Whole-body cryotherapy (extreme cold air exposure) for preventing and treating muscle soreness after exercise in adults (Protocol)

Costello JT, Baker PRA, Minett GM, Bieuzen F, Stewart IB, Bleakley C

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[Intervention Protocol]

Whole-body cryotherapy (extreme cold air exposure) for preventing and treating muscle soreness after exercise in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects (benefits and harms) of whole-body cryotherapy (cold air exposure) for preventing and treating muscle soreness after exercise in adults.

BACKGROUND

Elite-level athletic participation necessitates recovery from many physiological stressors, including fatigue to the musculoskeletal, nervous and metabolic systems (Nédélec 2013). Athletic participation may also result in exercise-induced muscle damage (EIMD), which may lead to delayed-onset muscle soreness (DOMS) and decrements in subsequent performance (Howatson 2008). Various therapeutic modalities of recovery are currently used by athletes in an attempt to offset the negative effects of strenuous exercise (Bieuzen 2013; Bleakley 2012; Nédélec 2013).

Description of the condition

DOMS is a broad term used to describe the muscular pain, tenderness and stiffness experienced after high-intensity, eccentric (when the muscle is forcibly stretched when active) or unaccustomed exercise (Cheung 2003; Ebbeling 1989; Howatson 2008; Newham 1987). Clinically associated with EIMD, DOMS is proposed to result from mechanical disturbances of the muscle membrane that evoke secondary inflammation, swelling and free radical proliferation (Connolly 2003). These events typically peak 24 to 96 hours post exercise (Cheung 2003) and may reduce physical capacity via alterations in muscle length, maximal force and range of motion (Prasartwuth 2006; Saxton 1995). Although damage to the exercised musculature is linked to the biochemical expression of

intracellular enzymes, compensatory neuromuscular recruitment patterns may contribute both central and peripheral factors to DOMS aetiology (Byrne 2004).

Symptoms associated with DOMS typically dissipate within five to seven days post exercise with adequate rest (Cheung 2003). Nevertheless, various interventions have been advocated to prevent or treat, or both prevent and treat, EIMD and associated DOMS, including cool-down, stretching, nutritional supplements, massage, hydrotherapy, compression, electrotherapy and non-steroidal anti-inflammatory medications (Bieuzen 2013; Bleakley 2012; Herbert 2011). Despite their widespread popularity (Nédélec 2013), empirical support for the use of these interventions for DOMS remains tenuous (Bleakley 2012; Herbert 2011).

Description of the intervention

Whole-body cryotherapy (WBC) is increasingly used in sports medicine as treatment for muscle soreness after exercise. This treatment involves exposing individuals to extremely cold dry air (below -100°C) for two to four minutes. To achieve the subzero temperatures required for WBC, two methods are typically used: liquid nitrogen and refrigerated cold air. During these exposures, individuals wear minimal clothing, which usually consists of shorts for males and shorts and a crop top for females. Gloves, a woollen headband covering the ears, and a nose and mouth mask, in addition to dry shoes and socks, are commonly worn to reduce the risk of cold-related injury.

The first WBC chamber was built in Japan in the late 1970s, but WBC was not introduced to Europe until the 1980s, and has only been used in the USA and Australia in the past decade (Miller 2012). The treatment was initially intended for use in a clinical setting to treat patients with conditions such as multiple sclerosis (Miller 2012) and rheumatoid arthritis (Hirvonen 2006; Metzger 2000); however, elite athletes have recently reported using the treatment to alleviate DOMS after exercise (Costello 2012a; Fonda 2013; Hausswirth 2011; Pournot 2011; Ziemann 2012). WBC is commonly employed shortly (within 0 to 24 hours) after exercise, and the treatment is often repeated on the same day (Costello 2012a) or over several days (Lubkowska 2012; Ziemann 2012). Recently, recreational athletes have started to emulate elite athletes in using the treatment after exercise.

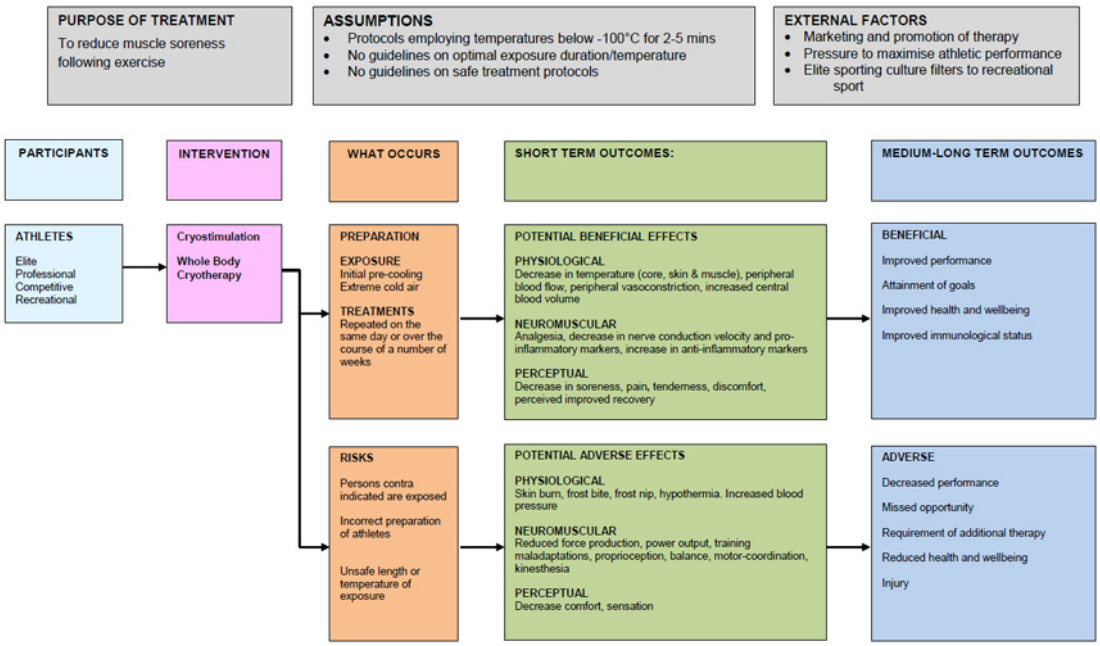
How the intervention might work

Reductions in muscle and skin tissue temperature after WBC exposure (Costello 2012b; Costello 2012c; Costello 2013) may stimulate cutaneous receptors and excite the sympathetic adrenergic fibres, causing constriction of local arterioles and venules (Savic 2013). Consequently, WBC may be effective in relieving soreness through reduced muscle metabolism, receptor sensitivity and nerve conduction velocity. In addition, both Bleakley 2012 and Cochrane 2004 describe the potential psychological benefits of using other modalities of cold exposure (e.g. cold water immersion) to reduce the subjective feeling of DOMS following exercise.

Although the research examining WBC is typically limited in terms of quality and statistical power (Costello 2012a; Costello 2012b), some studies have described a reduction in creatine kinase activity after training (Wozniak 2007), increases in parasympathetic activation (Hausswirth 2013) and an increase in anti-inflammatory cytokines (proteins that serve to regulate the inflammatory response) (Lubkowska 2010; Lubkowska 2011) after WBC exposure. A reduction in the severity of muscle damage after exercise and an increase in anti-inflammatory cytokines post-treatment may help to reduce both the initial damage and the secondary inflammatory damage associated with EIMD. However, from a mechanistic perspective, very little is known about the physiological and biochemical rationale for using WBC in the management of DOMS.

Using the approach described by Anderson 2011, we developed a logic model to capture the wide range of potential effects of WBC exposure (Figure 1). This model is divided into two sections: (1) potential recovery benefits and (2) potential adverse effects. Missing from this model is any appraisal of the logistical, environmental and financial costs associated with WBC.

Figure 1. Logic Model describing the potential benefits and adverse effects of whole-body cryotherapy



Why it is important to do this review

This review aims to examine the effects, both beneficial and harmful, of WBC used for the purpose of preventing or treating muscle soreness after exercise. Currently, no guidelines for a clinically effective or safe WBC protocol are available. Because of the extreme temperatures employed during WBC, the potential for short- and long-term adverse effects needs to be elucidated. A systematic review of the evidence is also important because of the increasing use of WBC by elite and recreational athletes and the potential for long-term use throughout a sporting career in an attempt to alleviate DOMS.

OBJECTIVES

To assess the effects (benefits and harms) of whole-body cryotherapy (cold air exposure) for preventing and treating muscle soreness after exercise in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised and quasi-randomised (method of allocating participants to a treatment that is not strictly random, e.g. by date of birth) controlled clinical trials evaluating WBC for prevention and treatment of muscle soreness after exercise in adults.

Types of participants

No restrictions will be placed on gender or on type or level of exercise. All field- and laboratory-based (including eccentric) exercise modalities will be included. Studies focusing on children (< 18 years of age) or injured participants will be excluded. We anticipate that people with vascular problems, such as Raynaud's disease, who are contraindicated for cryotherapy, will be excluded from trials.

Types of interventions

At least one group in the trial will comprise participants treated with whole-body cryotherapy before or after exercise. WBC will be defined as exposure of the body (trunk, arms and legs) to extremely cold dry air (below -100°C). These exposures can be administered as a once-off treatment, or they can be repeated several times on the same days or over several days.

Consistent with the logic model included in this protocol, comparisons can be made with any other form of intervention designed to prevent or treat DOMS, including, but not limited to, passive interventions (rest, no treatment or placebo treatment), cold water immersion (immersion in water colder than 15°C), warm water immersion (immersion in water warmer than 15°C), contrast water immersion (alternating hot and cold water immersion), cool-down, stretching, massage and compression garments. Studies comparing different durations or dosages of WBC will be included. Trials in which the same WBC protocol is used in both arms as a co-intervention will not be included. Comparisons with pharmacological interventions will be excluded.

Types of outcome measures

Primary outcomes

- Muscle soreness (e.g. pain measured with the use of visual analogue scales and algometer data)
- Subjective recovery (return to previous activities without signs or symptoms)
- Immediate or long-term complications or adverse effects (e.g. frost bite, adverse cardiac or vascular events, musculoskeletal injury)

Secondary outcomes

- Muscle strength and power (muscle contractile properties)
- Objective test of function and performance (e.g. hop test)

Resource use

We will collect cost and resource data, including cost of the intervention and cost of time off work or professional sports activity.

Timing of outcome assessment

We plan to collect data at the following follow-up times: immediately and 24, 48, 72, 96 and more than 96 hours post intervention. These are typical follow-up times for studies assessing treatment for DOMS.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials (to present), MEDLINE (1946 to present), EMBASE (1974 to present), Cumulative Index to Nursing and Allied Health (CINAHL) (1982 to present), British Nursing Index and archive (BNI) (1985 to present) and the Physiotherapy Evidence Database (PEDro) (1929 to present).

In MEDLINE, the subject-specific search will be combined with the sensitivity- and precision-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011). This strategy will be modified for use in other databases (see Appendix 1 for the MEDLINE search strategy).

We will also search Current Controlled Trials and the WHO International Clinical Trials Registry Platform for ongoing and recently completed trials.

We will apply no language restrictions.

Searching other resources

The reference lists of relevant articles will be searched in addition to the table of contents of the following journals not registered as being handsearched by the Cochrane Collaboration.

- *(Australian) Journal of Science and Medicine in Sport* (1998 to present).
- *British Journal of Sports Medicine* (1964 to present).
- *Clinical Journal of Sport Medicine* (1991 to present).
- *International Journal of Sports Medicine* (2005 to present).
- *Journal of Applied Physiology* (1948 to present).
- *Journal of Sports Medicine and Physical Fitness* (1998 to present).
- *Journal of Sports Sciences* (1985 to 1987; 1990 to 1991; 1994; 1996; 2000 to present).
- *Medicine and Science in Sports and Exercise* (1980 to present).
- *Physical Therapy in Sport* (2000 to 2002; 2007 to present).

We will also search the conference proceedings of the following organisations.

- American College of Sports Medicine (1986 to present) (in *Medicine and Science in Sports and Exercise*).
- American Physical Therapy Association (1980 to present) (in *Physical Therapy*).
- British Association of Sport and Exercise Medicine (BASEM) (1964 to present) (in *British Journal of Sports Medicine*).
- British Association of Sport and Exercise Sciences (BASES) (1964 to present) (in *Journal of Sports Sciences*).
- World Confederation for Physical Therapy (2003, 2007, 2011) (CD-ROM).

Data collection and analysis

Selection of studies

Two review authors (JTC, GMM) will independently select trials for inclusion. First, we will screen titles and abstracts of publications obtained by the search strategy and will remove only those

that are obviously outside the scope of the review. We will be over-inclusive at this stage and will seek the full text for any papers that might meet the review inclusion criteria. We will aim to link together multiple publications and reports of the same study. The same two review authors will then independently select trials using a standardised form to record their choices. We will not be blinded during this process with respect to authors' names, journal or date of publication. When possible, translation of non-English language studies will be undertaken. Primary authors will be contacted when necessary to ask for clarification of study characteristics. Disagreement between the review authors will be resolved by consensus or by third party adjudication (CB, PRAB, IBS).

Data extraction and management

Two review authors (JTC, CB) will use a customised form to independently extract relevant data on methodology, eligibility criteria, interventions (including detailed characteristics of the exercise protocols and the whole-body cryotherapy protocol employed), comparisons and outcome measures. Details of the characteristics of included participants such as training status, age, sex and health status will also be recorded. When available, we will also extract data on participant subgroups, including any equity considerations such as ethnicity and socioeconomic status. Any included study written by one of the current review authors will be reviewed by review authors who did not participate in the original study. Any disagreement will be resolved by consensus or by third party adjudication (GMM, PRAB). Primary authors will be contacted to clarify any omitted data or study characteristics. For intention-to-treat analysis, data will be extracted according to the original allocation groups, and losses to follow-up will be noted when possible.

Assessment of risk of bias in included studies

Two review authors (JTC, CB) will independently assess risk of bias using the tool described (and the criteria outlined) in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). To minimise bias in the interpretation of this scale, two review authors (JTC, CB) will initially assess a small sample of unrelated studies (not included in the current review); disparities in risk of bias judgements will be reviewed and discussed before any of the included studies is evaluated.

Each study will be graded for risk of bias in each of the following domains: sequence generation, allocation concealment, blinding (participants and intervention providers; outcome assessment), incomplete outcome data and selective outcome reporting. Two other sources of bias will be considered on the basis of the following questions: (1) Was the exercise protocol clear and consistent between groups? (2) Were co-interventions used, and if so, were they standardised across groups? For each study, the information pertaining to each of the domains will be described as reported in the published study report (or, if appropriate, based on information from related protocols or published comments or after discussion with the relevant authors) and the associated risk of bias judged by the review authors. Studies will be assigned 'high risk', 'low risk' or 'unclear risk' when there is uncertainty or when information is insufficient to allow review authors to make a judgement. Disagreements between review authors regarding the risk of bias assessment will be resolved by consensus.

Measures of treatment effect

For each study, risk ratios and 95% confidence intervals will be calculated for dichotomous outcomes, and mean differences and 95% confidence intervals for continuous outcomes. For continuous outcomes that are pooled on different scales, standardised mean differences will be used. When possible, follow-up scores will be used in preference to change scores.

Unit of analysis issues

If trials include data from a cluster-randomised study design, the data will be adjusted for clustering when possible. It is possible that studies will include repeated observations of the same outcome; consequently we will extract data at clinically relevant time points. When available, the following time points will be included: immediately after the exercise, immediately after the intervention and then at 24-hour intervals (0 to 24 hours, 25 to 48 hours, 49 to 72 hours, 73 to 96 hours and over 96 hours).

Dealing with missing data

In cases where data are missing, we will consider why they are missing. Whenever possible, we will contact study authors to request missing data or to ask for an explanation as to why data are missing. Unless missing standard deviations can be derived from confidence intervals, standard errors or exact P values, we will not assume or impute values for these in order to present results in the analyses.

Assessment of heterogeneity

Assessment of heterogeneity between comparable trials will be evaluated visually with the use of forest plots, as well as Chi^2 tests and I^2 statistics. The level of significance for the Chi^2 test will be set at $P = 0.1$ (Deeks 2011): a P value for $Chi^2 < 0.1$ will be considered to indicate statistically significant heterogeneity between studies. Values of I^2 will be interpreted as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.

Assessment of reporting biases

We will be vigilant in watching for duplicate publications of the same studies. Funnel plots of the effect estimates against standard error (on a reversed scale) will be created using Review Manager (RevMan 2011); these will be used to assess reporting bias when 10 or more trials are included in a comparison. Standard errors will be plotted on the vertical scale. Effect estimates will therefore be plotted on the horizontal scale, with continuous data represented as standardised mean differences, and dichotomous data represented as risk ratios on a logarithmic scale.

Data synthesis

When considered appropriate, results of comparable groups of trials will be pooled using both fixed-effect and random-effects models. The choice of the model to report will be guided by careful consideration of the extent of heterogeneity and whether it can be explained, in addition to other factors, such as the number and size of included studies. Ninety-five per cent confidence intervals will be used throughout. We will consider not pooling data when considerable heterogeneity ($I^2 > 75\%$) that cannot be explained by the diversity of methodological or clinical features is observed among trials. When it is inappropriate to pool data, we will still present trial data in the analyses or tables for illustrative purposes and will report them in the text.

Subgroup analysis and investigation of heterogeneity

When data allow, we intend to perform the following subgroup analyses.

- Gender (male versus female)
- Exposure dose (single versus repeated exposures; short versus long exposure durations)
- Exercise type (normal sporting activities and laboratory-induced DOMS)
- Training status (elite versus recreational)

We have chosen these subgroup analyses because gender, type of athletic activity and training status may impact the severity of DOMS experienced after exercise (Howatson 2008; McGinley 2009). In particular, DOMS may be augmented in untrained males after eccentric exercise when compared with trained females performing concentric exercise. Moreover, reductions in tissue temperature may be more pronounced after repeated, or longer, WBC exposures (Costello 2012c). We will investigate whether the results of subgroups are significantly different by inspecting the overlap of confidence intervals and by performing the test for determining subgroup differences that is available in Review Manager (RevMan 2011).

Sensitivity analysis

If some of the included trials are at high risk of bias for one or more domains, we will perform sensitivity analysis to determine whether inclusion of such trials significantly influences the effect size. We will consider trials at high risk of bias in sensitivity analysis if allocation concealment is unclear or at high risk of bias, or if attrition is greater than 20%. We will also carry out sensitivity analysis to explore the effects of using fixed-effect or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made, such as the value of the intracluster correlation coefficient used for cluster-randomised trials.

Summary of findings table

We will prepare a 'Summary of findings' table for each of the main comparisons using the GRADE profiler (Schünemann 2011). We will summarise the quality of evidence by applying the principles of the GRADE framework and following the recommendations and worksheets of Cochrane Effective Practice and Organisation of Care Group for creating 'Summary of findings' tables (EPOC 2011). Thus, we will use four levels of quality (high, moderate, low and very low) to describe the body of evidence.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 Cryotherapy/
2 Hypothermia, Induced/
3 cryotherapy.tw.
4 cryostimulation.tw.
5 cooling.tw.
6 ((cold or cool*) adj3 (air or treat* or chamber*)).tw.
7 "liquid nitrogen".tw.
8 (low adj2 temp*).tw.
9 or/1-8
10 Exercise/
11 Sports/
12 Muscle, Skeletal/
13 Athletic Injuries/
14 Soft Tissue Injuries/
15 exp Creatine Kinase/
16 Physical Exertion/
17 Muscle Fatigue/
18 Muscle Cramp/ or Spasm/ or Muscle Rigidity/ or "Sprains and Strains"/ or Muscle Weakness/
19 (sore$ adj3 musc$).tw.
20 DOMS.tw.
21 (exercise induced and (muscle$ adj2 (damage$ or injur$))).tw.
22 Lactic Acid/
23 (lactate$ or lactic).tw.
24 or/10-23
25 9 and 24
26 Randomized controlled trial.pt.
27 Controlled clinical trial.pt.
28 randomized.ab.
29 placebo.ab.
30 Clinical Trials as Topic/
31 randomly.ab.
32 trial.ti.
33 26 or 27 or 28 or 29 or 30 or 31 or 32
34 exp Animals/ not Humans/
35 33 not 34
36 25 and 35

CONTRIBUTIONS OF AUTHORS

JTC is the guarantor for this protocol, developed the research idea and wrote the original protocol.

PRAB, GMM, FB, IBS and CB contributed to writing the protocol, commented on earlier drafts and approved the final version.

DECLARATIONS OF INTEREST

Joseph Costello (Costello 2012a) and François Bieuzen (Hausswirth 2011; Pournot 2011) have previously co-authored studies that are likely to be included in this review. Decisions on inclusion of these studies, the risk of bias assessment and data extraction of these studies, if included, will be undertaken by other review authors (PRAB, CB and GMM), who had no involvement in these studies.

SOURCES OF SUPPORT

Internal sources

- None to declare, Not specified.

External sources

- None to declare, Not specified.