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Literature review

Effectiveness and safety of cryotherapy after arthroscopic anterior cruciate ligament reconstruction. A systematic review of the literature

Ana Luiza Cabrera Martimbianco*, Brenda Nazaré Gomes da Silva, Alan Pedrosa Viegas de Carvalho, Valter Silva, Maria Regina Torloni, Maria Stella Peccin

Department of Internal Medicine, Federal University of Sao Paulo, Rua Botucatu, 740, 04023-900 São Paulo, SP, Brazil

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ABSTRACT

Cryotherapy is widely used in rehabilitation; however, its effectiveness after anterior cruciate ligament (ACL) reconstruction remains uncertain. To investigate the effectiveness and safety of cryotherapy following ACL reconstruction through a systematic review, randomized and quasi-randomized clinical trials were searched in the databases: MEDLINE, EMBASE, CENTRAL, PEDro, SportDiscus, CINAHL, LILACS (June 2013). The primary outcomes measures were pain, edema and adverse events; the secondary outcomes were knee function, analgesic medication use, range of motion, blood loss, hospital stay, quality of life and patient satisfaction. The methodological quality of studies was evaluated using the Cochrane Collaboration risk-of-bias tool. Ten trials (a total of 573 patients) were included. Results of meta-analysis showed that the use of cold compression devices produced a significant reduction in pain scores 48 h after surgery ($p < 0.00001$), compared to no cryotherapy. The risk for adverse events did not differ between patients receiving cryotherapy versus no treatment ($p = 1.00$). The limited evidence currently available is insufficient to draw definitive conclusions on the effectiveness of cryotherapy for other outcomes. There is a need for well designed, good quality randomized trials to answer other questions related to this intervention and increase the precision of future systematic reviews.

1. Introduction

Rupture of the anterior cruciate ligament (ACL) of the knee is currently one of the most common musculoskeletal injuries related to sports activities, with an estimated 200,000 new cases per year in the United States (Gianotti, Marshall, Hume, & Bunt, 2009; Siegel, Vandenakker-Albanese, & Siegel, 2012). Arthroscopic ACL reconstruction surgery is the gold standard for treating ACL tears (Adams, Logerstedt, Hunter-Giordano, Axe, & Snyder-Mackler, 2012; Lobb, Tumilty, & Claydon, 2012). However, the post-operative period is generally associated with important clinical symptoms, including local pain, edema and reduced knee range of motion, which delay functional recovery time (van Grinsven, van Cingel, Holla, & van Loon, 2010; Yabroudi & Irrgang, 2013).

The use of ice, or cryotherapy, is an easily available, low-cost and popular intervention that has been widely used for acute musculoskeletal injuries. Cold reduces cellular metabolism, nerve conduction, edema formation and pain, thus helping injured tissues to recover (Ho, Coel, Kajawa, & Richardson, 1994; Nadler, Weingand, & Kruse, 2004; Warren, McCarty, Richardson, Michener, & Spindler, 2004). Cold has also been used in post-operative patients. By relieving acute symptoms including pain and edema, cryotherapy is believed to accelerate post-operative rehabilitation and the return to regular activities. Several studies have tested the effects of cryotherapy in the relief of post-operative pain after knee surgery (Glenn, Spindler, Warren, McCarty, & Secic, 2004; Lessard, Scudds, Amendola, & Vaz, 1997; Martin, Spindler, Jeremy, Tarter, Detwiler, & Petersen, 2001; Woolf, Barfield, Merrill, & McBryde, 2008). It has been hypothesized that this effect may be due to decreased release of inflammatory mediators, such as prostaglandin E2, in the synovial membranes (Stålman, Berglund, Dungnerc, Arner, & Felländer-Tsai, 2011).

Cold therapy can be applied through different methods, including cold packs, ice massages, crushed-ice bags and cold compression devices. Up to the present, there is no consensus on which of these methods is most effective, nor on what is the ideal duration of therapy or whether it should be used intermittently or continuously (Dykstra, Hill, Miller, Cheatham, Michael, & Baker,

* Corresponding author. Tel./fax: +55 11 5575 2970.
E-mail address: analuizacabrera@hotmail.com (A.L.C. Martimbianco).

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2009; Rupp, Herman, Hertel, & Saliba, 2012; Warren et al., 2004; Wilke & Weiner, 2003). The safety of cryotherapy also needs to be considered, since ice can lead to skin burns (frostbite) and superficial nerve paralysis, as well as urticarial reactions and Raynaud's phenomenon (McGuire & Hendricks, 2006; Nadler et al., 2004).

In 2005, a systematic review concluded that cryotherapy was effective in reducing post-operative pain after ACL reconstruction (Raynor, Pietrobon, Guller, & Higgins, 2005). Since more trials have been published over the last years, we decided to update, critically appraise and synthesize the existing evidence on the effectiveness and safety of cryotherapy following arthroscopic ACL reconstruction. This review will help to inform the clinical decisions of patients and physicians and to map existing controversies and research gaps in this area.

2. Methods

This systematic review was conducted according to the recommendations of the Cochrane Collaboration (Higgins & Green, 2011) and the PRISMA reporting guidelines (Moher, Liberati, Tetzlaff, & Altman, 2010).

2.1. Eligibility criteria

Types of studies: Randomized and *quasi*-randomized controlled trials (e.g. allocation by patient record number, date of birth).

Participants: Skeletally mature patients (≥18 years old) submitted to primary ACL arthroscopic reconstruction. Studies including patients with bilateral ACL reconstruction, re-rupture or concurrent knee ligament surgery were excluded.

Interventions: Any type of cold application around the knee (e.g. ice packs, cooling pads or cold compression devices) compared to any control group (e.g. placebo, no cold therapy, different types of cold therapy, other clinical interventions – pharmacological or not). A cold compression device (CCD) is a cooling system that consists of a reservoir filled with cold water that is connected to two rubber plates or braces, via a rubber hose, which completely involves the joint. The cold water circulates through the hose to the knee and temperature is controlled by the device's control system (Nadler et al., 2004).

2.2. Outcome measures

Primary outcomes: (1) Pain intensity (measured by e.g. visual analog scale (VAS)), (2) Edema (e.g. knee circumference measured using tape) and (3) Adverse events (thermal injury, such as burn, transient nerve palsy).

Secondary outcomes: (1) Function measured by knee scores (e.g. Lysholm score, IKDC score); (2) Post-operative analgesic medication use; (3) Knee range of motion; (4) Blood loss (as measured from the intra-articular drain before removal); (5) Length of hospital stay; (6) Quality of life measures (e.g. SF-36 questionnaire); (7) Patient satisfaction.

2.3. Search strategy

The following databases were searched: MEDLINE (via Pubmed, 1966 to June 2013); EMBASE (via Elsevier, 1980 to June 2013); Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 5, 2013); PEDro (1999 to June 2013); SportDiscus (1985 to June 2013); CINAHL (1982 to June 2013) and Literature of Latin America and the Caribbean: LILACS (1982 to June 2013). We also searched ClinicalTrials.gov for ongoing and recently completed trials. No restrictions were placed on language of publication. The search was complemented by screening the reference lists of the retrieved articles.

The search strategies were based on the strategy developed for MEDLINE (via Pubmed), combined with the high-pass sensitivity filter developed by the Cochrane Collaboration (Higgins & Green, 2011) to identify randomized controlled trials. The following search terms were used: *"Anterior Cruciate Ligament" OR "Anterior Cruciate Ligament Reconstruction" OR "Bone-Patellar Tendon-Bone Graft" OR "Arthroscopy", AND "Cryotherapy" OR "Cold Therapy"* and related terms adapted for each database **(**Appendix**)**.

2.4. Study selection

Two reviewers (ALCM and BNGS) independently screened the titles and abstracts retrieved through the search strategy. The full texts of all studies considered potentially relevant were obtained and read independently by the same two reviewers. The studies fulfilling the aforementioned selection criteria were included in the review. Disagreements between the two reviewers were settled by a third reviewer (MSP).

2.5. Data extraction

Two independent reviewers (ALCM and VS) extracted data from all included studies using a standardized extraction form especially created for this review. The form collected information on participants, methodological aspects of the study, interventions, outcomes and results. The two individual forms were discussed by the reviewers until consensus was reached and merged into a single extraction form. Persistent disagreements were settled by a third reviewer (MSP). When necessary, authors of the included studies were contacted for further information.

2.6. Assessment of risk of bias in individual studies

Two reviewers (ALCM and APVC) independently assessed the methodological quality of the included studies using The Cochrane Collaboration's risk-of-bias tool (Higgins & Green, 2011). This tool assesses 7 study domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other sources of bias. Each of these domains was classified by the reviewers as being at high, low or unclear risk of bias. Disagreements between the two reviewers were settled by a third reviewer (MSP).

2.7. Quantitative data synthesis and analysis

2.7.1. Measures of treatment effect

For dichotomous outcomes, results were reported using risk ratio (RR) or risk difference (RD). Outcomes presented as continuous data were reported using mean difference (MD); if different scales were used to measure the same outcome, standardized mean difference (SMD) was used. The 95% confidence interval was calculated for all reported outcomes. If continuous outcome data were not reported and contacting trial authors was not successful, standard deviations were calculated using available standard errors, *p*-values or 95% confidence intervals. Data presented only in graphs were extracted using the "Digitizelt" software (available from: http://www.digitizelt.de/). Whenever possible, meta-analyses were performed (Higgins & Green, 2011; Levy, Hubbard, & Eisenberg, 2009) using a review manager software (RevMan, Version 5.2, The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2011).

2.7.2. Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plots and by using the I^2 statistical test in fixed-effect meta-analyses; I^2 values $> 50\%$ were interpreted as indicative of significant heterogeneity. The Tau^2 statistical test was used in random-effect meta-analyses: results > 1 were interpreted as being suggestive of substantial statistical heterogeneity. Statistical significance ($P < 0.10$) was also assessed. When heterogeneity was detected, possible reasons were investigated and reported (Higgins & Green, 2011).

3. Results

The electronic search resulted in a total of 341 references which were reduced to 255 after the exclusion of duplicates. At first screening (titles and abstracts) 239 studies were excluded because they were outside the scope of this review and 16 were selected as potentially relevant. After reading these 16 full texts, 6 studies were excluded (5 because of different participant selection criteria (Fang, Hung, Wu, Fang, & Stocker, 2012; Lessard et al., 1997; Ling-li, Ning, Xiao-ling, Hong, Jia-li, & Zhong-lan, 2010; Whitelaw, DeMuth, Demos, Schepsis, & Jacques, 1995; Zaffagnini, Iacono, Petitto, Loreti, Fu, & Marcacci, 1998) and 1 due to study design (Daniel, Stone, & Arendt, 1994)) and 10 studies were included in the review (Fig. 1).

3.1. Characteristics of included studies

Table 1 presents the main characteristics and results of the studies included in the review. The 10 studies included recruited a total 573 participants. Seven were randomized clinical trials (Brandsson et al., 1996; Cohn, Draeger, & Jackson, 1989; Dambros, Martimbianco, Polachini, Lahoz, Chamlian, & Cohen, 2012; Edwards, Rimmer, & Keene, 1996; Konrath, Lock, Goitz, & Scheidler, 1996; Schröder & Pässler, 1994; Waterman et al., 2012) and three were quasi-randomized clinical trials (Barber, McGuire, & Click, 1998; Dervin, Taylor, & Keene, 1998; Ohkoshi, Ohkoshi, Nagasaki, Ono, Hashimoto, & Yamane, 1999). All studies involved patients diagnosed with ACL rupture who underwent arthroscopic ACL reconstruction and were treated with cryotherapy in hospital settings during the post-operative period, before discharge. In two studies (Barber et al., 1998; Waterman et al., 2012) the participants were instructed to continue cryotherapy after discharge for a total of 6 weeks and 1 week, respectively.

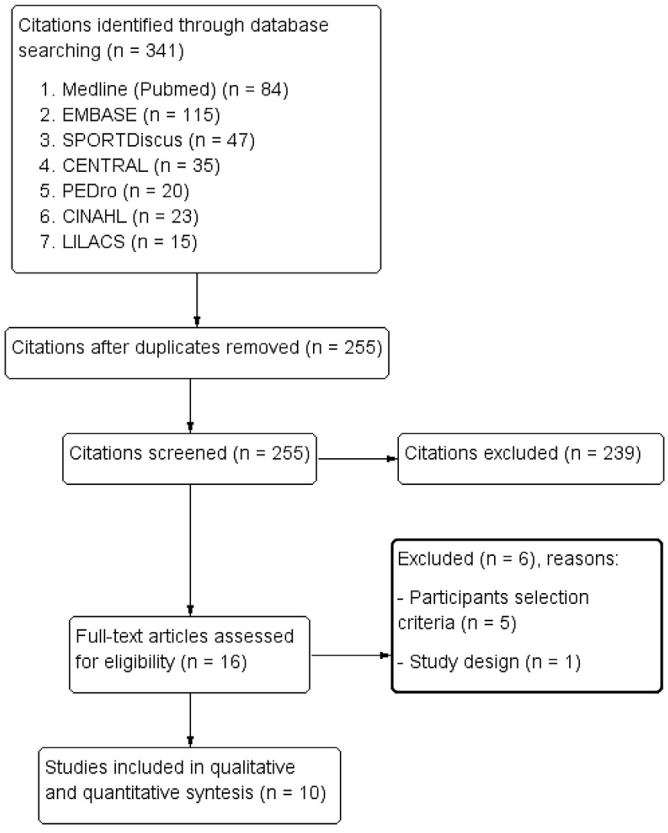

Fig. 1. PRISMA study flow diagram.

Most of the participants were men (69%) with a mean age ranging from 22 to 34 years. One study (Dambros et al., 2012) compared the use of knee ice packs versus no treatment, while the other nine studies reported the use of a cold compression device (CCD) versus ice packs (Cohn et al., 1989; Konrath et al., 1996; Schröder & Pässler, 1994; Waterman et al., 2012), CCD versus placebo (CCD filled with water at room temperature) (Edwards et al., 1996; Konrath et al., 1996) and CCD versus no cold therapy (Barber et al., 1998; Brandsson et al., 1996; Edwards et al., 1996; Konrath et al., 1996; Ohkoshi et al., 1999). All the authors reported that occlusive dressings had been used on the surgical incision prior to applying the cooling device.

3.2. Assessment of risk of bias

The methodological quality of the 10 studies is described in Fig. 2. We contacted the authors of all 10 studies via e-mail to clarify details related to the risk of bias and to obtain additional information; only four authors responded (Dambros et al., 2012; Dervin et al., 1998; Ohkoshi et al., 1999; Waterman et al., 2012). Three studies (Barber et al., 1998; Dervin et al., 1998; Ohkoshi et al., 1999) were quasi-randomized trials (patients were allocated according to the number of their medical record or date of birth) and were categorized as being at high risk of bias for two domains — random sequence generation and allocation concealment (risk of selection bias). All trials were classified as being at high risk of bias for blinding of participants and personnel because, given the nature of the intervention, patients could not be blinded, thus introducing potential bias. Two studies (Dambros et al., 2012; Dervin et al., 1998) were classified as having an unclear risk of bias for incomplete outcome data reporting because they did not provide information on excluded participants. This fact may cause imbalance between the groups thus influencing the results. Based on the recommendations of the Cochrane Collaboration, all 10 studies were judged to be at high risk of bias because at least one of the first three domains were scored as being at high risk of bias (Higgins & Green, 2011).

3.3. Effects of interventions (quantitative analysis)

3.3.1. Continuous outcomes

Given the lack of data and the unsuccessful contact with trial authors, we were able to obtain outcome data for pooling in meta-analyses from only two studies (Brandsson et al., 1996; Ohkoshi et al., 1999) which reported one of our primary outcomes (pain intensity). These two studies compared the use of a cold compression device (CCD) versus no cold therapy. Pooling of results indicated a significant reduction in pain intensity (VAS pain score 48 h after ACLR) in the group receiving the intervention: mean difference (MD) −1.41, 95% CI −1.66 to −1.17, $p < 0.00001$], with low heterogeneity (Fig. 3).

Results of the outcomes that could not be pooled in a meta-analysis (individual clinical trials) are described in Table 1.

Table 1
Main characteristics and findings of ten studies on cryotherapy after anterior cruciate ligament reconstruction.

Study design	Participants	Intervention	Outcomes measured and results
Cohn et al., 1989 RCT	54 Patients G1 ($n = 26$) 17 M/9 W Mean age 22.9 y G2 ($n = 28$) 15 M/13 W Mean age 25.1 y	G1: CCD (10 °C) (continuously up to hospital discharge) G2: ice bags (applied once − 30 min)	1. Use of analgesic medication (total doses, mg/kg) of IM meperidine, oral hydroxyzine and hydrocodone, measured 48 h after surgery 2. Length of hospital stay 3. Adverse events G1 patients used significantly less IM meperidine and oral hydroxyzine ($p < 0.01$). One G2 patient had transient peroneal nerve palsy.
Schröder & Pässler, 1994 RCT	44 Patients G1 ($n = 21$) 15 M/6 W Mean age 24.2 y G2 ($n = 23$) 18 M/5 W Mean age 24.8 y	G1: CCD (continuously up to hospital discharge) G2: ice bags (three times/day)	1. Pain intensity (VAS) 2. Edema (knee circumference measured using tape) 3. Range of motion-ROM (in degrees) 4. Knee function (knee score of Noyes and McGinniss) 5. Use of analgesic medication (total doses, mg/kg) of oral tilidine, IM pethidine and piritramide 6. Blood loss (in ml) 7. Adverse events Outcomes were measured on days: 1, 2, 3, 6, 14, 28. G1 had significant differences in: ROM on all days ($p < 0.01$); VAS pain scale on the 6th day ($p < 0.01$); knee edema on the 3rd and 6th days ($p < 0.035$), knee function ($p < 0.025$) and used less oral tilidine and IM piritramide ($p < 0.04$). There were no adverse events.
Konrath et al., 1996 RCT	100 Patients G1 ($n = 27$) 21 M/6 W Mean age 27 y G2 ($n = 23$) 13 M/10 W Mean age 25 y G3 ($n = 23$) 17 M/6 W Mean age 26 y G4 ($n = 27$) 16 M/11 W Mean age 26 y	G1: CCD with cold water (10 °C) (continuously up to hospital discharge) G2: CCD water at room temperature (25 °C) (continuously up to hospital discharge) G3: ice packs changed every 4 h (up to hospital discharge) G4: no cold therapy	1. Use of analgesic medication (total doses, mg/kg) of IM meperidine and hydroxyzine; and oral hydrocodone 2. ROM (in degrees) 3. Length of hospital stay 4. Blood loss (in ml) 5. Adverse events All outcomes were measured before hospital discharge There were no significant differences between the groups. There were no adverse events.
Brandsson et al., 1996 RCT	50 Patients G1 ($n = 20$) G2 ($n = 20$) G3 ($n = 10$) 31 M/19 W Mean age 26 y	G1: CCD (continuously − first 24 h) + IA injection of physiological saline. G2: CCD (continuously − first 24 h) + IA injection of morphine hydrochloride and bupivacaine. G3: IA injection of physiological saline.	1. Pain intensity (VAS), measured 1, 2, 4, 6, 24 and 48 h after surgery. 2. Use of analgesic medication (total doses, mg/kg) of codeine and morphine measured 24 and 48 h after surgery. 3. Length of hospital stay (measured in days) 4. Patient satisfaction 5. Adverse events G1 had significantly less pain ($p < 0.05$) and use of analgesic medication ($p < 0.05$), compared with G3. In G1, 80% were satisfied with their pain relief, compared with 30% in G3 ($p < 0.05$). There were no adverse events.
Edwards et al., 1996 RCT	71 Patients G1 ($n = 26$) 18 M/8 W Mean age 28.7 y G2 ($n = 21$) 17 M/4 W Mean age 26 y G3 ($n = 24$) 15 M/9 W Mean age 28 y	G1: CCD cold water (continuously − first 36 h) G2: CCD water at room temperature (continuously − first 36 h) G3: no cold therapy	1. Pain intensity (VAS) 2. Use of analgesic medication (total doses, mg/kg) of injectable morphine, oral paracetamol and codeine 3. ROM (in degrees) 4. Blood loss (in ml) 5. Adverse events Outcomes measurement: 24 and 48 h after surgery There were no significant differences between groups. There were no adverse events.
Dervin et al., 1998 Quasi-RCT	78 Patients G1 ($n = 40$) 27 M/13 W Mean age 30.6 y G2 ($n = 38$) 27 M/11 W Mean age 26.9 y	G1: CCD with cold water (continuously up to hospital discharge) G2: CCD with water at room temperature (continuously up to hospital discharge)	1. Pain intensity (VAS) 2. Use of analgesic medication; total doses (mg/kg) of morphine and number of codeine tablets (30 mg) 3. Length of hospital stay (in days) 4. Blood loss (ml) 5. Adverse events Outcomes measurement: 24 h after surgery. There were no significant differences between the groups. There were no adverse events.
Barber et al., 1998 Quasi-RCT	100 Patients G1 ($n = 51$) 34 M/17 W Mean age 34 y G2 ($n = 49$) 40 M/9 W Mean age 34 y	G1: CCD continuously G2: no cold therapy	1. Pain intensity (VAS and Likert categorical pain score) 2. Edema (knee circumference measured using tape) 3. ROM (in degrees) 4. Use of analgesic medication (total doses, mg/kg) of oxycodone/paracetamol and hydrocodone Outcomes measurement: 1, 2, and 8 h, and daily evaluations lasting up to 1 week after surgery. G1 had marginally significant pain reduction, 24 h after

Table 1 (*continued*)

Study design	Participants	Intervention	Outcomes measured and results
			surgery ($p = 0.059$) and significant reduction in hydrocodone use ($p = 0.013$). There were no adverse events.
Ohkoshi et al., 1999 Quasi-RCT	21 Patients G1 ($n = 7$) G2 ($n = 7$) G3 ($n = 7$) 10 M/11 W Mean age 22.1 y	G1: continuous CCD (5 °C) G2: continuous CCD (10 °C) G3: no cold therapy	1. Pain intensity (VAS) 2. Use of analgesic medication : total doses of 25 mg of diclofenac sodium consumed, via suppository. 3. Blood loss (ml) Outcomes measurement: 48 h after surgery G2 had significantly lower VAS pain scores and fewer number of analgesic doses than G3 ($p < 0.05$). Blood loss was significantly lower in G1 than in G3 ($p < 0.01$). There were no adverse events.
Dambros et al., 2012 RCT	19 Patients G1 ($n = 10$) G2 ($n = 9$) 19 M/0 W Mean age 29.5 y	G1: ice packs 20 min, twice a day G2: no cold therapy	1. Pain intensity (VAS) 2. ROM (in degrees) Outcomes measurement: 24 h after surgery. There were no significant differences between groups. There were no adverse events.
Waterman et al., 2012 RCT	36 Patients G1 ($n = 18$) 15 M/3 W Mean age 28.7 y G2 ($n = 18$) 15 M/3 W Mean age 30.9 y	G1: CCD (3 sessions (30 min)/day for 6 weeks) G2: conventional ice pack therapy (3 sessions (30 min)/day for 6 weeks)	1. Pain intensity (VAS) 2. Edema (knee circumference measured using tape) 3. Use of analgesic medication (not reported) 4. Knee function (Lysholm score) 5. Quality of life (SF-36) Outcomes measurement: 1, 2, and 6 weeks after surgery G1 had significantly lower VAS pain scores ($p < 0.0001$) and discontinued use of pain medications, by 6 weeks ($p = 0.0008$). There were no adverse events.

CCD, Cold compression device; **G1**, group 1; **G2**, group 2; **G3**, group 3; **G4**, group 4; **IM**, intramuscular; **IA**, intra-articular; **M**, men; **ml**, milliliters; mg/kg, milligrams/kilograms; **Quasi-RCT**, quasi-randomized controlled trial; **RCT,** randomized clinical trial; **ROM**, range of motion; **VAS,** visual analog scale; **W**, women; **y**, years.

Edwards et al. (1996), Barber et al. (1998) and Konrath et al. (1996) reported no statistical differences with or without cold therapy for pain intensity. When comparing CCD with cold water against CCD with room temperature water (placebo), Dervin et al. (1998), Edwards et al. (1996) and Konrath et al. (1996) did not find statistically significant differences for the pain measured 24 and 48 h after ACL reconstruction. Two studies which compared the use of CCD versus ice pack reported significant improvement favoring CCD after the 1st week ($p < 0.01$) (Schröder & Pässler, 1994) and after 6 weeks after surgery ($p < 0.0001$) (Waterman et al., 2012).

Despite the difficulty in comparing the different drugs prescribed in each study, the same clinical trials (Barber et al., 1998; Brandsson et al., 1996; Cohn et al., 1989; Ohkoshi et al., 1999; Schröder & Pässler, 1994; Waterman et al., 2012) that reported improvement in pain intensity, also showed a statistically significant reduction in the amount of medication taken by the patients after the use of CCD, when compared to both ice pack and control (no cold therapy). Three studies assessed knee edema (Barber et al., 1998; Schröder & Pässler, 1994; Waterman et al., 2012) and only one (Schröder & Pässler, 1994) reported a small but statistically significant improvement in this outcome in patients using CCD compared to those randomized to receive ice packs ($p < 0.035$). Among the studies that assessed the amount of blood drained after surgery (Dervin et al., 1998; Edwards et al., 1996; Konrath et al., 1996; Ohkoshi et al., 1999; Schröder & Pässler, 1994), only Ohkoshi et al. (1999) reported significant reduction in the volume of blood drained immediately after surgery (48 h) with the use of CCD at 5 °C, compared to CCD at 10 °C and no cryotherapy (control group) ($p < 0.01$).

Five studies assessed knee range of motion (Barber et al., 1998; Dambros et al., 2012; Edwards et al., 1996; Konrath et al., 1996; Schröder & Pässler, 1994) and only one (Schröder & Pässler, 1994) reported statistically significant results favoring the intervention group (CCD) versus ice pack group ($p < 0.01$). Schröder and Pässler (1994) and Waterman et al. (2012) evaluated knee function. Only Schröder and Pässler (1994) reported a small but statistically significant improvement favoring the CCD group when compared to the ice pack group ($p < 0.025$). Brandsson et al. (1996) analyzed patient satisfaction and reported a statistically significant difference in favor of the CCD group when compared with no treatment ($p < 0.05$). The individual clinical trials did not detect significant differences in duration of hospital stay (Brandsson et al., 1996; Cohn et al., 1989; Dervin et al., 1998; Edwards et al., 1996; Konrath et al., 1996) and quality of life (Waterman et al., 2012).

3.3.2. *Dichotomous outcomes*

All the included studies assessed the safety of cryotherapy by evaluating the occurrence of adverse events. Only one study (Cohn et al., 1989), that compared the use of a cold compression device (CCD) versus ice pack, reported the occurrence of transient peroneal nerve palsy in one patient who received the ice pack. Results of meta-analysis for adverse events showed no statistically significant difference between comparison groups: CCD versus ice pack (risk difference (RD) −0.01, 95% CI −0.06 to 0.04, $p = 0.66$); CCD versus no treatment (risk difference (RD) −0.00, 95% CI −0.04 to 0.04, $p = 1.00$) and CCD versus CCD placebo (risk difference (RD) −0.01, 95% CI −0.06 to 0.04, $p = 0.66$).

4. Discussion

Cryotherapy after arthroscopic anterior cruciate ligament (ACL) reconstruction significantly reduced immediate post-surgery pain and did not increase the risk of adverse events, in the short-term (up to 48 h after surgery). The limited evidence currently available from randomized trials is insufficient to draw definitive conclusions on the effectiveness of cryotherapy for other outcomes such as edema, knee function, post-operative blood loss, duration of hospital stay, range of motion, post-operative analgesic medication use, patient satisfaction or quality of life. Observational studies suggest that cryotherapy may produce immediate benefits by reducing pain and edema during the inflammatory response after surgery, decreasing muscle spasm and improving knee function, thereby accelerating the post-operative rehabilitation and the

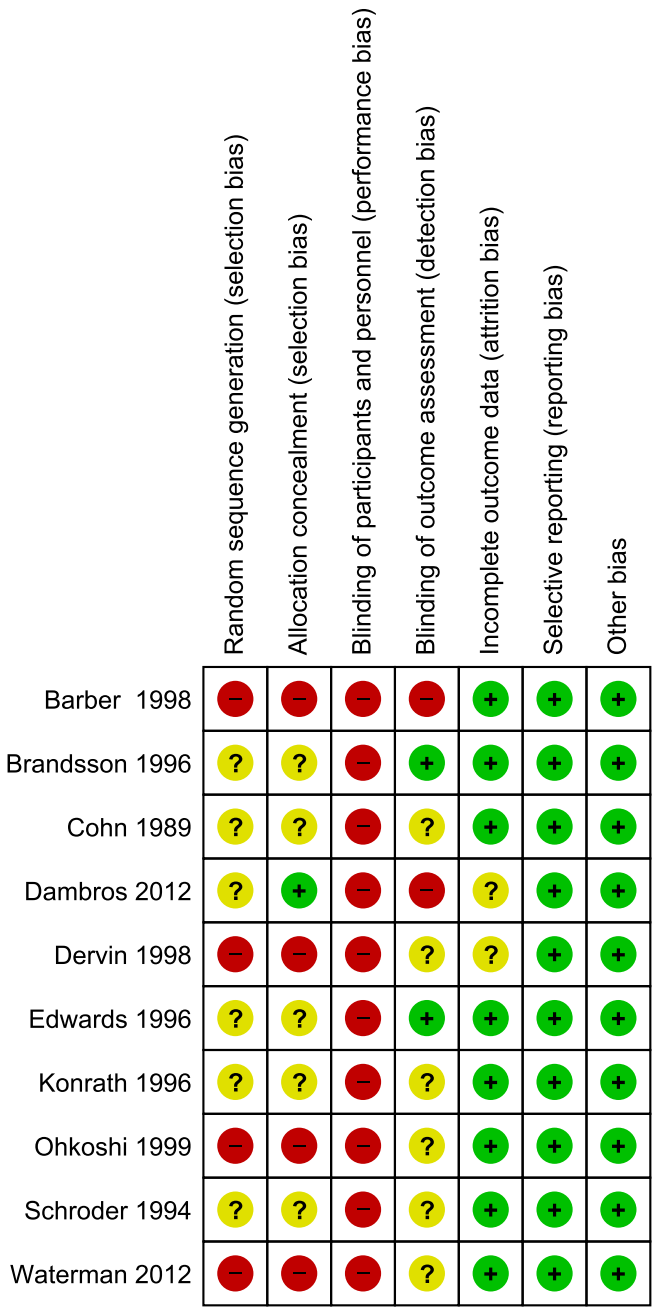

Fig. 2. Risk-of-bias summary: review authors' judgments about each risk-of-bias item, for each included study. (+ = low risk of bias; − = high risk of bias; ? = unclear risk of bias).

return to routine activities (Dykstra et al., 2009; Osbahr, Cawley, & Speer, 2002; Rashkovska, Trobec, Avbelj, & Veselko, 2013).

Our meta-analysis indicates that CCD, compared to no cold therapy, leads to a significant reduction in knee pain measured 48 h after arthroscopic ACL reconstruction ($p < 0.00001$). Based on the existing evidence, it was not possible to determine what are best type, frequency and duration of cryotherapy to reduce pain after ACL reconstruction. The use of CCD can reduce pain by compression or by cold therapy; therefore it is difficult to separate the actual effects of each component. Some investigators question the effectiveness of the compression produced by CCD, claiming that it might not have much influence on pain relief as the cooling itself (Dervin et al., 1998; Morsi, 2002; Raynor et al., 2005).

Knee edema can also be influenced by cryotherapy associated with compression (Kullenberg, Ylipää, Söderlund, & Resch, 2006; Morsi, 2002). Some investigators consider this outcome as somewhat subjective, since it is difficult to obtain a precise measurement of the edema (Dervin et al., 1998; Edwards et al., 1996); this could help to explain the lack of data on this outcome. Low temperatures might reduce post-surgery blood loss, thus helping to reduce swelling (Adie, Kwan, Naylor, Harris, & Mittal, 2012).

All the included studies investigated the occurrence of adverse events related to cold therapy. The results from the meta-analysis indicate that cold therapy after ACL reconstruction is safe. Cohn et al. (1989) reported that one patient in the ice pack group developed transient peroneal nerve palsy, after the pack had been left in place for nearly 40 min. According to these authors, this type of complication could be avoided by using ice packs for no longer than 30 min and by protecting superficial nerves with knee bandages prior to applying the intervention.

The evidence provided partial answers to the core questions raised in this review. In most trials, assessment of outcomes was limited to a short period, between 24 and 48 h after surgery. Only one study (Waterman et al., 2012) assessed results of the intervention in the long term (6 weeks after the surgery).

A recent systematic review assessed the effectiveness of cryotherapy after total knee arthroplasty, and reported that it is associated with a small but statistically significant reduction in pain and blood loss, as well as improvement in the range of motion (Adie et al., 2012). As in the present study, the authors of that review noted methodological limitations in the included studies, which could have influenced most of the outcomes assessed. According to a systematic review on cryotherapy for acute soft tissues injuries (Bleakley, McDonough, & MacAuley, 2004), there was small but statistically significant effect of compression combined with cryotherapy (CCD) compared to ice packs. However, as in our review, the studies included in that review were limited to interventions carried out before hospital discharge. Those authors recommend caution when interpreting the results due to the heterogeneity and poor methodological quality of the included studies.

A similar review was published by Raynor et al. (2005) eight years ago and, in concordance with our findings; it concluded that cryotherapy after ACL surgery significantly reduced immediate

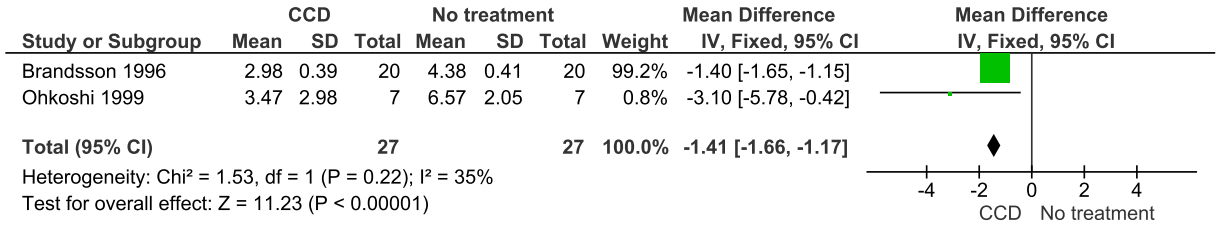

Fig. 3. Forest plot for pain intensity scores 48 h after anterior cruciate ligament reconstruction surgery, comparing cold compression versus no treatment. Abbreviations: CCD, cold compression device; CI, confidence interval; SD, standard deviation.

post-surgery pain, without significant improvement in post-operative blood loss or range of motion. However, there are several differences between our reviews. Raynor et al. (2005) included only seven studies and 420 participants, while we included ten studies and 573 participants. Although two studies included in our review were published recently (Dambros et al., 2012; Waterman et al., 2012), we also included two studies which had already been published at the time of that previous review (Cohn et al., 1989; Schröder & Pässler, 1994) but were not included by those authors. This was in part due to our more sensitive search and to the fact that we ran our search in three additional electronic databases that had not been included by those investigators (EMBASE, LILACS and PEDro). Due to different selection criteria, our review excluded one study (Daniel et al., 1994) which was included by Raynor et al. (2005). Contrary to Raynor's review, we assessed the methodological quality (risk of bias) of the included studies which is an important step in systematic reviews of the literature (Higgins & Green, 2011). Finally, besides the outcomes evaluated by Raynor et al. (2005) (pain, post-operative drainage and range of motion), our review included additional clinically relevant outcomes such as knee edema and function, use of post-operative analgesics, length of hospital stay, quality of life, patient satisfaction, and safety of cryotherapy.

All studies included in our review were at high risk of bias, recruited a small number of participants and provided sparse data on most of our pre-established outcomes of interest, thus precluding pooling of their results into meta-analyses. These studies were heterogenous in several aspects: they compared different forms of cryotherapy (Cold Compression Device (CCD) × ice pack; CCD × CCD placebo (with water at room temperature); CCD × no cold therapy; ice pack × no cold therapy), different frequencies and durations of sessions, and different follow-up periods. The main methodological limitations of the included studies were the lack of description of random sequence generation and allocation concealment, as well as difficulties in blinding of participants and outcome assessors due to the nature of the intervention. This may in part be explained by the fact that most of these studies (8/10) were published in the 80s and 90s, a period when most trials did not follow the internationally accepted standard recommendations for reporting clinical trials (CONSORT – *Consolidated Standards of Reporting Trials*) and did not have published protocols. We admit the possibility that relevant studies may have been missed, despite our rigorous and ample search strategy without language or date restrictions. Another potential limitation of this review is the lack of success in obtaining additional information from the trial authors, precluding additional meta-analyses. According to GRADE system (The Grades of Recommendation, Assessment, Development and Evaluation Working Group) (Higgins & Green, 2011), the general analysis of the quality of the evidence (internal validity) was moderate, since most information was obtained from studies that presented "unclear risk of bias".

5. Conclusion

There is moderate quality evidence that cryotherapy is safe and effective in reducing pain after ACL reconstruction, in the first 48 h after surgery. The limited evidence currently available is insufficient to draw definitive conclusions on the effectiveness of this intervention for other important outcomes, such as knee edema and function, use of post-operative analgesic medication, knee range of motion, blood loss, duration of hospital stay, quality of life measures and patient satisfaction. There is a need for more, well designed, good quality randomized trials to answer several remaining questions related to this intervention and increase the precision of future systematic reviews.

Conflict of interest

None declared.

Ethical approval

This study was approved by the Ethics Committee of Federal University of Sao Paulo (CEP 0142/11).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ptsp.2014.02.008.

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