analysis of variance was conducted for the primary outcome (visual analogue scale for pain) and secondary outcomes, with time (baseline and post-intervention) as the within-subject factor and group (experimental or control) as the between-subject factor. Tukey's test was used for post-hoc analysis when necessary and an intention-to-treat analysis was performed for all randomised participants. Missing data were replaced using the expectation maximisation method. Between-group differences and their 95% CIs were reported and interpreted against the nominated thresholds for minimum clinically important difference. For the algometry and thermography data, where minimum clinically important differences were not nominated, Cohen's *d* coefficient was calculated to aid interpretation. An effect size > 0.8 was considered large, around 0.5 moderate, and ≤ 0.2 small.[25]

Sample size was based on a significance level of 0.05 and power of 0.90 to detect a difference of 1.75 cm on the visual analogue scale, assuming a standard deviation of 2.00 cm.[26] Based on these criteria, 29 participants with knee OA were required in each group. To allow for possible dropouts during the intervention period, 30 participants were recruited per group.

Results

Flow of participants through the study

Figure 1 shows the design of the trial and flow of participants through the trial. Of the 188 volunteers, 83 attended the physical and radiographic screening. Of these, 60 participants matched the eligibility criteria and were randomised, of whom 58 completed the intervention. The baseline demographic characteristics of each group of participants are presented in Table 2. The baseline scores on the outcome measures are presented in the first two columns of Table 3.

Adherence to the study protocol

All registered outcome measures are reported in this manuscript. One participant in each group did not complete the four scheduled intervention sessions. These participants also declined to attend the post-intervention assessments, so their data were imputed as described above.

In the experimental group, the adherence diary showed that 12 (41%) of the participants used the cryotherapy intervention at home. Of these, 10 participants used it between one and three times and two participants used it more than three times.

In the control group, the adherence diary showed that 19 (66%) of the participants used the sham intervention at home. Of these, five participants used it between one and three times and 14 participants used it more than three times.

Effect of intervention

Primary outcome

The data about pain severity measured using the 10-cm visual analogue scale are presented in Table 3. The individual participant data are presented in Tables 4 and 5 on the eAddenda.

The mean between-group difference in change in pain severity was −0.8 cm (95% CI −1.6 to 0.1). That is, although pain severity reduced in both groups, the mean between-group difference favoured the experimental group by indicating 0.8 cm greater reduction in pain severity than in the control group. Neither that mean estimate nor the 95% CI reached the nominated threshold (ie, a reduction in pain severity of 1.75 cm) for the minimum clinically important difference. Therefore, the data in this study are consistent with a range of possible effects on pain severity that are not beneficial enough to make undertaking the intervention worthwhile.

Secondary outcomes

Pre-intervention and post-intervention results of the WOMAC, KOOS, Timed Up and Go test, and 30-Second Chair to Stand test are

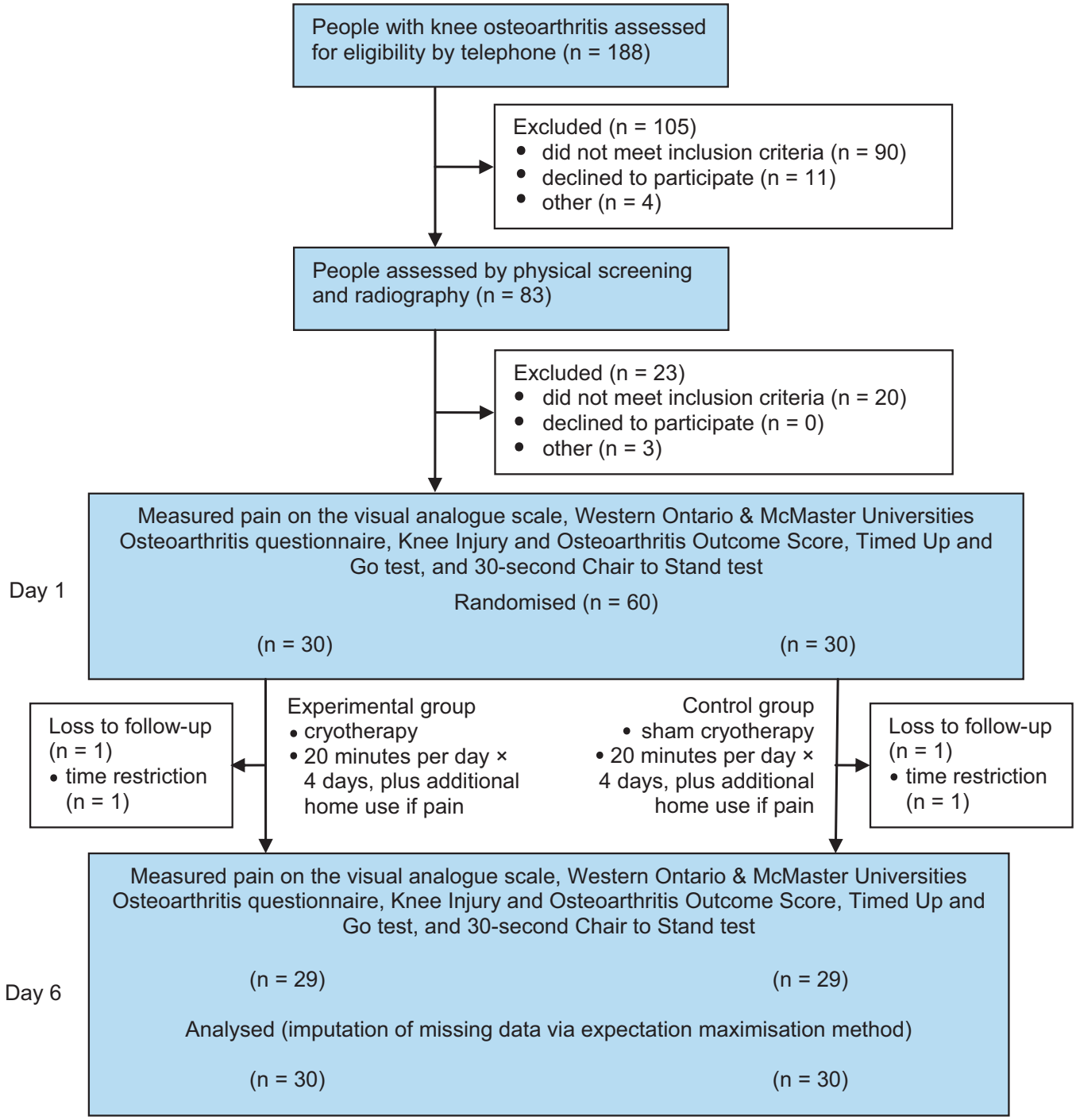

Figure 1. Design and flow of participants through the trial.

shown in Table 3. The individual participant data are presented in Tables 4 and 5 on the eAddenda.

The mean between-group difference in change in WOMAC score was −6 points (95% CI −13 to 2). That is, the mean difference favoured the experimental group by indicating 6 points greater reduction (ie, improvement) in the WOMAC score than in the control group. In order to compare this result with the minimum clinically important difference, the score can be converted into percentage change: −8% (95% CI −21 to 5). The mean estimate of −8% does not reach the nominated threshold (ie, a change of −12% from baseline), whereas the 95% CI spans the smallest worthwhile effect and also spans no effect. Therefore, the WOMAC data in this study do not provide a very precise estimate; the true average effect of cryotherapy may be worthwhile (−21 to −12%), too small to be worthwhile (−11 to 0%), or mildly harmful (1 to 5%).

The results for the remaining secondary outcome measures are similar to the results for WOMAC (Table 3). For each outcome measure, the 95% CI spans the minimum clinically important difference and no effect, so the study data are consistent with worthwhile, trivial and mildly harmful effects, as detailed below.

Table 2
Baseline characteristics of the participants.

Characteristic	Exp (n = 30)	Con (n = 30)
Age *(yr)*, mean (SD)	60 (7)	60 (7)
Gender, n (%) female	15 (50)	15 (50)
Weight *(kg)*, mean (SD)	85.0 (18.4)	83.5 (19.6)
Height *(cm)*, mean (SD)	166 (9)	164 (9)
Body mass index *(kg/m^2)*, mean (SD)	30.7 (5.8)	31.0 (7.6)

Con = control group, exp = experimental group.

Table 3
Mean (SD) of groups and mean (95% CI) within and between-group differences.

Outcome	Groups				Difference within groups		Difference between groups
	Day 1		Day 6		Day 6 minus Day 1		Day 6 minus Day 1
	Exp (n = 30)	Con (n = 30)	Exp (n = 30)	Con (n = 30)	Exp	Con	Exp minus Con
Pain visual analogue scale *(0 to 10)*	6.8 (1.8)	6.8 (1.2)	1.6 (1.7)	2.3 (1.9)	−5.2 (2.5)	−4.4 (2.3)	−0.8 (−1.6 to 0.1)
WOMAC *(0 to 96)*	44 (15)	41 (18)	12 (12)	15 (14)	−32 (19)	−26 (22)	−6 (−13 to 2)
KOOS *(0 to 168)*	89 (23)	84 (25)	27 (18)	30 (23)	−62 (29)	−54 (33)	−8 (−20 to 4)
Timed Up and Go test *(s)*	8.6 (1.7)	9.0 (2.1)	7.5 (1.2)	8.3 (1.5)	−1.1 (2.2)	−0.8 (6.0)	−0.3 (−1.1 to 0.4)
30-s Chair to Stand test *(repetitions)*[a]	10 (2)	10 (3)	13 (3)	12 (4)	3 (3)	2 (3)	1 (−1 to 2)

Shaded row = primary outcome.
Small anomalies in subtraction are due to the effects of rounding.
Negative between-group differences favour the experimental group, except where indicated.
Con = control group, exp = experimental group, KOOS = Knee Injury and Osteoarthritis Outcome Score, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
[a] A positive between-group difference favours the experimental group for this outcome.

The mean between-group difference in change in KOOS was −8 points (95% CI −20 to 4). That is, the mean difference favoured the experimental group by indicating 8 points greater reduction (ie, improvement) in the KOOS than in the control group. However, the confidence interval spanned from −20 points (ie, a worthwhile reduction in KOOS because it is greater than the minimum clinically important difference) to 4 points (ie, a mildly harmful effect).

The mean between-group difference in change in the Timed Up and Go test was −0.3 seconds (95% CI −1.1 to 0.4). That is, the mean difference favoured the experimental group by indicating a 0.3-second greater reduction (ie, improvement) in the Timed Up and Go test than in the control group. However, the confidence interval shows that the effect of cryotherapy on the Timed Up and Go test may be worthwhile (95% CI −1.1 to −0.8), trivial (−0.7 to 0.0), or mildly harmful (0.1 to 0.4).

The mean between-group difference in change in the 30-Second Chair to Stand test was 1 repetition (95% CI −1 to 2). That is, the mean difference favoured the experimental group by indicating greater improvement by 1 repetition than in the control group. However, the confidence interval shows that the effect of cryotherapy on the 30-Second Chair to Stand test may be worthwhile (2 repetitions), trivial (1 repetition), or mildly harmful (−1 repetition).

Medication use

In total, 27 (93%) of the participants in the cryotherapy group did not use any analgesic or anti-inflammatory drugs during the intervention period; two participants (7%) used medication only once for other symptoms but not knee pain. In the control group, 29 (100%) of the participants did not use any analgesic or anti-inflammatory drugs during the intervention period.

Adverse events

All 29 patients in each group who were followed up at the end of the study reported no adverse events during the intervention period.

Discussion

We believe that this is the first study to assess the isolated effects of short-term cryotherapy compared with a sham control in people with knee OA. The results showed that the effects of short-term cryotherapy application were not sufficiently superior to a sham control to make the intervention worthwhile. The study's estimate of the effect on pain severity was small enough that the confidence interval did not exceed the nominated smallest worthwhile effect. Therefore, although this study indicates that the effect of short-term cryotherapy on pain severity is beneficial, the effect is small enough that people with knee OA typically would not consider that the effect on pain severity justifies the use of cryotherapy on a short-term basis. The estimates of the effect of short-term cryotherapy on the secondary outcome measures were less precise. For each secondary outcome, the confidence interval ranged from worthwhile to mildly harmful effects. Therefore, this study does not generate any clear implications about whether or not short-term cryotherapy should be recommended to improve WOMAC, KOOS, Timed Up and Go test or the 30-Second Chair to Stand test in people with knee OA.

As a natural analgesic and anti-inflammatory,[6] cryotherapy is widely used in clinical practice to reduce pain and thereby improve function and quality of life. However, our findings do not support such widespread use. Our results also do not support the tentative observation (based on low-quality evidence) from a previous systematic review that cryotherapy was more effective than control groups using untuned short-wave diathermy and electrodes with no electrical current, respectively, for pain, stiffness, knee range of motion, and physical performance improvements.[16] Our results indicate that any beneficial effect of cryotherapy on pain is meagre, and would not be considered worthwhile, which seems consistent with a study that suggests that people with knee OA prefer heat rather than cryotherapy.[8] However, that result does not seem consistent with a previous study where cryotherapy was found to be as effective as transcutaneous electrical nerve stimulation for quadriceps activation in people with knee OA.[27]

Regarding the secondary outcomes, the between-group differences that were observed were smaller than the smallest worthwhile effects recommended for use in OA research, but the 95% CIs were wide enough to be unclear about whether the effect was or was not of clinical importance. While this suggests that further research into the effect of cryotherapy on the secondary outcomes could be undertaken, worthwhile effects seem unlikely because benefits on the secondary outcomes would presumably occur via reducing pain, and the effect on pain was small.

The differences observed within groups cannot be taken as an indication of the effect of the intervention, since there are a number of factors that can explain what happened. These include regression to the mean,[28] where participants are more likely to improve after a consultation regardless of intervention, due to symptom fluctuation;[29] polite patients effect,[29] where patients do not want to fail the therapist treating them; and the placebo effect,[30–32] where the knowledge of receiving a topical treatment, with the considerable attention given to all the participants, their expectations concerning the upcoming therapy, and bio-psychosocial elements could all have indirectly influenced the responses to the interventions applied.

The recommendations of current clinical guidelines vary regarding cryotherapy for knee OA.[2] The American College of

Rheumatology and the National Institute for Health and Care Excellence conditionally recommend cryotherapy as a complementary treatment option for people with knee OA.[9,10] However, the Osteoarthritis Research Society International, the European League Against Rheumatism, and the Ottawa Panel did not achieve expert panel consensus and failed to report cryotherapy in their final recommendations.[11–13] Our results agree with these latter guidelines. However, the most appropriate interpretation of the total body of evidence will come when our study is incorporated into a high-quality systematic review on this topic.

It is important to underscore that well-established reporting guidelines were followed to improve the evidence synthesis regarding this topic.[18,19] The methodology of this study was designed to minimise potential for bias by including concealed treatment allocation, and blinding of the outcome assessor and biostatistician. Participants presented radiographically confirmed knee OA and a sufficient level of pain to ensure ample scope for improvement. Moreover, the amount of missing outcome data was relatively small for a randomised controlled trial. Despite these strengths, the study also exhibited some limitations. The therapist who delivered cryotherapy or the placebo intervention, and the patients were not blinded. Although this may have resulted in bias, given the study design, a method of blinding patients and therapists to thermal agents has yet to be established. In addition, there was not a no-treatment group and there was not a follow-up period to evaluate the residual effect of each intervention.

In conclusion, in people with symptomatic knee OA, the short-term use of cryotherapy was not substantially superior to a sham control in terms of relieving pain, and it had uncertain effects on function and quality of life. Although cryotherapy is widely used in clinical practice, and recommended by some treatment guidelines, the estimates of its effects in this study suggest that it might not have a worthwhile effect as a treatment for knee OA.

What was already known on this topic: People with symptomatic knee osteoarthritis experience pain and disability. Cryotherapy is sometimes used to treat knee osteoarthritis. Clinical guidelines for osteoarthritis differ in their recommendations about cryotherapy. Recent systematic reviews conclude that further evidence about cryotherapy for knee osteoarthritis is needed.

What this study adds: In people with symptomatic knee osteoarthritis, any beneficial effect of short-term application of cryotherapy on pain was small enough that most people would not consider it to be worthwhile. The effects of short-term cryotherapy on function and quality of life in people with symptomatic knee osteoarthritis were unclear.

Footnotes: [a] SPSS 24.0 software, SPSS Inc, Chicago, USA.

eAddenda: Tables 4 and 5 and Appendix 1 can be found online at https://doi.org/10.1016/j.jphys.2019.08.004.

Ethics approval: This study was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: (CAEE: 65966617.9.0000.5504). All participants gave written informed consent before data collection began. The trial was conducted according to the Helsinki Statement.

Competing interests: All authors have completed a uniform disclosure form and declare that they have no conflicts of interest.

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