PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR KNEE OSTEOARTHRITIS: A PROTOCOL FOR A DOUBLE-BLIND SHAM CONTROLLED RANDOMIZED TRIAL
AUTHORS	Ogura Dantas, Lucas; Serafim Jorge, Ana Elisa; Serrao, Paula R; Sendín, Francisco A; Salvini, Tania F

VERSION 1 – REVIEW

REVIEWER	Pawel Lizis Cracow College of Health Promotion, Department of Physiotherapy, Poland
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	Will the same therapist deliver the cryotherapy and sham intervention to the participants? It is needed to be explain clearly. Please include the name of computer program used for the randomization. How was the randomiazation obtained? It is needed to be explained accurately.

REVIEWER	Cid Gomes Nove de Julho University, Brazil
REVIEW RETURNED	21-Jan-2020

GENERAL COMMENTS	- A hypothesis for the study was not structured. - It is clear that the therapists had been trained. However, it is not clear how long they have been experimenting. What's more, how many groups are they responsible for? how many will be the therapists? - Will evaluators be trained? How many will there be? - Assessors, therapists will be blinded? - Regarding the inclusion criteria, there are no notable contraindications regarding the use of cryotherapy. - How volunteers will be recruited. - The simulation of the application of cryotherapy in the Sham group is questionable. Understanding that the volunteer will know, by signing the consent form, that there is a treatment approach involving cryotherapy. It was clear that this procedure will not be used. The characterization of the placebo group is questionable.

	- It is not very clear whether cryotherapy will be used before or after the exercises. The definition and explanation of these points may be important. Since the topic has several studies with methodological problems1. - The description of the instruments to be used is remarkable. However, characteristics such as reproducibility, validity, translation were not mentioned. - I understand the justification for conducting the study. Especially when we look at the result of a recent review 1. However, if we look at the plausible rationale for using cryotherapy. What's more, if we expand the principles of applying evidence-based practice, shouldn't greater complacency be adopted regarding the use of cryotherapy for Knee Osteoarthritis? Since the clinical and physiological effects of this resource are well established, even with the highlighted limitations, is it necessary to prepare and execute a study using cryotherapy? - The literature and clinic for patients with Knee Osteoarthritis offer the therapist great concern with functionality. Thinking about it, would pain intensity at rest be the best parameter for monitoring these patients? And thinking like that, to be defined as a primary outcome? 1. Dantas LO, Moreira RFC, Norde FM, Mendes Silva Serrao PR, Alburquerque-Sendín F, Salvini TF. The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rehabil. 2019; 33 (8): 1310–1319. doi: 10.1177 / 0269215519840406

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. *Will the same therapist deliver the cryotherapy and sham intervention to the participants? It is needed to be explain clearly.*

   Reply: We have added the requested information in our text. Page 08, lines 20-21

   "Both therapists will be responsible for delivering cryotherapy and sham interventions."

2. *Please include the name of computer program used for the randomization. How was the randomization obtained? It is needed to be explained accurately.*

   Reply: We have added the requested information in our text. Page 12, lines 02-10"

   "Eligible patients who consent to participate will be randomly allocated into three groups of 40: (1) active control group that will receive the STE protocol only, (2) STE + cryotherapy group, and (3) STE + sham cryotherapy group. The allocation of patients will be performed using permuted block randomization stratified by gender (20 men and 20 women in each group); randomization sequences will be determined by a computer-generated random numbers program (www.randomization.com). Allocation will be concealed by placing randomization assignments in opaque sealed envelopes that will be locked in a central location. A biostatistician will be responsible for generating the random numbers and each participant's random allocation will be revealed to the therapist administering the intervention just before study onset"

Reviewer #2:

1. *A hypothesis for the study was not structured.*

   Reply: We have added a hypothesis for the study in our introduction section. Page 05, lines 12-13: “We hypothesize that cryotherapy combined with the STE protocol will achieve better treatment effects on KOA patients when compared to the other two groups.”

2. *It is clear that the therapists had been trained. However, it is not clear how long they have been experimenting. What's more, how many groups are they responsible for? how many will be the therapists?*

   Reply: We have added the requested information in our text. Page 08, lines 10-21”

   “Two physical therapists will administer the interventions in the physiotherapy clinic of the University. The study will take place over the course of eight weeks, with three 90-minute sessions per week occurring on non-consecutive days, for a total of 24 sessions. All randomized participants will perform the STE protocol and then, according to random allocation, each patient will subsequently receive either cryotherapy or sham interventions in individual rooms.

   Prior to the beginning of the study, the therapists responsible for the interventions will participate in a 10-hour training module, which will consist of scientific information and clinical training regarding KOA, the STE protocol, and the use of cryotherapy. After the first training module is completed, the therapists will do an eight-week training module, which will consist of practicing the full-length protocol and intervention application(s) three times per week. Both therapists will be responsible for delivering cryotherapy and sham interventions.”

3. *Will evaluators be trained? How many will there be?*

   Reply: There are two assessors in our study. We have added more information regarding assessors training in our methods section. Page 06, line 16-18: “To reduce bias, the therapists responsible for applying the intervention and the outcome assessors will follow standardized scripts that describe the general objective of the study.” Page 10, line 23 and Page 11 line 1: “Before the study begins, the two outcome assessors will be trained to conduct interviews and perform data collection measurements, following a standard protocol.”

4. *Assessors, therapists will be blinded?*

   Reply: The assessors in the study will be blinded. Page 10, line 22: “The same blinded assessor will measure all outcomes before and after the intervention, and at the 3- and 6-month follow-up periods.” However, due to the nature of the chosen treatment modality (cryotherapy) and to the best of our knowledge, blinding is not possible. Therefore, on this study, the therapists and the patients will not be blinded regarding the interventions.

5. *Regarding the inclusion criteria, there are no notable contraindications regarding the use of cryotherapy.*

   Reply: We have added this information in our exclusion criteria. Page 08, lines 03-05: “Additionally, participants presenting with contraindication(s) to cryotherapy application (i.e., those that feel a high level of discomfort or pain during the application) will be excluded.”

6. *How volunteers will be recruited.*

   Reply: Please, see that the recruitment method is described at Page 07, lines 10-13: "Participants will be recruited through public announcements on social media, advertisements via local news outlets, University community newsletters, and banners or leaflets posted at strategic locations in the city."

7. *The simulation of the application of cryotherapy in the Sham group is questionable. Understanding that the volunteer will know, by signing the consent form, that there is a treatment approach involving cryotherapy. It was clear that this procedure will not be used. The characterization of the placebo group is questionable.*

   Reply: We have tried hard to mimic the application of cryotherapy with our sham therapy and we understand the theoretical rationale behind creating a sham. However, the sham we will use on this study is the best alternative we could find so far to mimic the intervention. We are following the proposed methodology accepted in our latest publication in the Australian Journal of Physiotherapy (https://doi.org/10.1016/j.jphys.2019.08.004), where we demonstrated that cryotherapy short-term effects is no better than placebo for similar outcomes.

8. *It is not very clear whether cryotherapy will be used before or after the exercises. The definition and explanation of these points may be important. Since the topic has several studies with methodological problems[1].*

   Reply: Please, see that the use of the cryotherapy or sham intervention is described at Page 08, lines 12-14: "All randomized participants will perform the STE protocol and then, according to random allocation, each patient will subsequently receive either cryotherapy or sham interventions in individual rooms."

9. *The description of the instruments to be used is remarkable. However, characteristics such as reproducibility, validity, translation were not mentioned.*

   Reply: We did not add this information to the tables due to space and layout. However, we have added the information now into the text, in outcomes measures section, described at Page 11, lines 13-21: "To subjectively assess physical function and associated problems, the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) will be used. WOMAC is a frequently used questionnaire in KOA and is translated, reproducible, and valid to Brazilian Portuguese.[40] The Medical Outcomes Survey Short-Form 36 (SF-36) questionnaire will be used to asses quality of life. The questionnaire is translated, reproducible, and valid to use in Brazilian Portuguese.[41] Three objective physical function tests will also be used: The 30-Second Chair Stand test, the Stair Climb test, and the 40-Meter fast-paced walk test. The questionnaires and physical function tests described are well-established core assessment measures of pain and physical function in patients with KOA, and presenting good scores for reliability, validity, and ability to detect change.[42–46] "

10. *I understand the justification for conducting the study. Especially when we look at the result of a recent review 1. However, if we look at the plausible rationale for using cryotherapy. What's more, if we expand the principles of applying evidence-based practice, shouldn't greater complacency be adopted regarding the use of cryotherapy for Knee Osteoarthritis? Since the clinical and physiological effects of this resource are well established, even with the highlighted limitations, is it necessary to prepare and execute a study using cryotherapy?*

    Reply: We understand your rationale regarding the use of cryotherapy in knee osteoarthritis (OA). However, as shown by the latest review that our group conducted[1], there is still insufficient primary studies to draw any conclusions about the effectiveness of cryotherapy on pain and physical function on individuals with knee OA. This is of paramount importance, since recent guidelines are still not certain about the recommendation of the thermal agent for knee OA

individuals due to lack of high-quality evidence[2,3]. We hope that this study supports the future guidelines recommendations to use or not the thermal agent for knee OA treatment.

11. *The literature and clinic for patients with Knee Osteoarthritis offer the therapist great concern with functionality. Thinking about it, would pain intensity at rest be the best parameter for monitoring these patients? And thinking like that, to be defined as a primary outcome?*

Reply: This was a writing mistake. We are indeed measuring pain intensity after each physical function test. We have added this information in our text. Page 11, lines 07-10 "The primary outcome will be pain intensity at rest, assessed with a Visual Analogue Scale (VAS). This self-reported pain score is a valid and reliable measure for KOA.[39] The VAS will be administered at rest and after each physical function test, occurring at baseline, on the final assessment day, and at the 3- and 6-month follow-up periods."

REFERENCES:

1. Dantas LO, Moreira RFC, Norde FM, Mendes Silva Serrao PR, Alburquerque-Sendín F, Salvini TF. The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rehabil. 2019; 33 (8): 1310–1319. doi: 10.1177 / 0269215519840406
2. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020; 0: art.41142.
3. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil* 2019; 27: 1578–1589.

VERSION 2 – REVIEW

REVIEWER	Cid Gomes Nove de Julho University
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	The authors will carry out and respond to all requests by two reviewers. Satisfactory work has been done. I do not want, about what: 7. *The simulation of the application of cryotherapy in the Sham group is questionable. Understanding that the volunteer will know, by signing the consent form, that there is a treatment approach involving cryotherapy. It was clear that this procedure will not be used. The characterization of the placebo group is questionable.* **Reply**: We have tried hard to mimic the application of cryotherapy with our sham therapy and we understand the theoretical rationale behind creating a sham. However, the sham we will use on this study is the best alternative we could find so far to mimic the intervention. We are following the proposed methodology accepted in our latest publication in the Australian Journal of Physiotherapy (https://doi.org/10.1016/j.jphys.2019.08.004), where we demonstrated that cryotherapy short-term effects is no better than placebo for similar outcomes. The authors must then reference and justify this approach in the description of the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author

1. *Please state any competing interests or state 'None declared': None declared'*

Reply: We have already declared the competing interests on page 14, line 22.

2. *The authors must then reference and justify this approach in the description of the manuscript*.

7. *The simulation of the application of cryotherapy in the Sham group is questionable. Understanding that the volunteer will know, by signing the consent form, that there is a treatment approach involving cryotherapy. It was clear that this procedure will not be used. The characterization of the placebo group is questionable.*

Reply: We have tried hard to mimic the application of cryotherapy with our sham therapy and we understand the theoretical rationale behind creating a sham. However, the sham we will use on this study is the best alternative we could find so far to mimic the intervention. We are following the proposed methodology accepted in our latest publication in the Australian Journal of Physiotherapy (https://doi.org/10.1016/j.jphys.2019.08.004), where we demonstrated that cryotherapy short-term effects is no better than placebo for similar outcomes.

Reply: We have added this information in our manuscript and referenced it. Page 8, lines 10-11: "The intervention protocol is based on a previously accepted methodology developed in our research laboratory.[31]"