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Acute Management of Soft Tissue Injuries

Protection, Rest, Ice, Compression, and Elevation Guidelines

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Management of acute soft tissue injury using Protection Rest Ice Compression and Elevation: Recommendations from the Association of Chartered Physiotherapists in Sports and Exercise Medicine (ACPSM)

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Background

The need for guidelines

Soft tissue injury is a common problem in sport, recreational and physical activities. Indeed, sprains, strains and contusions are the most commonly encountered injuries in amateur and professional sporting disciplines including; professional football,[1-2] gaelic football,[3] rugby,[4] triathlon,[5] and Australian rules football.[6] Almost 8-12% of referrals from General Practitioners for physiotherapy are for soft tissue injuries,[7] and it is estimated that the annual cost of sport and exercise related soft tissue injuries in the United Kingdom and the Netherlands is approximately 9.8 million pounds.[8]

Following an injury incident one of the main objectives of physiotherapeutic interventions is the restoration of full function and the re-gaining of pre-injury status. However for a commonly encountered injury such as an ankle sprain it has been reported that just between 36-85% of individuals report full recovery within 3 years; with one third suffering persistent pain, instability and re-injury.[9] Inadequate recovery after soft tissue injury could have a detrimental effect on future physical activity levels, and general health. Currently, ankle sprains are one of the primary causes of post-traumatic ankle joint osteoarthritis,[10] and a history of ligament injury and/or joint laxity have been implicated in the aetiology of knee joint osteoarthritis.[11-14]

The quality of acute stage management of a soft tissue injury is thought to be an important determinant for short and long term recovery. In the early stages, soft tissue injuries are characterised by an acute inflammatory response. This is manifested clinically by the presence of pain, redness, swelling and loss of function. Traditionally, the clinical management of soft tissue injury has placed most emphasis on minimising or controlling acute inflammation. Protection, Rest, Ice, Compression and Elevation (PRICE) remains one of the most popular approaches for the management of acute injuries and in particular the control of inflammation. Some or all components of PRICE continue to be combined, based on the type or severity of soft tissue injury.

Original ACPSM guidelines

Previous recommendations[15] for using PRICE in the management of acute soft tissue injury were provided by the Associated of Chartered Physiotherapists in Sports Medicine and endorsed by the Chartered Society of Physiotherapy (London). These recommendations were made based on evidence published up to 1996, and included guidelines for the practical application of each component of PRICE. Evidence from studies using physiological and clinical outcomes were used to inform the recommendations. The strength of the recommendations were made based on study quality which was graded from level three (poorly performed observation research) to level one [well performed randomised controlled trial (RCT)]. In the event that there was no empirical evidence, recommendations were made using consensus agreement from a panel.

The guidelines[15] recommended all components of PRICE immediately after acute injury. Protection and rest were recommended for at least 3 days post injury, with longer periods advised according to injury severity. Only isometric type exercises were recommended during the acute stages. Compression was recommended immediately after injury, with continuous use over the first 72 hours only. Guidance on its practical application included: ensuring uniform pressure, proximal to distal application, with additional intermittent compression permitted. Elevation was recommended for as long as possible in the first 72 hours, however, immediate restoration of the injured body part to a gravity dependant position was not advised. The only recommendation based on evidence from an RCT, was to avoid concomitant use of compression and elevation. Ice application was recommended in the immediate stages post injury. The optimal protocol was chipped ice (with damp barrier) for durations of 20-30 minutes, repeated every 2 hours; variations were suggested according to body fat levels, and the presence of a superficial nerve at the injury site. Athletes were advised not to return to competition immediately after applying ice.

Updating the original guidelines

Making judgements about evidence and developing recommendations for clinical practice is complex and requires a systematic and explicit approach. The original ACPSM guidelines were developed largely based on Thompson's model[16] which followed a stepwise process of: identifying a topic; composing a developmental group with appropriate skills; literature searching; critical appraisal and formation of recommendations. Recommendations were made and presented based on a hierarchy of study quality derived from the Canadian Task Force Classifications.[17]

Recently, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group have developed a refined template for the development of guidelines in healthcare.[18] This was produced to provide a more systematic, explicit and transparent approach. Our methods will therefore follow the sequential process set out by GRADE. This has many similarities to methods used in the original guidelines, but with the following updates: we will consider the importance of outcomes and weight them prior to making recommendations; we will judge the overall quality of available evidence on: study design, study quality [based on Cochrane risk of bias tool[19] (sequence generation, allocation concealment, assessor blinding, incomplete outcome data)], directness (ie. the extent to which the people, interventions and outcomes in the studies, are similar to those of interest) and consistency (the similarities of estimates across studies); finally, we will make judgements on the strength of recommendations based on the overall quality of the evidence, costs and benefits/harms.

Purpose

The purpose of the current study is to review the clinical effectiveness and pathophysiological rationale for using PRICE for acute soft tissue injury. We will focus on research published after 1996. In accordance with the GRADE guidelines,[18] relevant evidence will be synthesized to provide an update for the original ACPSM recommendations.[15] It is anticipated that the results of the recommendations will target physicians and healthcare professionals (particularly those involved in sports medicine), first aiders, and adults self managing an acute soft tissue injury.

Overview of methods

In January 2009, a number of ACPSM members volunteered to form a working group responsible for developing the guidelines. This initial working group was composed of a number of health and allied health professionals (physiotherapy, physiology and biochemistry), with a diversity of expertise (content experts, front line clinicians, academics). All members stated that they had no conflicts of interests in participating in the development of the guidelines. One member of the group (CMB) was assigned to co-ordinate the research.
Our methods were based on the recommendations developed by the GRADE working group.[18] The following milestones were made and addressed in the following order: 1) develop specific clinical questions; 2) literature searching; 3) address importance of outcomes; 4) extract data/grade quality of evidence; 5) develop final recommendations.

1). Developing specific clinical questions

We devised five clinical questions (or clinically related questions) following group consensus in March 2009. Our primary aim was to update the clinical evidence for using PRICE in the management of acute soft tissue injuries. Our first clinical question was:

- Which components of PRICE are effective in the clinical management of acute soft tissue injury?

Our secondary aim was to update the pathophysiological rationale for using PRICE in the management of acute soft tissue injury. The following 4 questions were considered to be relevant to the clinical effectiveness of PRICE:

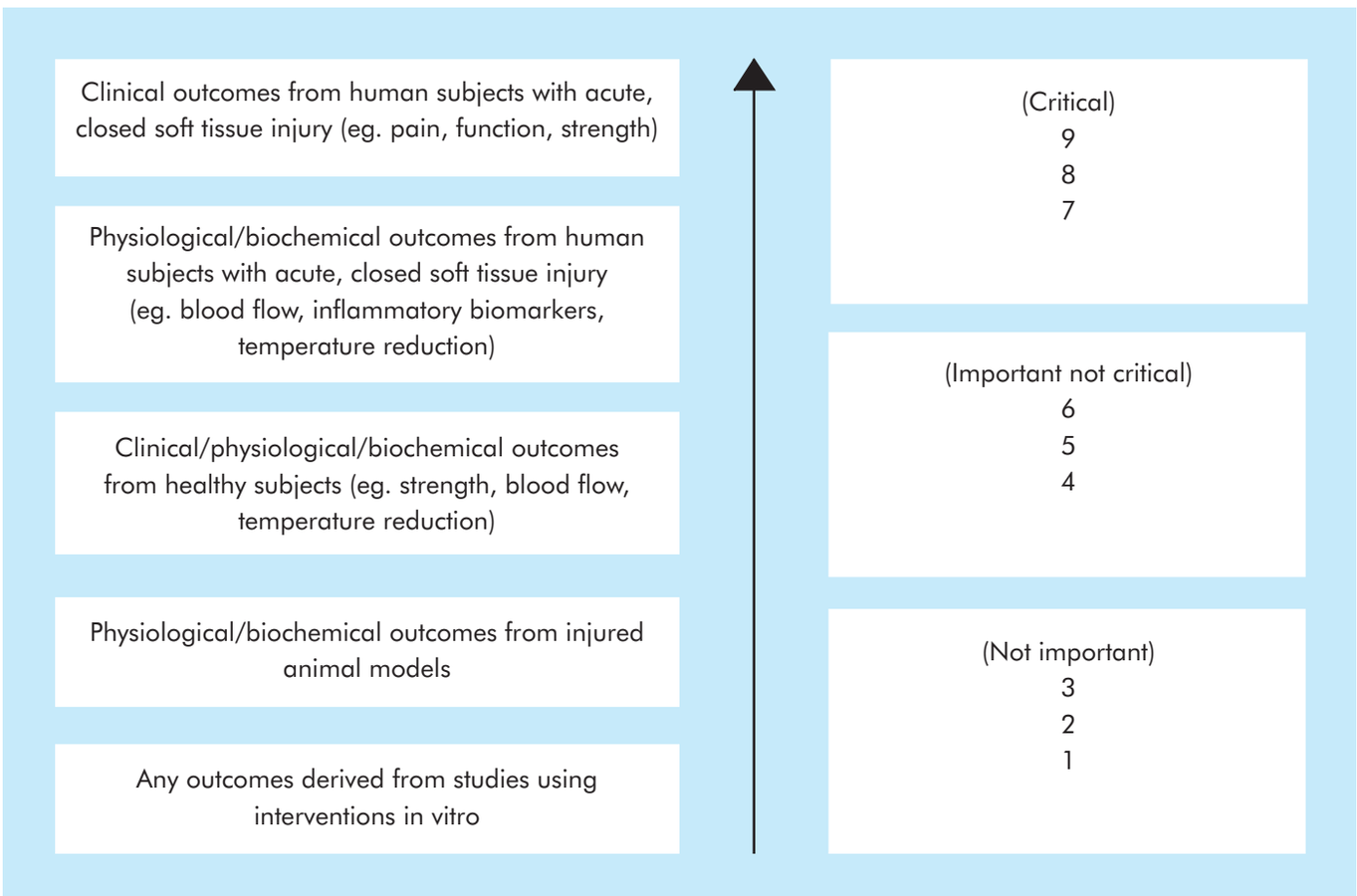
- What is the magnitude and depth of cooling associated with ice?
- Can PRICE decrease the inflammatory response after acute soft tissue injury?
- What effect does mechanical loading have on inflammation and healing after acute soft tissue injury?
- Do the physiological effects of local tissue cooling affect function, sporting performance and injury risk?

2). Literature searching

A series of literature searches were undertaken on the following databases; MEDLINE, EMBASE, and the Cochrane database (Ovid SP). The following limitations were imposed: January 1996-October 2009. The main search strategy is detailed in Appendix Table 1-3. Each search was undertaken independently by at least two researchers following standardised written guidelines on the search strategy and study inclusion criteria (CMB; SK). Supplementary searches were undertaken based on related article searches on Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/), citation tracking of original and review articles (n=350) and a convenience sample of text books (Appendix Table 4a), we also checked the results of literature searches from related reviews, previously completed by the lead author (Appendix Table 4b). Studies were included or excluded (with reasons) according to their relevance to each clinical question (Appendix Table 5).

3). Addressing the importance of outcomes

Outcomes were differentiated according to their importance to patients with an acute soft tissue injury. Members of the working group were presented with a summary of the outcomes and a nine point scale was used to gain consensus on their importance. The upper end of the scale, [7-9] identified outcomes of critical importance to an individual with an acute soft tissue injury; [4-6] represents outcomes that are important but not critical for decision making, and rating of [1-3] were not important for decision making. As these guidelines covered a wide range of both interventions and injuries, we sub-grouped outcomes for ease of discussion. The hierarchy of outcomes according to their importance to subjects with acute soft tissue injuries is shown in Figure 1.



4) Data extraction / grading the quality of evidence

Members of the ACPSM working group were each assigned to small specialist working groups relating to each of the 5 clinical questions. The scientific evidence/data relevant to each clinical question was then collected, extracted, graded and summarised following a standardised written protocol. A separate review article was then written up for each clinical question.[20-24] Full methodological details are described in each chapter within the main document. Each review was sent for evaluation by relevant external professionals or experts at this stage (GD, TH, ED), and modifications made if applicable. This process was completed for each specialist working group by using either group meetings or iterative discussion by e-mail.

5) Developing final recommendations

Final recommendations were made in September 2010. Each member of the working group attended this one day meeting to review the process by which final recommendations would be made. Prior to this meeting each member was provided with a full written copy of the relevant evidence (Chapter 2-7 of the main document).[20-24]

The strength of the recommendations (for or against the intervention) was graded as strong (definitely do: indicating judgement that most well informed people will make the same choice); weak (probably do: indicating judgment that a majority of well informed people will make the same choice, but a substantial minority will not, ie. different patients, in different clinical contexts, with different values and preferences, will likely make different choices), or uncertain (indicating that the panel made no specific recommendation for or against interventions). The strength of the recommendation represents the degree of confidence that we felt the desirable effects outweighed the undesirable effects of an intervention; this judgement was based on the quality of evidence (we primarily focused on evidence derived from outcomes that were of critical importance, but were appropriate we also considered those deemed to be important but not critical, as per Table 1), with desirable effects considered to be beneficial health outcomes, low burden and low costs. Undesirable effects were associated harms and side effects, more burdens and expense.18 Typically a strong recommendation is based on high or moderate quality evidence on a critically important outcome. Exceptionally, a strong recommendation can be made based on low quality evidence; panel members were given an example of when this may be appropriate (Figure 2).

To explore the range and distribution of the opinions held by every member of the working group, we implemented the GRADE grid[25] (Figure 2). This approach allows each member of the consensus panel to record their views about the balance between the benefits and disadvantages of each component of PRICE, based on their analysis of the available evidence. At the end of the meeting each member of the panel were provided with full restatements of the proposition, a summary presentation of the relative evidence from the primary author (CMB), and a further review of the potential sources of disagreement. They were then presented with a number of specific clinical scenarios relating to the 5 clinical questions, and were asked to devise recommendations for each one. They each had two weeks to formulate his/her judgements on the quality of the evidence, and the strength of the recommendations. Grids were returned to the primary reviewer (CMB) before the final write up and publication.

Figure 2

GRADE grid for recording panellists' views in the development of final recommendations

	GRADE score				
	1	**2**	**0**	**2**	**1**
Balance between desirable and undesirable consequences of intervention	Desirable clearly outweigh undesirable	Desirable probably outweigh undesirable	Trade-offs equally balanced or uncertain	Undesirable probably outweigh desirable	Undesirable clearly outweigh desirable
Recommendation	Strong "definitely do it"	Weak "probably do it"	No specific recommendation	Weak "probably don't do it"	Strong "definitely don't do it"
For each intervention below, please mark an "X" in the cell that best corresponds to your assessment of the available evidence, in terms of benefits versus disadvantages for its use in the management of acute soft tissue injury					
Protection					
Rest					
Ice					
Compression					
Elevation					

Strong recommendations are more likely to be warranted with: larger differences between the desirable and undesirable effects, less variability/uncertainty in values and preferences, lower costs and higher quality evidence.
Note: Example of a strong recommendation from low quality evidence: There is low quality evidence, but it is based on a large number of observational studies, with clear evidence and consistency of effect on at least one critically important outcome after acute soft tissue injury. The intervention is of low cost (in comparison to other related or available treatment options), can be applied with little burden (to the patient and therapist), it is comfortable and easily tolerable, has a low risk of minor side effects, and is not time consuming (for patient or therapist).

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Chapter 2

What is the magnitude and depth of cooling associated with ice application?

What is known in this area: The basic premise of cold therapy is to cool injured tissue to achieve analgesia and lower local cell metabolism. There is much confusion around how much cooling is adequate, and how this can be achieved clinically. Current best evidence suggests that to optimise the clinical effectiveness of icing, we must achieve a critical level of tissue cooling. These are skin temperatures of <13°C for cold induced analgesia, and tissue temperatures of 5-15°C for metabolic reduction.

Aim: To update the pathophysiological rationale for using PRICE in the management of soft tissue injury.
Clinical question: What is the magnitude and depth of cooling associated with ice application?
Objective: To review recent literature to determine the rate and magnitude of tissue temperature reduction with ice. Values were compared with current recommended threshold temperatures deemed necessary for optimal cold induced analgesia (skin temperature <13°C) and metabolic reduction (tissue temperature 5°C-15°C) after injury.

What this review adds: Current evidence confirms that icing dosage should be guided by the circumstances of injury, and clinical rationale. Optimal levels of analgesia can be achieved clinically using crushed ice for durations of 5-15 minutes. Other modes of icing may require longer durations to cool skin temperature to optimal levels, and there is further evidence that skin temperature is a poor predictor of deep tissue temperature. Based on healthy human models, it is difficult to induce large decreases in intra-muscular or joint temperature; particularly in circumstances of deep tissue injury, areas of higher levels of body fat, or when dry barriers are used at the cooling interface. Reaching currently accepted threshold temperatures for metabolic reduction (5°C-15°C) seem unlikely. The lowest reported superficial muscle temperature (1cm sub-adipose) after icing was 21°C, in a lean athletic population. No study has considered temperature reductions after a closed soft tissue injury to the joint. Based on a surgical model, untreated joints increase in temperature after surgery, however ice seems to minimise the extent of this increase, or in some cases, cool slightly below baseline temperature (maximum decrease of 4°C).

Limitations and future study recommendations: Most evidence on skin and muscle temperature reductions is derived from healthy human subjects. Joint cooling models are derived from post surgical models of the knee and shoulder. No studies have assessed the magnitude of or depth of temperature reductions obtainable in smaller joints with less surrounding adipose tissue (eg. wrist, elbow, ankle), in the absence of tourniquet and post operative dressings. Our conclusions are based on the assumption that in order to induce a clinically meaningful effect on pain reduction or cell metabolism, critical levels of skin temperature (<12°C) and tissue temperature (5°C-15°C), must be achieved. Although these values currently represent the best available evidence, they are not definitive. These values may be subject to change based on emerging understanding of the biochemical and physiological events surrounding acute injury and inflammation.

Background

Ice is a popular intervention for soft tissue injury within the first aid, sporting and post surgical settings. Its simple premise is to extract heat from the body tissue to attain various clinical benefits. These include: limiting the extent of injury by decreasing tissue metabolism thereby reducing secondary cell death,[1] providing analgesia,[2] and facilitating rehabilitation.[3]

In spite of this, controversy and confusion exist within clinical practice and published literature over the therapeutic benefits, and the most effective icing protocol. Textbooks,[4] clinical guidelines, and surveys of practice[5] show wide discrepancies in its application. Many clinical research models may have employed an inadequate treatment dosage;[6] and there may be an erroneous supposition that one universal icing protocol will be equally effective, regardless of the pathological condition or body tissue affected.

It is increasingly apparent that the clinical effectiveness of an electro-physical agent relates to the relative adequacy of parameter choice and dosage.[7] Current best evidence also suggests that to optimise the clinical effectiveness of cold therapy, we must achieve a critical level of tissue cooling. Furthermore, the magnitude and depth of this critical cooling level may change depending on the desired clinical effect (eg. decreasing secondary injury vs analgesia), or stage of injury (immediate stages vs later stages of rehabilitation).[3]

It is common practice to apply ice to decrease pain. This is often seen in pitch side management of an acute sports injury, whereby (in the absence of any serious structural damage), the primary objective is to reduce pain, and return the athlete to the field of play as quickly as possible. In this situation, cold induced analgesia seems to work via a number of mechanisms including: decreased receptor sensitivity,[8,9] decreased receptor firing rate,[9,10] decreased nerve conduction velocity (NCV), reduced muscle spasm or as a counter irritant to pain.[11] Evidence shows that cooling skin temperature to between 10°C and 13°C results in localised analgesia,[12,13] and a 10%-33% reduction in NCV.[13,14] This is currently regarded as the threshold for optimally inducing analgesia in the clinical setting.

Van't Hoff's law states that for every 10°C reduction in tissue temperature, the rate of chemical reaction will decrease between 2 and 3-fold. This forms some of the rationale for applying ice in the immediate stages after an acute injury. Reducing cellular metabolism will decrease the risk of secondary ischaemic and enzymatic injury, thereby limiting the overall extent of tissue damage.[3,15] In this regard it is generally assumed that better clinical outcomes result from greater and faster cooling of tissue temperature;[16] however, it is often difficult to provide an exact magnitude or threshold. The current best evidence seems limited to animal models, which advocate that metabolism is optimally reduced after injury, at tissue temperatures between 5°C and 15°C.[15,17,18] Furthermore, to maximise this effect, the relevant temperature reductions must occur within the injured tissue, (eg. the muscle layer at and around the point of injury), and not simply the over lying skin.

Objectives

The objective of Chapter 2 was to review recent literature to determine the rate and magnitude of tissue temperature reduction associated with popular ice dosage. Results were compared and discussed in terms of the critical temperature reductions, currently deemed necessary for achieving optimal analgesia, and metabolic decrease after injury.

Methods

Literature search

We searched the titles generated from the main search strategy outlined in Appendix Table 1-4. Relevant studies were extracted, with exclusions made based on titles, abstracts or full text versions.

Inclusion criteria

No restrictions were made on study design. Participants could have been injured (post surgery/acute soft tissue injury) or healthy and of any age or gender. Any type of ice/compression intervention was included, providing adequate details of the mode and duration were provided. Outcomes must have included at least one of the following: skin temperature, intramuscular temperature, joint temperature, measured before and after ice pack application. No restrictions were made on the measuring device, however, for subcutaneous or muscle temperatures, the depth of measurement must have been provided or calculable from the data.

Risk of bias

All included studies were assessed in terms of design, and methodological quality based on Cochrane risk of bias tool[19]

Results

Excluded studies (with reasons) are listed in Appendix Table 5.

Skin temperature

9 studies[16,20-27] reported skin temperature reductions after ice based on applications directly onto the skin or through a damp barrier; of which two[21,24] compared to groups with a dry barrier or bandage between the cooling interface and the skin. Two others compared ice applied over different types of dry, thick bandaging.[28,29] Full details of the methods, interventions and risk of bias are summarised in Appendix Table 6. Only two studies used adequate randomisation,[24,29] three performed allocation concealment,[22,24,29] and none of the outcomes were based on blinded assessment. Only one of the studies[29] used a group of injured subjects.

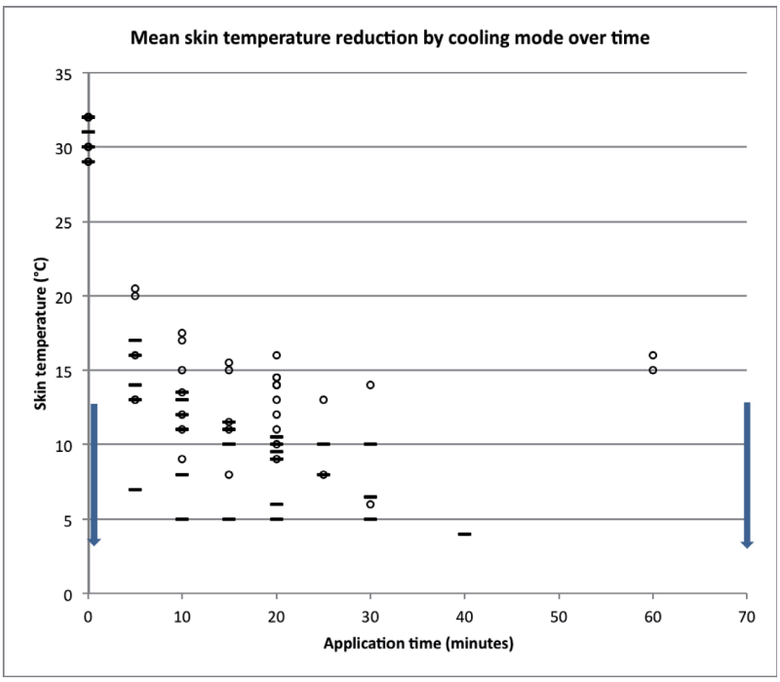

Figure 1

-Circles represent values from participants treated with other cooling modes (frozen peas, cryocuff, water and alcohol, gel packs)[16,22,24,25,26]

-Lines represent values from participants treated with crushed ice[16,20,21,23,25,26]

-The arrows overlap the area showing the critical SKIN temperature reduction of <10°C.

-All studies applied either directly onto the skin, or via a damp barrier[22,23,25,26]

Figure 1 summarises the mean skin temperature reductions associated with different modes of ice application over time. Studies show that crushed ice reduces skin temperature to below 10°C after [5,23] [10,16,20] [15,16,23] or 20 minutes of application.[21,25,26] In contrast, [13] sub-groups of participants, from six different studies[16,22,24-27] using other modes of cooling (frozen peas, gel pack, cryo-cuff, and cold water immersion) produced skin temperature reductions that were more likely to be outside the defined critical range of <13°C, after 5-20 minutes of application. One study[30] also found evidence that lower skin temperatures are achieved with heavier crushed ice packs; a 0.8kg and a 0.3kg pack resulted in final skin temperatures of 5.1°C and 7.7°C respectively.

Numerous cooling modalities remain popular amongst clinicians; however it is clear that these should not be used interchangeably. Each cooling modality has a different thermal property, and therefore a different cooling potential. Although gel packs tend to have very low pre-application temperatures, (sometimes between -10°C and -14°C), solid crushed ice at 0°C has much more potential to extract heat energy from the skin based on its ability to undergo phase change.[16] The consensus from the current literature is that crushed ice consistently results in the fastest reduction in skin temperature with, clinically important reductions (<10°C) after as little as 5 minutes.

There is a trend in Figure 1 that for the majority of cooling modes, the fastest reduction in skin temperature occurs within the first 5 minutes. More modest reductions seem to occur thereafter, and in many instances, skin temperature seemed to plateau after approximately 10-15 minutes of cold application. Continuing clinical applications beyond this time period, may offer little further reduction in skin temperature. This is important to consider if our goal is to simply induce short term analgesia. However, removal of the ice pack after just 10 or 15 minutes might be associated with a faster re-warming rate and therefore may not suitable in instances when pain reduction is required over a longer period of time.

Muscle temperature

4 studies[31-34] were excluded as we were unable to determine the depth at which temperature was recorded. This left 11 studies[16,35-44] measuring intra-muscular temperature reductions after ice application. Methods, intervention and risk of bias details are summarised in Appendix Table 7. All used healthy subjects, and the majority focused on 1cm muscle depths. In most cases, accuracy was controlled by inserting thermocouple needles to a depth of ½ subcutaneous fat (over the treated area) + 1 cm. Four studies recorded muscle temperatures down to approximately 2-3 cm[16,38,42-44] by similar means. Four of the studies used a randomised design;[35-37,39] the remainder were observational. No study used blinded outcome assessment. Sample size was small ranging from 6-47.

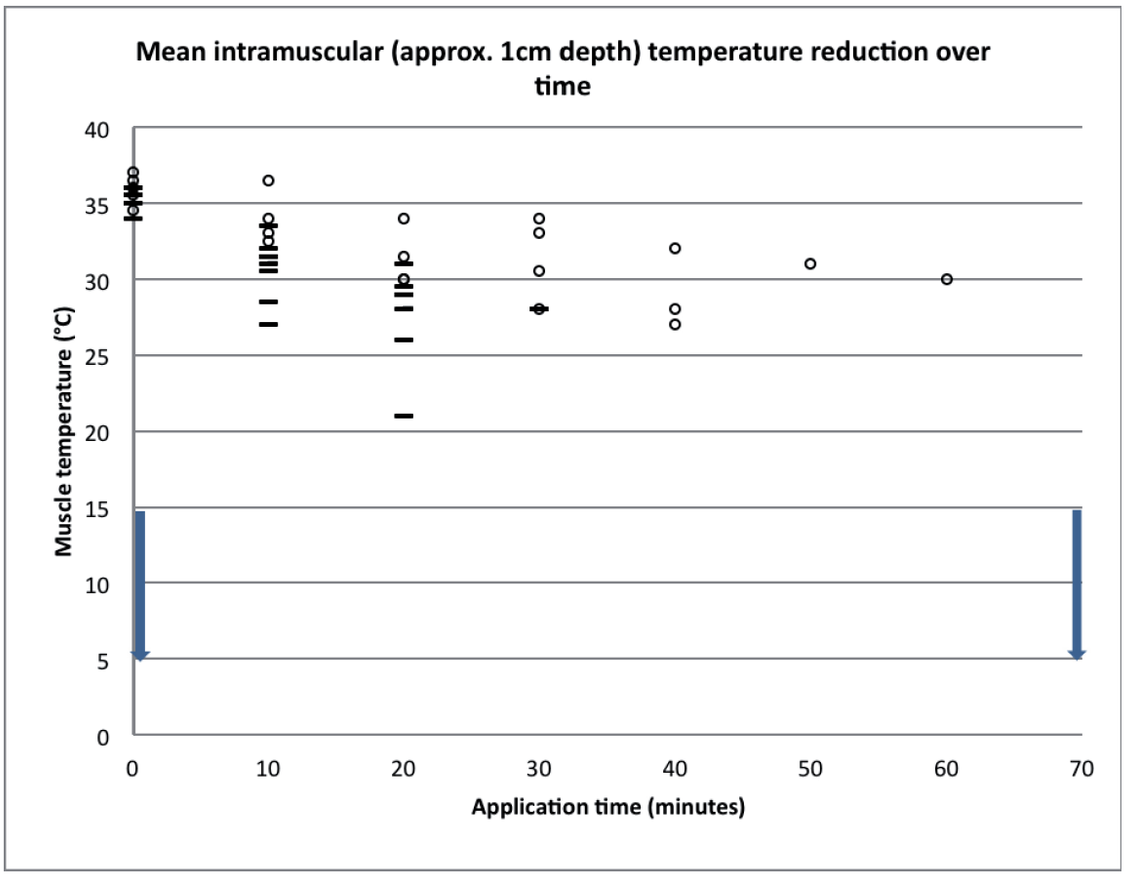

Figure 2

-Circles represent values from participants with 21-40mm skin-fold at the point of ice application
-Lines represent values from participants with <20 mm skin-fold at the point of ice application
-Arrows overlap the area representing potentially optimal INTRA-MUSCULAR temperature reduction of 5-15°C.
-All data is based on crushed ice, applied directly onto the skin surface 16,35-44
-Three studies applied additional external compression16,41,42

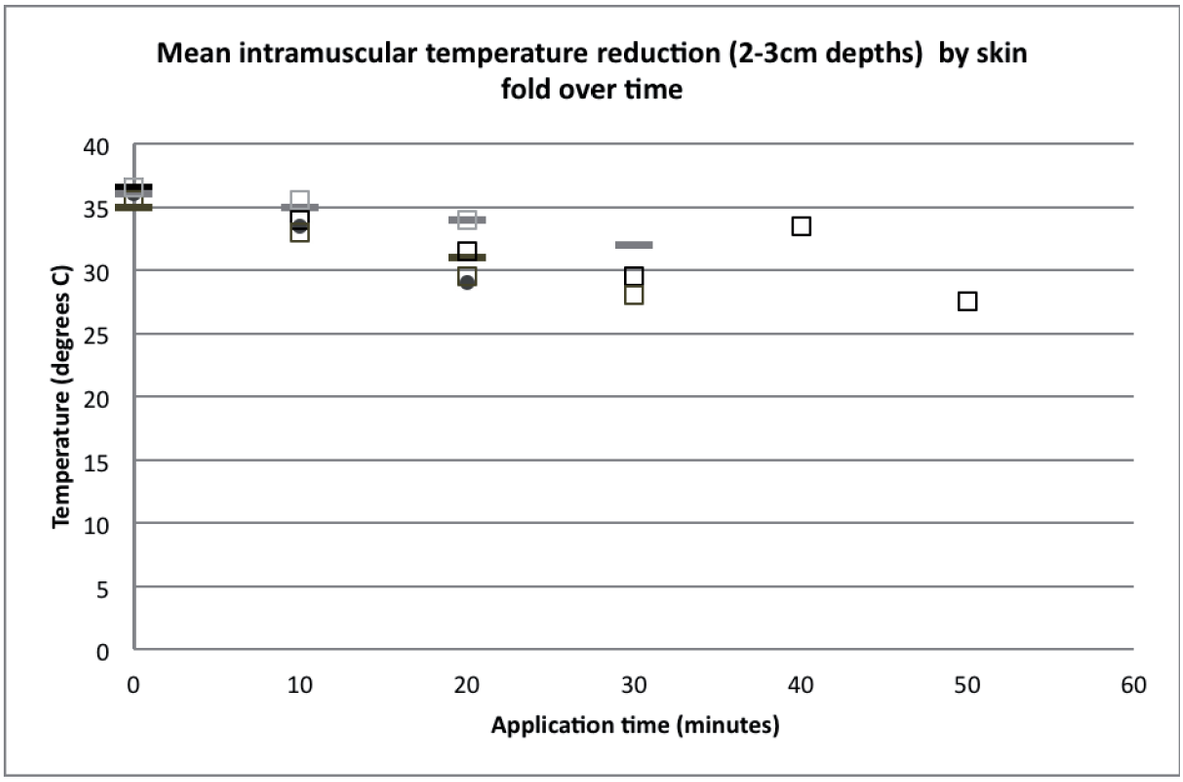

Figure 3

Circles represent < 10 mm skin fold at the point of ice application38
Lines represent 11-20mm skin fold at the point of ice application16,38,43
Squares represent 21-30 mm skin fold at the point of ice application38,42,44

Joint temperature

Eight studies measured joint temperature reductions after either knee or shoulder surgery.[45-52] In all cases, post operative dressings and/or bandages were used between the cooling medium and the skin. Methods, intervention and risk of bias details are summarised in Appendix Table 8. Sample size ranged from 12 to 30. All but one study[51] used a control group. Four [45-47,52] used a randomised controlled design, only one of which did not use adequate allocation concealment.[47]

Figure 4 shows that in each study, surgery increased joint temperatures in untreated controls. However, ice either reduced the magnitude of this increase, or decreased joint temperature post surgery. Osbahr's results[52] are not included in Figure 4 as there was no data on the post operative temperatures; values extracted from graphs show that ice caused intra-articular temperatures to remain around 1°C lower than untreated controls for the first day post operatively. Of note this was the only study to use randomisation, allocation concealment and blinded outcome assessment.

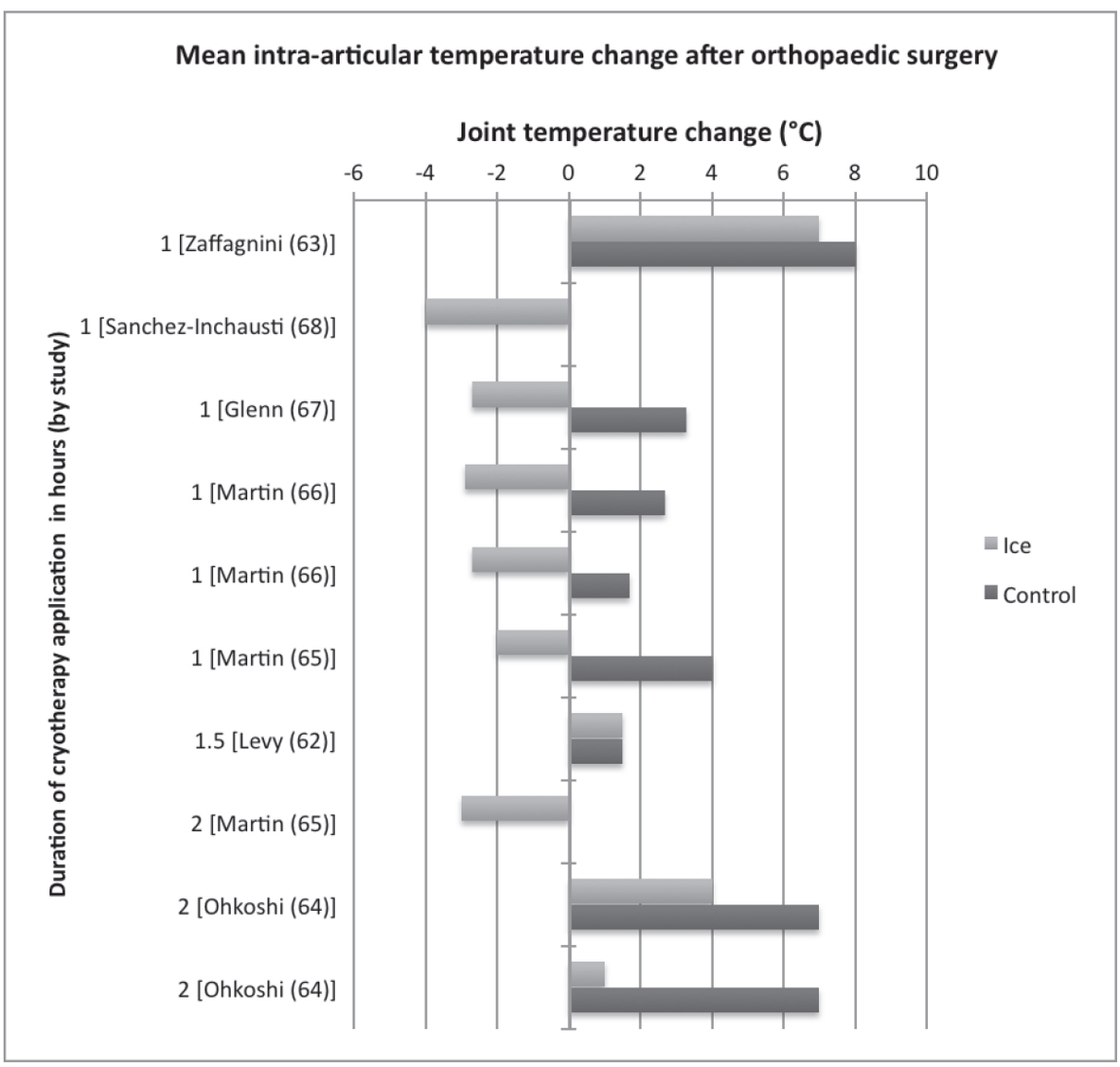

Figure 4

Chapter 3

Can PRICE decrease the inflammatory response after acute soft tissue injury?

What is known in this area: PRICE is one of the simplest and oldest approaches for treating acute soft tissue injuries. The rationale is that components of PRICE have an 'anti' inflammatory effect after injury, but few clinicians may look beyond the cardinal signs when providing justification for intervention. There have been a number of recent advances in understanding the physiological and biochemical events associated with acute inflammation after soft tissue injury.

Aim: To update the pathophysiological rationale for using PRICE in the management of soft tissue injury.

Clinical question: Can PRICE decrease the inflammatory response after acute soft tissue injury?

Objective: To review the rationale for PRICE intervention in the acute phases of soft tissue injury based on physiological, cellular and molecular models of inflammation.

What this review adds: There is limited evidence from human studies that ice may reduce metabolism or aspects of the inflammatory response based on tissue perfusion and microdialysis. Other human models based on EIMD had a high risk of bias, and there were conflicting results; furthermore few have focused on biomarkers of inflammation per se. There is evidence from animal models that ice seems to have a consistent effect on key cellular and physiological events associated with inflammation after injury. This includes cell metabolism, white blood cell activity within the vasculature, and potentially apoptosis. The relative benefits of these effects have yet to be fully elucidated and it is difficult to contextualize within a human model. The effects on micro-circulation after injury are contrasting, potentially due to heterogeneity of injury, intervention and outcome.

Limitations and future study recommendations: The evidence from human studies is of low methodological quality and the inflammatory models used may have limited application to closed soft tissue injury. The remainder of the evidence is derived solely from animal models, some of which is based on excised tissues samples. The models are also limited to lab induced muscle injuries, and in many cases anaesthesia may have confounded the outcomes. Future research should use human subjects and focus on more direct examination of inflammatory related markers, and cellular oxidative stress. Considerations must be given to the type of soft tissue affected (eg. muscle vs ligament) and the injuring force (crush vs tensile).

Background

PRICE is one of the simplest and oldest approaches for treating soft tissue injuries such as sprains, contusions, and dislocations. The immediate phase after soft tissue injury is characterised by an acute inflammatory response. This often presents clinically with cardinal signs such as heat, redness, pain and swelling. Currently few clinicians may look beyond the cardinal signs when providing justification for intervention; and it is commonly accepted that components of PRICE, particularly ice and compression have an 'anti' inflammatory effect after soft tissue injury. Applying a cold compress to hot, red and swollen tissue may seem pragmatic; however there is not always an obvious link between inflammation visible under the microscope and that clinically apparent and characterised by the original cardinal signs.[1] Paradoxically, recent trends in sports medicine involve delivering growth factors into healing muscle tissue (eg. via platelet rich plasma or autologous blood injections)[2] which seems to lean more towards a pro-inflammatory treatment approach.

Objectives

The objective of this chapter was to review the rationale for PRICE intervention in the acute phases of soft tissue injury based on physiological, cellular and molecular models of inflammation.

Methods

Literature search

We searched the titles generated from the main search strategy outlined in Appendix Tables 1-4. Relevant studies were extracted, with exclusions made based on titles, abstracts or full text versions.

Inclusion criteria

No restrictions were made on study design; and both animal and human subjects with acute soft tissue injury were considered. Acute injuries induced in a laboratory situation were included. Studies using exercise induced muscle damage (EIMD) were included provided that it was induced with a well defined resistance (concentric or eccentric) or plyometric exercise protocol. No restrictions were placed on the type of PRICE intervention. Outcomes could include any physiological, cellular or molecular measurement associated with inflammation; recorded before injury, and up to one week post injury. We were particularly interested in the following data: injury site, type and severity of injury, intervention technique and dosage, and influence of anaesthesia (in the case of induced injury). If applicable, outcomes were extracted pre-injury and post-injury. Qualitative comparisons were made and results were grouped and discussed by outcome.
Based on the difficulties associated with measuring haemodynamics in acutely injured subjects, we felt it was appropriate to also consider evidence on the effect of cooling/compression on local blood flow in human participants, with no restrictions made on injury type, or depth of measurement.

Risk of bias

All included studies were assessed in terms of design, and methodological quality based on Cochrane risk of bias tool3 (sequence generation, allocation concealment, assessor blinding, incomplete outcome data).

Results

Excluded studies (with reasons) are listed in Appendix Table 5.

Human

Overview of study methods

We found 20 relevant human models based on EIMD;[4-23] Figure 1 provides a summary of risk of bias across studies. All used randomisation, half of which were cross over designs. There were a number of methodological limitations; only one[14] adequately described the methods of sequence generation and allocation concealment, and two[7,14] used blinded outcome assessors. In the majority of cases, comparisons groups were untreated controls; one was placebo ultrasound.[8]
Interventions focused on cooling,[4,8,10,11,13-18] compression[6,7,19-23] or protection/rest.[5,9,12.] Cold intervention largely involved CWI, with two studies[8,11] using 15 minutes of ice massage. CWI times ranged from 10-15 min, except Sellwood et al.[14] who used a 1 minute CWI repeated 3 times. Water temperature ranged from 15C°10 to 5°C.[14] Compression interventions were clothing garments (tights or sleeves), put on immediately after EIMD and worn continuously for up to 4 days. Their associated compressive forces were reported between 10 and 30mmHg. One study used a whole body compression suit.[23] The remaining relevant studies undertaken on humans used post surgical[24] or inflammatory arthritic models.[25] Figures 2-5 summarise the key characteristics of relevant studies using injured human models.

PRICE and inflammation post EIMD

The EIMD studies mostly considered biomarkers of muscle damage after exercise, and all undertook daily recording of serum Creatine Kinase (CK), for up to 5 days after exercise. 5 studies,[11,14,15,17,18] found CK levels were similar across cooling and control (no cooling) groups. In contrast others reported significantly lower CK levels within cold treated groups, at 24,[13,16] 48,[4,13] 72[4,8,16] and 96 hours[10] post exercise. In two studies, compression sleeves were associated with lower levels of CK at 72[7] and 120 hours;[6] and a full body compression garment produced lower levels at 24.[23] Graduated compression tights[19-22] did not affect CK levels after lower limb EIMD. In two cases[5,9] rigid immobilisation significantly reduced CK levels between 2 and 5 days after EIMD to the upper limb; whereas partial immobilisation in a sling had little effect.[12]
Others also recorded biomarkers of inflammation, these were: myoglobin,[9,11,16,19] interleukin-6 (IL-6),[16] C-Reactive Protein (CRP)[21] and lactate dehydrogenase (LDH);[6,10,16,20,23] there were no significant differences between treatment groups and controls for any of these outcomes.

PRICE and inflammation post surgery / arthritis

Using a case control design, Stalman et al[24] used microdialysis to determine local metabolic and inflammatory responses in knee synovium after ACL reconstruction, or minor arthroscopic surgery. The ACL group only was treated with intra-articular morphine and ice and compression post surgery; they had significantly lower levels of PGE2, and lower levels of synovial lactate levels compared to the arthroscopic group. This provides promising evidence that the magnitude of the metabolic and inflammatory responses can be reduced after surgery, however we cannot yet ascertain whether this relates to the effects of ice and compression, morphine or both.

Animal models

Overview of study methods

There were 16 animal studies[26-41] all of which used randomised controlled or controlled methods. Six[26,28, 29,30,39,40] included a blinded assessment of outcome. In all cases animals were subjected to a standardised injury, and then divided into either a treatment group, or an untreated control group. Two studies injected cytokine (hrTNF α)[34] or formalin[35] to induce inflammation, one used EIMD[41] and all others used blunt trauma to induce a muscle contusion. In all but one study,[41] cooling was the primary intervention. Outcomes focused on secondary cell death, white blood cell behaviour, apoptosis, blood flow and oedema formation. These were measured largely using immumohistological analysis of excised tissue, and/or intravital microscopy (with and without laser Doppler imaging). Details of relevant animal models are summarised in Figure 6.

In most of the animal models, cooling was initiated less than 15 minutes after injury. The duration of the interventions ranged from 20 minutes up to 6 hours of continuous cooling. In two cases cooling was undertaken directly on exposed animal muscle,[38,39] with others applying over intact skin (both shaven and unshaven). Three studies[26,28,33] used concomitant compression when cooling and one study used cyclic compression alone.[41] In all but three studies,[29,30] the animals were under anaesthesia for the duration of the intervention.

Figure 7 provides an overview of all studies assessing the effect of PRICE on inflammation by: model, injury type and cooling dose

Secondary cell injury

Perhaps the most commonly cited rationale for applying ice after acute soft tissue injury relates to the 'secondary injury model'.[42] This is based on the premise that after an initial trauma (e.g. muscle strain or contusion), the patho-physiological events associated with acute inflammation can induce secondary damage to cells around the injury site. Of particular concern is that this can involve collateral damage to healthy cells not injured in the initial trauma. This phenomenon is known as secondary cell injury, and may be caused by both enzymatic and ischaemic mechanisms.[43] One of the most important cellular effects associated with icing is its potential to reduce the metabolic rate of tissues at, and surrounding the injury site. This reduction in metabolic demand may allow the cells to better tolerate the ischaemic environment in the immediate phases after injury, and thus minimising the potential for secondary cell injury or death.

Evidence to support secondary injury theory is based largely on studies of limb preservation. Osterman et al.[44] and Sapega et al.[45] both used, phosphorous 31 nuclear magnetic resonance imaging to monitor cellular metabolism in ischaemic (amputated) cat limbs, stored at a range of temperatures between 22°C to 1°C. Overall, they found that cells survived better at lower muscle temperatures. This was exemplified by lower levels of ATP and PC depletion, and lower levels of acidosis, during the period of ischaemia. Of note, these effects appeared to be reversed at more extreme muscle temperatures reductions below 5°C. This was attributed to extreme temperature reductions causing inhibition of the calcium pump of the muscle's sarcoplasmic reticulum.[45]

The current search found one related study in this area; Merrick and colleagues[33] tried to quantify the effect of icing on mitochondrial function after injury. Specifically they measured the activity of the mitochondrial enzyme, cytochrome c oxidase, after experimental crush injury; comparing outcomes in cold treated and untreated muscle tissue. Fitting with the 'secondary injury model', five hours of continuous cooling inhibited the loss of mitochondrial oxidative function after injury when compared to the untreated controls. Although the model used by Merrick et al.[33] does not directly determine the effects of ice on the inflammatory process or muscle injury per se, it is the first study to have taken a novel approach to indirectly assess the effects of secondary generated free radicals, and their possible interference with enzymes controlling oxidative phosphorylation (cytochrome c oxidase) and thus ATP production after injury.

White Blood Cells

When muscle or joint injury occurs, phagocytic white cells, such as neutrophils, monocytes, eosinophils and macrophages become activated and dominate the inflammatory response in the early stages. Although these cells have a critical role in healing through their removal of necrotic debris and release of cytokines;[46] they can also have a negative effect on soft tissue healing after injury.[46,47] For example, white cell activation results in a series of reactions termed the 'respiratory burst'.[48] These reactions are a source of reactive oxygen species (ROS) such as superoxide (O2.-), hydrogen peroxide (H2O2) and hydroxyl (OH.); and hypochlorous acid (HOC1) which is a powerful antibacterial agent. In certain circumstances the production of ROS and antibacterial agents are important immune defense mechanisms, however they can also be a potentially dangerous mechanism if inappropriately activated. For example, overproduction of ROS may cause unwanted collateral damage to adjacent tissues and surrounding molecules.[49] This may be particularly likely in the event of a closed soft tissue injury such as an ankle sprain, which is not associated with bacteria or infection. Indeed, there is evidence that blocking the respiratory burst, using anti-CD11b antibody (M1/70), produces a three-fold reduction in myofibre damage in an animal model at 24 h post-injury.[50]

We found three animal models; studying the effect that ice has on WBC behaviour after soft tissue injury. A popular approach has been to use fluorescent intravital microscopy[34,38-40] to observe the effect that ice has on leukocyte activity within the microvasculature. These studies found a clear trend that icing significantly lowered the percentage of both adherent and rolling neutrophils after injury, in comparison to injured untreated tissue. This finding was consistent over the first 24 hours after injury.[34,38-40] Cyclic compression initiated 30 minutes after EIMD in rat a model, attenuated leukocyte infiltration.[41]

Other animal models[26,28,35,39,40] undertook histological analysis on excised tissue after soft tissue injury. In each case, various staining techniques were used to identify leukocyte sub-types at the injury site. Again each study made comparisons between ice treated, and untreated injured tissue samples. Using an injured ligament model and assessor blinding, Farry et al.[26] found that ice treated groups had lower levels of WBC's (polymorphs, lymphocytes and plasma cells) at 48 hours, in comparison to injured contra-lateral untreated limbs. Hurme et al.,[28] who also used blinded outcome analysis; found that at various time points post injury, the ice treated animal tissue had lower levels of erythrocytes (1 hour), neutrophils (6 hours) and macrophages (at 24 hours) in comparison to the untreated control limbs. Although Schaser et al.[39] also found cooling decreased neutrophilic granulocyte muscle infiltration, in comparison to control muscle, there were higher levels of macrophages. In a follow up study[40] using longer periods of cooling (5 hours), tissue analysis at 24 hours post trauma, also found lower levels of neutrophilic granulocytes in the cold treated muscle.

In a related model, Kenjo et al.[35] measured Fos protein expression in neural tissue, after formalin induced inflammation in rat hind paws. Quantification of Fos labelled cells is thought to be a valuable marker of neuronal response to noxious stimuli. Cold water immersion (CWI) of the paw immediately after formalin injection significantly reduced the number of Fos labelled cells; in addition, the peak time for their expression was delayed when compared to an untreated control. This provides further evidence that cooling influences the body's response to inflammatory pain, and potentially highlights a delay in the inflammatory reaction.

Although the examination of adherent and rolling neutrophils following injury and ice may, in some instances be beneficial, these models must be developed if we are to further our understanding in this area. It may be more relevant for future research to quantify the amount of direct neutrophil activation that occurs following injury. This approach may allow for estimation as to how much secondary cell and surrounding tissue damage and inflammation will likely occur. A popular marker that is commonly used to determine neutrophil activation is myeloperoxidase. This is produced by an increase in ROS activity and it has been successfully used in studies looking at free radical production and immune response after stretch injury in animal skeletal muscle.[51]

Apoptosis

Apoptosis is a programmed cell death. It is characterized by a cascade of biochemical events cumulating in altered cell morphology and eventual cell death. Although apoptosis is the normal means by which cells die at the end of their life span, its incidence may be affected by soft tissue injury. Higher numbers of apoptotic cells have been recorded around the edges of rotator cuff tears when compared to un-injured control muscles.[52] The reasons for this increase have not yet been fully elucidated; however, the accumulation of reactive oxygen species in injured tissues (oxidative stress) could again play a significant role.[53] Cell survival requires multiple factors, including appropriate proportions of molecular oxygen and various antioxidants. Although most oxidative insults can be overcome by the cell's natural defenses, sustained perturbation of this balance may result in apoptotic cell death.

There is limited evidence from animal models that ice can reduce the incidence of apoptosis after injury. Westermann[34] found that after chemically induced inflammation, the number of apoptotic muscle cells (quantified by the number of cells with nuclear condensation and fragmentation) was significantly higher in untreated controls, when compared to the ice group. This is an interesting finding as reduced levels of apoptosis may again represent a protective effect of ice after soft tissue injury. We can only postulate as to the reasons for this finding; however this may be further evidence that ice can reduce inflammation and decrease secondary free radical production (from the respiratory burst), thereby causing less interference with important proteins and other cell metabolites that control apoptosis.

Blood flow and Oedema

Acute soft tissue injury incurs a multitude of changes to local vasculature and microvasculature. These include: increased vessel diameter;[29,40] increased cell permeability and macromolecular leakage into the injured tissue;[40] and decreased tissue perfusion.[34,39,40] One of the proposed mechanisms for cooling in the immediate stages after injury is to reverse these effects, and it is well accepted that cooling has a vasoconstrictive effect on the vasculature. The original PRICE guidelines found consistent evidence that various modes of cooling decreased blood flow at the ankle joint and knee joint, based on impedance plethysmography or triple phase technetium bone scanning.[54-57]

Healthy human

Many recent studies have used laser Doppler fluxmetry to record microcirculation within the extremities (eg. fingers, hands). There is consistent evidence that cooling almost immediately decreases superficial blood flow and tissue perfusion.[58-63] This response is thought to relate to reflex sympathetic activity which increases the affinity of alpha adrenoceptors in the vascular walls for norepinephrine, causing vasoconstriction.[64] Interestingly, all cases also noted a paradoxical increase in blood flow, after around 3-8 minutes of cooling. This pattern is consistent with Lewis' original theory[65] that prolonged exposure of cooling leads to a secondary vasodilator effect. The precise mechanism for this is not known, and it may relate to either central or peripheral processes. Lewis[65] suggested an axon reflex whereby the decreasing local tissue temperatures, interrupts sympathetic nerve conduction, with resultant vasodilatation.

It is important to consider that these patterns are based on isolated immersion of the extremities (e.g. single finger), with outcomes limited to blood flow at depths of around 0.6 mm. This represents skin or superficial tissue blood flow, which is generally not the central site of injury. Other recent studies have focused on the effect of ice on healthy tendon haemodynamics at depths of 2-8mm. Using real time laser doppler spectrophotometry, Knobloch and colleagues[66-69] have found consistent evidence that various combinations of ice, and compression induce an immediate and significant reduction in capillary blood flow and oxygen saturation, with facilitated venous capillary outflow. Using a similar spectrometry technique, Yanagisawa[70] found a cold induced decrease in haemoglobin/myoglobin concentration within muscle tissue, again suggesting a decrease in local circulation. Of further interest was that none of these studies[66-70] found evidence of reactive vasodilatation during cooling. Similar patterns have been observed based on impedance or strain gauge plethysmography[57,71] with cold induced decreases in local blood flow in the ankle joint, and calf muscles, with no reports of reactive vasodilatation. Only one study[72] concluded that cooling did not result in any change to local tissue blood flow. The reported outcome was based on strain gauge (venous occlusion) plethysmography, and cooling was a 20 minute CWI in 13°C. In this regard, cooling was undertaken in a gravity dependant position which may have had a concomitant effect on blood flow.

Few have considered the effect of ice on the vasculature after significant soft tissue injury in humans; and models are restricted to EIMD. Based on MRI, Yanagaisawa and colleagues[73] found that short bouts of cooling prevented the usual accumulation of post exercise oedema in ankle dorsiflexor muscles.

Microcirculation (injured animal)

A number of animal studies have considered the effect of cooling on microcirculation after acute crushing injury, using intravital microscopy techniques. The results were often inconsistent: some studies found that ice application did not significantly change capillary diameter,[39,40] arteriole diameter;[29,31,39] or capillary velocity after injury.[39,40] In contrast, others found that ice either significantly increased[39] or decreased[34] arteriole diameter after injury.

There may be clearer patterns associated with venular diameters. Three studies[38-40] reported smaller venular diameters in ice treated groups in comparison to injured (untreated) controls when measured at both the initial stages[38,39] and at 24 hours[40] post injury. In two of these studies,[38,40] the differences were significant, and in one case, venular diameter in the cold group had returned to pre-injury levels.[40] Although this trend is supported with evidence that, iced tissue also had higher levels of venular blood flow velocity in comparison to controls in the immediate stages post injury;[34,38,39] this trend was reversed at 24 hours post injury.

There is conflicting evidence on the effect that ice has on tissue perfusion post injury. Using fluorescent microscopic assessment of the functional capillary density (length of erythrocyte-perfused capillaries per observation area), three studies; [34,39,40] found that ice application significantly increases tissue perfusion after injury, in comparison to untreated injured controls. Again, in two cases,[39,40] perfusion was restored to pre-injury levels. In contrast, based on laser Doppler imaging after injury, Curl31 found that cooling had little effect on microvascular perfusion.

Using a related outcome measurement, Schaser and colleagues[39,40] monitored intramuscular pressures in rat limbs after soft tissue injury, randomising limbs to receive either cold saline, or no intervention. Lower intramuscular pressures [17.7 mmHg (SD: 4.7)] were recorded at 1.5 hours post injury in the cooling group (treated with 20 minutes of saline cooling), when compared to untreated controls [19.2 mm/Hg (SD: 3.1)]. Their follow up study, also found that longer periods muscle cooling (5 hours) was associated with lower intramuscular pressures 18 (95% CI: 5.5 mmHg) in comparison to untreated controls [26 (95% CI: 1.9 mmHg)], at 24 hours post injury.

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Figure 1

Risk of bias graph for Human EIMD inflammatory models: Review authors' judgements about each risk of bias item presented as percentages across studies.

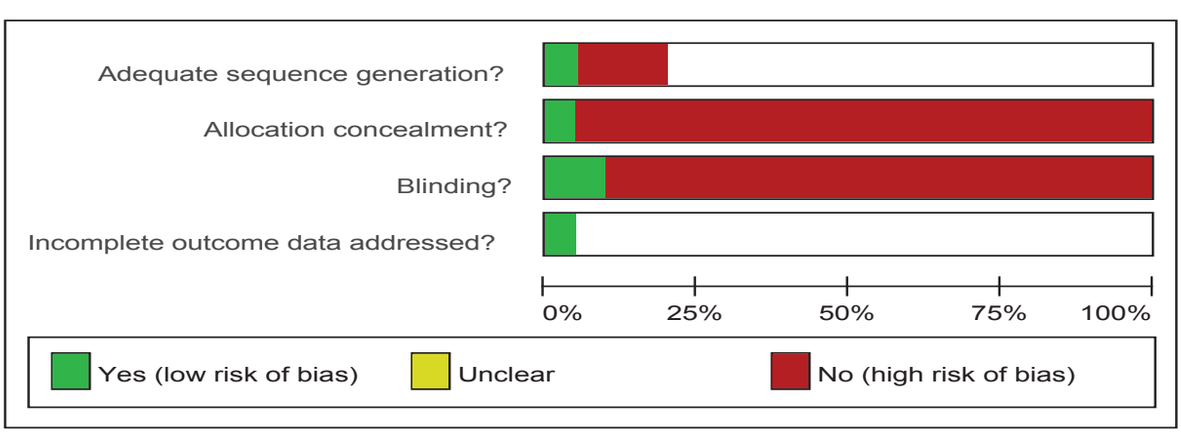


Figure 2

Summary of Human models (Ice and EIMD)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
ICE INTERVENTIONS				
Eston, 1999 RCT	N=15 healthy females; mean age 22 +/-2 y	5 sets of 8 maximal elbow flexions (eccentric and concentric), 60 s rest between each set	-I (n=8): CWI at 15°C for 15 min, immediately post exercise, and every 12 hours thereafter for 3 days -C (n=7): No treatment	Plasma CK I<C (48h*, 72h*)
Howatson, 2003 Randomised cross over: 2 weeks wash out; opposite arms (Sequence generation)	N=9 healthy resistance trained males; mean age 23.3 (SD: 3y)	3 sets of 10 biceps curls at 70% 1RM	-I (n=9): 15 mins of ice massage -C (n=9): 5 min sham ultrasound Both interventions: immediately, 24h and 48h post exercise	Plasma CK I<C (24h, 48h, 72 h*)
Yanagisawa, 2003 RCT	N=28 healthy untrained participants; mean age 23.8 (SD 1.8 y)	5 sets of 20 resisted calf raises at 30% of participants maximal voluntary contraction, 1 min rest between sets	-Single I (n=9): CWI in water at 5°C for 15 mins, Immediately after exercise -Double I (n=9): CWI in water at 5°C for 15 mins, immediately after exercise, and 24 hours after exercise -C (n=10): No I	CK [change within groups] Post C > Pre C (48, 96 hrs*) Post DI > Pre DI (48, 96 hrs*) Post I>Pre I (96 hrs) LDH Post C > Pre C (96 hrs*, 168hrs) Post DI > Pre DI (96 hrs, 168hrs) Post I>Pre I (96 hrs) For both outcomes, SI had the smallest increase above baseline
Howatson, 2005 Randomised cross over : 2 weeks wash out; contra-lateral arms (Sequence generation)	N=12 healthy physically active males; mean age 24.8 (SD: 5.3y)	3 sets of 10 maximal eccentric bicep contractions on isokinetic dynamometer, 3 min rest between sets	-I (N=12): Ice massage, 15 mins -C (n=12): 5 min sham ultrasound All interventions: immediately, 24, and 48 hrs post exercise	CK I=C (24, 48) I<C (72, 96) Myoglobin I=C (24, 48, 72, 96)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
ICE INTERVENTIONS				
Skurvydas, 2006 Randomised cross over: 9-10 month wash out	N=20 healthy physically active males; aged 20.4 (+/-1.7y)	100 countermovement jumps from a 0.75 height	-I (n=20): CWI at 15°C (+/- 1C) for 15 mins x 2. 10 mins between each immersion. Undertaken immediately after exercise and repeated at 4h, 8 h, 24 h -C (n=20): no I	Plasma CK I<C (24hll, 48hll)
Sellwood, 2007 RCT (Sequence generation; allocation concealment; blinded outcome assessment; follow up well described)	N=40 healthy adults; mean age 21 (SD: 4.3y)	5 sets of 10 repetitions of eccentric quadriceps exercise at 120% of 1 repetition maximum, 1 mins rest between sets	-I (n=20): CWI to ASIS at 5°C, 1 mins x 3, initiated immediately post exercise -C (n=20): CWI to ASIS in 24°C water, 1 mins x 3. Participants rested out of the bath for 60, initiated immediately post exercise	Plasma CK I=C (24h, 48h, 72h)
Goodall, 2008 RCT	n=18 physically active and healthy males; mean age: 24 (SD 5 y)	5 sets of 20 drop jumps on a concrete based floor. 10 s rest between each jump and 2 min rest between each set.	-I (n=9): Seated CWI 15°C to iliac crest for 12 mins. Undertaken immediately post exercise, and once every 24 for 3 days -C (n=9): Seated, no immersion	Plasma CK I=C (0-96h)
Vaile, 2008 Randomised cross over: 8 month wash out (Sequence generation)	N=38 healthy strength trained males	7 sets of 10 eccentric repetitions on a leg press machine; 3 min rest between sets)	-I (n=12): Whole body CWI (excluding head and neck) at 15°C -HWI (n=11): Whole body HWI (excluding head and neck) at 38°C -Contrast (n=15): Whole body CWI (excluding head and neck) at 15°C for 1 min, followed by whole body HWI (excluding head and neck) at 38°C for 1 min, repeated 7 times -C (n=38):Seated with minimal movement Interventions were undertaken immediately, 24, 48 and 72 hours after exercise. All interventions were 14 min durations	CK I<C (24h*, 72h*) HWI<C (48h) LDH I=C (0h, 24h, 48h, 72h) Myoglobin I=C (0h, 24h) IL-6 I=C (0h,24h)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
ICE INTERVENTIONS				
Howatson, 2009 Randomised Cross Over (Follow up well described)	N=16 healthy recreational male athletes; mean age 23.3 (SD 3y)	100 drop jumps from a 0.6m height (5 sets of 20 with 2 mins between each set)	-I (n=16): CWI in 15°C to ASIS for 12 min -C (n=16): Seated for 12 min Both interventions: undertaken immediately post exercise and at 24 hour increments for the following 3 days	Plasma CK I=C (24h, 48h, 72h, 96h)
Jakeman, 2009 RCT (Sequence generation)	N=18 healthy females; aged 19.9+/- 0.97 y	10 sets of 10 CMJ, adopting a 90 deg knee angle on each landing	-I (n=9?): Seated CWI at 10°C, for 10 min. Undertaken within 10 min of exercise. -C (n=9?): ?No I	Plasma CK I=C (1h, 24h, 48h,72h, 96 h)

EIMD: Exercise induced muscle damage
I: Ice
C: Control (unless otherwise stated control involved rest/sitting)
CWI: cold water immersion
HWI: hot water immersion
CMJ: Countermovement Jump
CK: Creatine Kinase
Deg: degree
s: S
Min: Mins
M: metre
Y: years
ASIS: anterior superior iliac spine
Pre: pre exercise values
Post: post exercise values
h: hours post exercise/loading (eg. 24h = 24 hours post exercise/loading)
*: $p<0.05$
ll: $p<0.001$

Figure 3

Summary of Human models (Compression and EIMD)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
Kraemer, 2001a RCT	N=20 healthy females; mean age: COMP 21.3 (SD: 2.9y), C 21.1 (SD: 3.3y)	2 sets of 50 passive arm curls with a maximal concentric and eccentric contraction every fourth rep	COMP (n=10): Compressive sleeves for 5days (10mmHg) C (n=10): no intervention	Serum CK COMP=C (24h) COMP<C (48h*, 72h*, 96h*, 120h*) Serum LDH COMP=C (24h, 48h, 72h, 96h, 120h)
Kraemer, 2001b RCT	N=15 healthy males; mean age: COMP 22.3 (SD: 2.9y), C 22.1 (SD: 3.3y)	2 sets of 50 arm eccentric curls, 3 minutes between sets	COMP (n=8) Compression sleeve for 3 days (10mmHg) C (n=7): no intervention	Serum CK COMP=C (24h, 48h) COMP<C (72h*)
French, 2008 RCT	N=26 healthy active males; aged 24.12 +/-3.2y	6 sets of 10 back squats at 100% body weight, each set included an eccentric squat at 1RM	Contrast (n=10): seated CWI 60 secs, immediately followed by seated HWI, 180 secs x 3 COMP (n=10):12 h wearing tights with mean compression of 12mmHg at the calf, 10mmHg at thigh C (n=6): no intervention	Serum CK COMP=C (1h, 24h, 48hr) Serum myoglobin COMP=C (1h, 24h, 48h)
Davies, 2009 Randomised cross over: 7 days between intervention	N=11 healthy netballers/ basketballers; 7 female (aged 19.7+/-0.5y), 4 male (aged 26.3 +/-5.1y)	5 sets of 20 CMJs	COMP (n=11): graduated compression tights (15mm/Hg) for 48h C (n=11): Passive recovery for 48h	Serum CK COMP=C (24h, 48h) Serum LDH COMP=C (24h, 48h)
Duffield, 2010 Randomised cross over: 7 days between interventions	N=11 team sport athletes; mean age 20.9 (SD 2.7y)	10 sets of 20 m sprints plus 10 sets of 10 double leg bounds; 1 min between sets	COMP (n=11): Compression garments, during exercise and for 24 h post exercise C (n=11): no compressive garments	Serum CK COMP=C (0h, 2h, 24h) AST COMP=C (0h, 2h) COMP<C (24h) trend, but not significant CRP COMP=C (0h, 2h, 24h)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
Jakeman, 2010 RCT	N=17 healthy female participants; mean age21.4 (SD: 1.7y)	10 sets of 10 CMJs from a 0.6metre height, 10 secs between jumps, 1 min between sets	COMP (n=8): Full leg compression stockings, 12 h post exercise C (n=9): Passive recovery	Serum CK COMP=C (1h, 24h, 48h, 72h, 96h)
Kraemer, 2010 RCT	N=20 healthy highly resistance trained participants; 11 males [mean age 23 (SD: 2.9y)]; 9 females [mean age 23.1(SD: 2.2y)]	3 sets of 8-10 reps of 8 different whole body resistance exercises; 2-2.5 min rest between sets	COMP: Whole body compressive garment for 24h C: non compression garments	Serum CK COMP<C (24h*) LDH COMP=C (24h)

AST: Aspartate transaminase
C-RP: C-Reactive protein
LDH: Lactate dehydrogenase
CMJ: countermovement jump

Figure 4
Summary of Human models (Protection / Rest and EIMD)

Study (Factors lowering risk of bias[3])	Inclusion	EIMD	Interventions	Summary of results
Sayers, 2000 RCT	N=26 participants	50 maximal eccentric contractions of the elbow flexors	IMM (n=9): Cast (immediately post exercise) at 90 deg elbow flexion for 4d EX (n=9): 2 sets of 25 biceps curls/d oer 4d, with a 5lb weight, 2 min rest between sets C (8): no intervention	Plasma CK IMM=C=EX (24 h) IMM<C=EX (48h*, 72h* , 92h*)
Sayers, 2003 RCT	N=25 healthy male participants	2 sets of 25 maximal eccentric contractions of elbow; 5 minutes between sets	IMM (n=12): Cast (immediately post exercise) at 90 deg elbow flexion for 4d C (n=13): no intervention	Plasma CK IMM=C (24h) IMM<C (48h*, 72h* , 96h*) Plasma myoglobin IMM=C=EX (0-5d)
Zainuddin, 2005 Randomised cross over: 2 weeks between interventions, contralateral arm as control	N=10 healthy participants; mean age 23+/- 4.2y; 5 male, 5 female	10 sets of 6 isokinetic eccentric contractions of elbow flexors	IMM arm: Sling (30 minutes post exercise) at 90 deg elbow flexion for 4d C arm: No intervention for 4d	Plasma CK IMM=C (24h, 48h, 72h, 96h; 7d)

Figure 5
Summary of Human Models (other soft tissue injury)

Study (Factors lowering risk of bias[3])	Inclusion	Interventions	Summary of results
Stalman, 2008 Case control	N=20 participants undergoing knee surgery	-Arthroscopy (n=10): I/A morphine and I/C -ACL reconstruction (n=10): No I/C	Microdialysis (Synovial membrane vs adipose reference tissue) Lactate levels post surgery -Arth: Syn Mem> ref tissue* -ACL: Syn Mem=ref tissue Consumption of glucose levels post surgery: -Arth: Syn Mem> ref tissue* -ACL: Syn Mem=ref tissue Glycerol levels post surgery - ACL: Syn Mem=ref tissue Prostaglandin (PGE2) levels post surgery -ACL<Arth*
Strunk, 2006 Case series (Blinded outcome assessor)	N= 13 participants with clinically active RA at the wrist	I: cold pack for 20 min (skin temperature reduced to 5.5°C)	**Power Doppler ultrasonography (2 and 3D PDUS)** Synovium vascularity (based on a semi-quantitative grading system) -Decreased in 54% of patients after I

I/C: ice and compression
Arth: arthroscopy
RA: rheumatoid arthritis
Syn Mem: synovial membrane
2 and 3 D: 2 and 3 dimensions

Figure 6

Summary of Animal Models

COOLING									
Study	**Injury site (severity):**	**Details of intervention [total dosage]**	**Directness of cooling**	**Time after injury of ice initiation**	**Control group**	**Anaesthetized during trauma (Y/N**	**Anaesthetized during cooling (Y/N)**	**Anaesthetized during outcome assessment (Y/N)**	**Outcomes (Blinded assessor Y/N)**
McMaster, 1980	Rolling crush injury forelimb (NS)	CWI at 20C; 1 hr (n=5) CWI at 30 C 1 hr (n=5) CWI both limbs; 1 hr x 3 (n=10)	CWI intact shaven skin	Immediate (likely)	No treatment (n=10)	Y	Y	Y	Water displacement (N)
Farry, 1980	Bilateral crush injury radiocarpal ligament (NS)	Crushed ice (n=5) and compression 20 mins x 2	Intact skin	Immediate (likely)	Compression at 106Nm2 to contralateral limb (n=5)	Y	Y	Y	IHA (Y)
Hurme, 1993	Blunt trauma left calf (NS)	Cold pack with compression and elevation; 5 mins every 14 x 4 (n=14)	Intact skin (lowest temperature recorded in deep muscle 20C)	Immediate	No treatment (n=14)	Yes	Yes	Yes	IHA (Y)
Smith, 1993	Blunt trauma skin side of DMC (a)	Ice cylinders; 20 mins every 6 hrs x 3 (n=6)	Intact unshaven skin	Immediate (likely)	No treatment (n=6)	Y (lightly)	Y (lightly)	Y (lightly)	Intravital microscopy with MC (Y) Laser Doppler fluxmetry

Study	Injury site (severity):	Details of intervention [total dosage]	Directness of cooling	Time after injury of ice initiation	Control group	Anaesthetized during trauma (Y/N	Anaesthetized during cooling (Y/N)	Anaesthetized during outcome assessment (Y/N)	Outcomes (Blinded assessor Y/N)
Smith, 1994	Blunt trauma on skin side of DMC (a)	Ice pellets directly against the fur; 20 minutes each day for 4 days)	Intact unshaven skin	6 days?	No treatment	Y	N	N	Intravital microscopy with MC Laser Doppler fluxmetry / perfusion imager (Y)
Curl, 1997	Blunt trauma cutaneous maximus muscle (NS?)	Ice cylinders; 20 mins every 6 hrs for 2 days (n=16)	Intact skin	5 minutes	No treatment (contralateral limb) (n=16)	Yes (n=8 Ketamine/ Xylazine; n=8 Isoflurane)	Yes (likely)	No	Intravital microscopy with MC Laser fluxmetry (N)
Dolan, 1997	Blunt trauma to plantar aspect of foot, bilateral (a)	CWI in 12.8 -15.6C); 30 mins x 4 (n=16)	CWI to intact shaved limbs	5 minutes	WI in 22-25.5C; 30 mins x 4 (n=16, contralateral limb)	Y	Y	Y	Water displacement (N)
Merrick, 1999	Blunt trauma right calf (NS)	Ice pack with elastic tape; 5 hrs (n=10)	Unshaven intact skin	Not explicitly stated (likely immediate)	No treatment (n=9); also contralateral limb of treatment group used for	Y	Y	Outcomes undertaken on excised tissue	Biochemical assay (N)

Study	Injury site (severity):	Details of intervention [total dosage]	Directness of cooling	Time after injury of ice initiation	Control group	Anaesthetized during trauma (Y/N	Anaesthetized during cooling (Y/N)	Anaesthetized during outcome assessment (Y/N)	Outcomes (Blinded assessor Y/N)
Westermann, 1999	hrTNF α: 2000 units (in 0.1mL phosphate-buffered solution) to striated muscle in back	Ice cold saline solution; 1 hr duration; surface temperature decreased to 10 (2C) (n=9)	Through microvasular chamber	Immediate	No treatment (n=8)	N	N	N	Intravital microscopy with MC (N)
Kenjo, 2002	Formulin injection Plantar aspect R hind paw	CWI at 20C; 30 mins duration	Unshaven intact skin	Immediate	No treatment?	Y	Y	Outcomes undertaken on excised tissue	Fos immune-reactivity expression (spinal cord) (N) Limb volume (N)
Deal, 2002	Blunt trauma cutaneous maximus muscle (b)	Cylinder of ice to skin side of chamber; 20 minutes (n=15)	Unshaven intact skin	15 mins	No treatment (n=5)	Y	Likely (cooling initiated 15 mins post injury)	N	Intravital fluorescent microscopy with MC (N)
Dolan, 2003	Blunt trauma to plantar aspect of foot, bilateral (a)	CWI at 12.8 C; 3 hrs, followed by 1 hrs rest CWI at 12.8 C) for 1 hr; 2 hrs HVES; 1 hrs rest	CWI intact shaven limbs	5 mins	HVES for 3 hrs	Y	Y	Y	Water displacement (N)
Lee, 2005	Blunt trauma to cremaster muscle (b)	Saline at 3C; 10 minutes (n=7) Saline at 27C; 10 minutes (n=7)	Cooling directly onto exposed muscle surface	5 minutes	Saline at 37C; 10 minutes (n=7)	Y	Y	Y	Intravital microscopy (N) Real time laser

Study	Injury site (severity):	Details of intervention [total dosage]	Directness of cooling	Time after injury of ice initiation	Control group	Anaesthetized during trauma (Y/N	Anaesthetized during cooling (Y/N)	Anaesthetized during outcome assessment (Y/N)	Outcomes (Blinded assessor Y/N)
Schaser, 2006	Blunt trauma to EDL muscle (c)	Saline at 8C; 20 minutes (surface temperature reductions to 10 C) (n=7)	Direct to surgically exposed muscle (muscle surface temperature cooled to 10C)	Immediate	No treatment (n=7)	Y	Y	Y	IIntravital microscopy IHA (Y)
Schaser, 2007	Blunt trauma left tibial muscle compartment (c)	Saline at 8C; 6 hrs (n=7)	Shaven intact skin (muscle surface temperature cooled to 10C)	Immediate	No treatment (n=7)	Yes (Likely)	Y(6 hrs)	Y	Intravital microscopy IHA (Y)

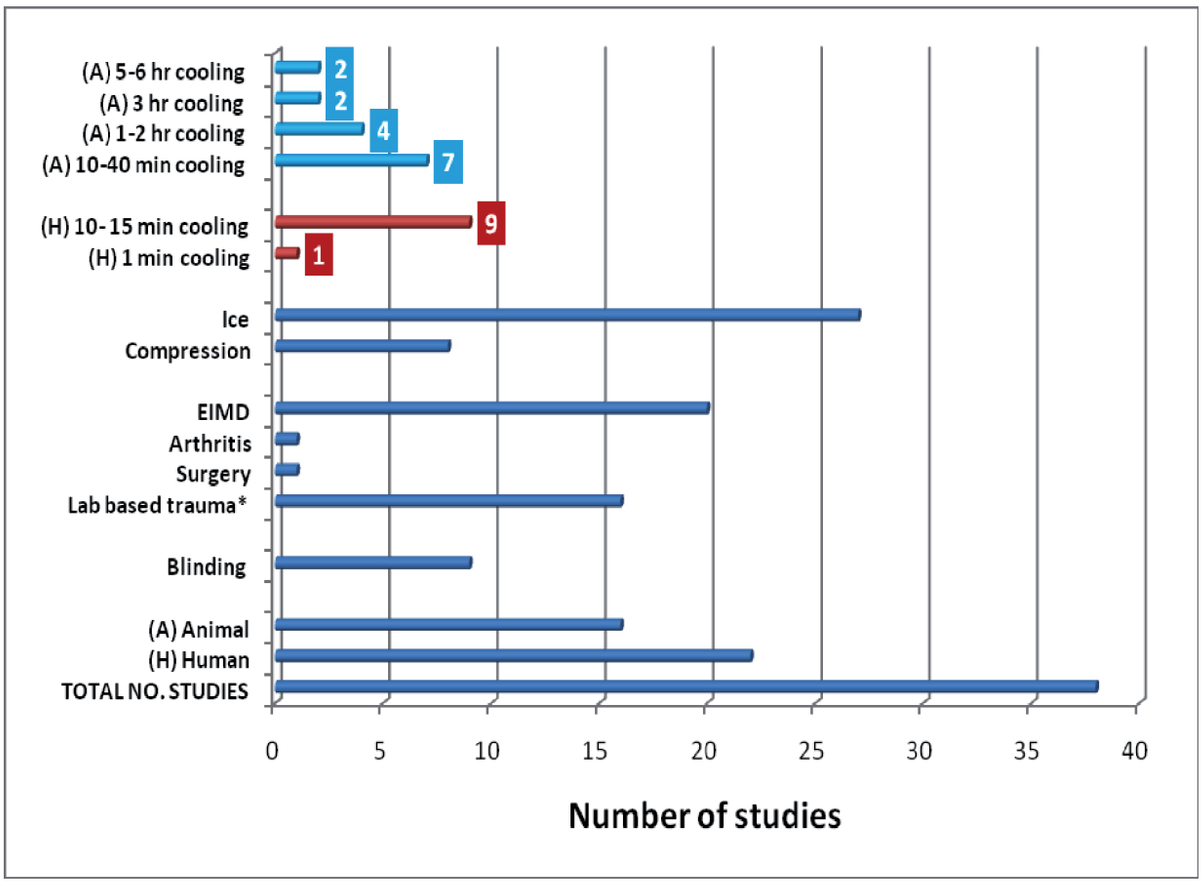
COMPRESSION

Study	Injury site (severity):	Details of intervention	Time after injury of treatment initiation	Control group	Anaesthetized during trauma (Y/N)	Anaesthetized during compression (Y/N)	Anaesthetized during outcome assessment (Y/N)	Outcomes (Blinded assessor Y/N)
Butterfield, 2008	EIMD, tibialis anterior: 7 sets of 10 cyclic lengthening contractions, 2 mins rest between sets	30 minutes of cyclical compression (0.5Hz), one treatment per day for 4 days (n=6);	30 min	Contralateral limb EIMD, no intervention	Y	Y	Y	IHA (Y)

a: injury severity enough to cause extravastation of RBC's, but not haemorrhage sufficient to obscure the vascular bed / bleeding suppressed to minimum / tissue trauma without rupturing major vessels
b: Rats with haematoma, local inflammation, ischaemia, necrosis, inconsistent microvascular flow, or an increased number of leukocytes were excluded.
c: Described as severe, but without incapacitating compartment syndrome
NS: Not stated
HVES: High voltage electrical stimulation
EDL: extensor digitorum longus
CWI: cold water immersion
WI: water immersion
Yes (Likely): although not stated specifically, it was likely based on the experimental set up that eg. Animals were anaesthetized during cooling.
IHA: Immunohistological analysis
MC: Microvascular chamber

Figure 7

Overview of studies assessing the effect of PRICE on inflammation by: model, injury type and cooling dose



Chapter 4

What effect does mechanical loading have on inflammation and soft tissue healing after acute injury?

What is known in this area: Acute soft tissue injury should be managed initially with protection/rest, followed by progressive mobilisation and stress induction on the healing tissue. The basic science mechanisms underpinning this approach have not been fully elucidated, and there are few definitive guidelines on optimal timing or dosage of loading during recovery.

Aim: To update the pathophysiological rationale for using PRICE in the management of soft tissue injury.

Clinical question: What effect does mechanical loading have on inflammation and soft tissue healing after acute injury?

Objective: To consider the basic scientific rationale for using protection, rest and progressive loading and consider whether the nature, timing and dosage of tissue loading effects molecular, histological and mechanical outcome after acute soft tissue injury.

What this review adds: There is further evidence from animal models that short periods of protection/rest are required after soft tissue injury, and that aggressive ambulation or exercise should be avoided in the acute stages. Longer periods of protection/rest are deleterious with adverse changes to tissue biomechanics and morphology within 2-3 weeks of stress shielding. Paradoxically, progressive mechanical loading is more likely to restore the strength and morphological characteristics of collagenous tissue after injury. The exact mechanism has yet to be fully elucidated but there are consistent findings that mechanical loading upregulates gene expression for key proteins associated with soft tissue healing.

Limitations and future study recommendations:
The clinical significance of many of these results is limited. Clearly, animal models are fundamentally different to humans in terms of metabolism, anatomy and movement pattern. We must also consider that the protection/rest protocols may not have been fully adhered. For example in an animal model, cast immobilisation was associated with weight-bearing, and even hind limb suspension would not fully inhibit muscle activity and joint motion.[10] Further limitations arise when we consider that the majority of injuries studied are based on surgical resection, whereas soft tissue tears in humans are usually associated with frayed ends across the wound site. Almost all of the studies have used a tendon model, and we can also not assume that other soft tissue will respond in the same way. This review has provided further rationale that mechanical load should be induced on healing tissue; and that there is an optimal window for its initiation. Further research is required on optimal intensities and durations for mechanical loading in human subjects. The idea of tissue memory in tendon injuries is an interesting concept,16 and is supported somewhat by evidence that mechanical loading can up-regulate or down-regulate gene expression for key proteins during healing. This concept requires further human research, particularly with ligament and muscle injury models.

Background

The protection and rest components of PRICE are commonly recommended after an acute soft tissue injury. The rationale is to prevent further bleeding, excessive distension or re-rupture at the injury site.[1] Protection and rest of an injured ligament, usually involves casting or bracing of the entire joint plus or minus weight-bearing; whereas for muscle strains or contusions, adhesive bandaging or crutch walking may be more practical.[2]

Deciding how long protection and rest should be enforced is controversial. Excessive immobilisation seems to result in poor mechanical and functional outcome.[1] Recent reviews1-5 suggest that 2-5 days of immobilisation is optimal, with similar consensus reached in the original ACPSM guidelines on PRICE. There is further evidence1-4 that immobilisation should be followed by progressive mobilisation and stress induction on the healing tissue. This is often defined as functional treatment, and in clinical terms, involves early mobilisation and weight-bearing. Anecdotal evidence suggests that most clinicians make the transition from protection/rest to weight-bearing carefully and within the limits of pain. However, evidence based guidance on the optimal timing, dosage and nature of initiating loading after injury is limited, and it is not clear if this should vary according to the type of soft tissue affected (eg. muscle, tendon, ligament).

Gaining a balance between protection/rest, and reloading after injury is important for optimal restoration of the biomechanical and functional properties of soft tissue. The complexity of tissues' response to the presence or absence of mechanical stimuli is complex however, particularly at a physiological, cellular and molecular level.

Objective

The objective of this chapter was to consider the basic scientific rationale for using protection, rest and progressive loading, and consider whether the nature, timing and dosage of tissue loading effects molecular, histological and mechanical outcome after acute soft tissue injury.

Methods

Literature search

We searched the titles generated from the main search strategy outlined in Appendix tables 1-4. Relevant studies were extracted, with exclusions made based on titles, abstracts or full text versions.

Inclusion criteria

No restrictions were made on study design. We included any animal or human participants with an acute muscle, ligament or tendon injury. Injury could have been either induced (eg. surgically) or naturally incurred. Injury models using surgical repair were not considered. Interventions were any form of intervention aiming to protect /rest, or modify activity, initiated in the acute phases post injury (<72 hours). Studies involving protection/rest for longer than 8 weeks post injury were not considered. Comparison could have been to different types of protection/rest, normal ambulatory activity or additional exercise. Exercise could have been either weight-bearing or non weight-bearing. Outcomes could have involved any type of histological or mechanical measures related to soft tissue healing. We also included outcomes relating to gene expression for key proteins associated with inflammatory or proliferative response after injury.

Data extraction

We extracted details on: type of soft tissue injury, timing and dosage of intervention and comparison groups, co-interventions, outcomes and statistical significance. All included studies were assessed in terms of design, and assessor blinding based on Cochrane risk of bias tool[6]

Results

Excluded studies (with reasons) are listed in Appendix Table 5. 12 studies were eligible for inclusion. Table 1 summarises the key subject characteristics and extracted data. All studies[7-18] focused on animal subjects, three[10,11,14] used an injured ligament model, with the remainder focusing on tendons. Injuries were induced surgically aside from one model,[13] which used a chemical irritant. In all studies, the tissues subjected to injury were part of a weight-bearing joint. Protection/rest was undertaken using a range of protocols: non weight-bearing using suspension,[16] cast[8] or pin[10] immobilisation, tenotomy,[7] or botulinum toxin injection.[15,18] In all cases, the comparison groups undertook unrestricted ambulation after injury, which in some cases included additional exercise.[9,12,13]

Outcomes focused primarily on mechanical and histological tissue properties, with a number including genetic expression for protein relevant to various inflammatory or proliferative healing events. All outcomes involved euthanizing animals for analysis of excised tissue samples. Studies used a range of follow up times and sub-groups of animals were euthanized at various time points during the study. Histological analysis was based on subjective assessment, and in one case10 this was facilitated with scanning electron microscopy (SEM). Three studies[16-18] reported blinded assessment of outcome.

Mechanical properties

Protection/rest vs ambulation

Halikis et al.[8] measured the work of flexion (WOF) (ie. the tissues' resistance to passive flexion), in healing chickens foot tendons. WOF increased in all groups during the first week after injury; however this was significantly greater in tendons subjected to immediate ambulation compared to cast immobilisation. This pattern was reversed after the first week and WOF continued to increase in the protected group only. At three weeks post injury, WOF had returned to normal in the ambulation groups, and values in the immobilised group remained 63% above baseline. In a related model, Kubota et al.[7] also found that longer periods of protection/rest had a negative effect on mechanical strength after injury. Chicken tendons treated with four weeks of protection/rest (using both tenotomy and cast immobilisation) had significantly lower tensile strength, compared to those subjected to full ambulation after injury.

As a secondary objective, this study also compared various combinations of tenotomy (to prevent tension) and casting (to prevent motion), concluding that both forces must be induced to fully benefit from ambulation. Anderson et al.[16] used a rat model comparing complete unloading with tail suspension, to full time cage activity, after Achilles tendon injury. Of note, all groups undertook full time activity for the first two days post injury, prior to intervention. 12 days post injury; the loaded tendons had the best mechanical properties, with significantly higher amounts of tendon stiffness, cross sectional area, and gap distance, ultimate stress, with three times the tensile strength of the unloaded group. Eliasson et al.[18] also used a rat model with injured Achilles tendons.

All animals undertook cage activity for three weeks post injury, however in one group; tendons were unloaded by injecting the calf muscle with botulinum toxin. Although there were no significant differences between groups in the early stages post injury, from day 8 onwards, the protection/rest group had poorer mechanical properties in terms of the length, stiffness and displacement at rupture.

There was evidence from two rat ligament models,[10,11] that prolonged immobilisation after injury is less effective than ambulation in terms of mechanical outcome. Thorton et al.[11] found that immobilisation in full knee flexion was associated with significantly higher chance of scar failures at week 6 and 14 post injury; during both static and cyclical tensile loading. Ambulation was also more likely to restore other visco-elastic properties such as creep and laxity. Using a similar model and follow up (albeit with a more severe ligament injury), Provenzano et al.[10] also noted similar patterns after shorter periods of unloading. Significant decreases in maximal force, ultimate stress and elastic modulus were evident after 3 weeks of hind limb unloading tissue, compared to a loaded, ambulatory group. Similar findings were reported 7 weeks post injury.

Ambulation plus exercise

Two rat studies[9,12] compared the effects of undertaking a structured exercise program after injury, in addition to regular cage ambulation. Murrel et al.[9] found that, ten bouts of daily swimming offered no additional effect over free cage activity alone, in terms of the mechanical properties of healing tendons. See et al.[12] undertook a follow up study but also included a running intervention group. Other notable differences were that only half of the Achilles tendon was transected, and rather than exercising immediately post injury, a 5 day period of rest period was enforced in each group. Again, swimming offered no additional effect over regular cage activity; however the addition of a daily running program resulted in some mechanical superiority and ultimate tensile strength was significantly higher in this group at 1 month post injury.

Andersson and colleagues[16] also considered whether there is an optimal dose of exercise after tendon injury; comparing regular cage ambulation, tail suspension (full time), or tail suspension interspersed with short bouts of daily exercise. Full time tail suspension resulted in the worst mechanical outcome, whereas, regular cage activity was associated with significantly higher tensile strength. Notably, groups undertaking one daily bout of 15 minute treadmill exercise had tissue strength that was approximately half that of the full time cage activity group at 12 days post injury. Of further interest, increasing the running dose to, two bouts of 15 minutes, or 30-60 minutes of continuous running offered little additional change to mechanical properties.

In a novel method of injury induction, Godbout et al.[13] injected rat TA with collagenase. All animals were permitted free cage activity; however two sub-groups undertook additional exercise on a running wheel. This was initiated either immediately after injury, or after a seven day delay. Mechanical testing at one month post injury found that the immediate exercise group had significantly lower levels of stiffness and force at rupture point. Interestingly, the inclusion of delayed exercise (in addition to free cage activity) produced the best mechanical outcome at 1 month.

Histology

Protection/rest vs ambulation

Three studies found evidence of superior tendon healing in ambulated animals, based on tissue histology,[7,17] and scanning electron microscopy (SEM).[10] In general, the ambulated groups exemplified more regenerative activity and superior tissue morphology in comparison to protection/rest groups. Specifically ambulation resulted in better ECM continuity,[10] better alignment collagen bundles in relation to the longitudinal axis of the ligament,[7,10,17] and higher numbers of newly formed capillaries, and spool shaped fibroblasts.[17] Many of these observations were made at around 1 week post injury,[17] with differences between groups becoming more evident at 3-4 weeks.[10,17]

Delayed vs immediate exercise

Godbout et al[13] used immunohistochemistry to assess inflammatory and proliferative cell accumulation at various time points after injury. Immediate exercise seemed to exacerbate the inflammatory response, exemplified by significantly higher levels of neutrophils, ED^{1+} and ED^{2+} macrophages, at day 3 and 7 post injury. There were no differences in proliferative cell accumulation at day 7 between groups.

Gene expression

Protection/rest vs ambulation

Three studies[10,17,18] measured the effect that protection/rest or ambulation had on mRNA expression after injury. In general, they focused on the expression levels of key proteins associated with inflammation, growth, tendon specificity and extracellular matrix (ECM) deposition. In the acute stages, ambulation was associated with a lower expression of TNF alpha, transforming growth factor-beta 1, and procollagens I and III, and a significantly lower expression for IL1 beta.[18]

By day 21, procollagen I, cartilage oligomeric matrix protein (COMP), tenascin-c, tenomodulin and scleraxis were more expressed in this group, two reaching significance (COMP and tenomodulin). Bring and colleagues[17] found similar patterns from at day 17 post injury, with ambulated groups displaying significant upregulation for collagen I and III,

versican, decorin and biglycan expression; many of these values were approximately 14 times higher than the protection/rest group. Ambulation was also associated with higher levels of expression for neuropeptide receptors [Substance P (NK1) - and calcitonin gene-related peptide (CRLR and RAMP-1)] between day 8 and 17 post injury.

Using an injured ligament model, Martinez et al.[14] compared unloading with tail suspension, to normal ambulation. After 3 weeks, there were trends towards increased gene expression for collagen Type I and III in the loaded group, and at 7 weeks, collagen type I and V were significantly down regulated in unloaded tissue, and collagen type III was significantly upgraded in loaded group. There were further significant differences between groups in the expression of other key ECM constituents; in the unloaded tissue, decorin, tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) and lysyl oxidase were all significantly down regulated at 3 weeks, with lower expression of matrix metalloproteinase 2 (MMP-2), and higher expression of TIMP-1 at 7 weeks. Unloaded ligaments also had increased cellularity measured via DNA content at weeks 3 and 7.[14]

An explorative study by Eliasson et al.[18] recorded gene expression of bone morphogenetic protein (BMP) signalling system. 8 genes were studied, however, the only significant finding, was a lower expression of the antagonist follistatin within the ambulated group. This was observed at multiple time points up to three weeks post injury.

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Table 1

Study Study type (assessor blinding Y/N)	Subject (injury)	Intervention	Time of euthanasia (follow)¶	Summary of results
Kubota, 1996 (N)	N=53 chickens (transverse partial laceration across 50% of FPT)	- PR (No motion or tension) - AMB (Motion and tension) - AMB (Motion only) - AMB(Tension only) Note: all groups were permitted unrestricted cage activity. 'No tension' was achieved by proximal tenotomy, and 'no motion was achieved by cast immobilisation.	Day: 14,30	Mechanical -Breaking strength: no differences (day 14); AMB (all types) > PR (day 30*); AMB (motion and tension)>AMB (motion only or tension only) (day 30*). Histology -Collagen fibre formation: AMB (all types) > PR (day 14 and 30)
Halikis, 1997 (N)	N=84 Chickens (surgical trauma to tendon)	-PR (cast immobilisation) -Immediate AMB (light dressing) -AMB after 3 days (cast for 3 days post injury) -AMB after 5 days (cast for 5 days post injury)	Day: 3, 7, 14, 21	Mechanical -WOF (Energy required to passively flex digit at 2.4cm/min): PR<Immediate AMB (day 3, 7); Immediate AMB < AMB after 3 days < AMB after 5 days < PR (day 14, 21) Note: At 21 days WOF had returned to normal (baseline un-injured values) in all AMB groups, whereas the PR group were 63% greater than baseline levels.
Murrell, 1998 (N)	N=20 Rats (surgical transection of TA)	-AMB (free cage activity) -SWIMMING EX (free cage activity PLUS swimming exercise = 15 minutes / day for 15 days)	Day: 15	Mechanical No differences: displacement, stiffness, energy, modulus, maximum stress (day 15)
Provenzano, 2003 (N)	N=60 Rats (MCL surgically ruptured)	-PR (hind limb unloading) -AMB (free cage activity)	Week: 3, 7	Mechanical -Elastic modulus: AMB > PR (week 3* and 7*) -Maximum force: AMB > PR (week 3* and 7) -Ultimate stress: AMB > PR (week 3* and 7*) -Strain at failure: no difference Histology (SEM) -AM group had more typical scar morphology at 3 and 7 weeks. -PR group had pockets of cell clusters with tissue voids at 3 weeks. At week 7 there was poor orientation of collagen bundles in relation to the longitudinal axis of the ligament.

Study Study type (assessor blinding Y/N)	Subject (injury)	Intervention	Time of euthanasia (follow)¶	Summary of results
Thornton, 2003 (N)	N=53 Rabbits (MCL surgically gapped at mid substance; bilateral or unilateral)	-PR (pin immobilised in full flexion) -AMB (free cage activity)	Week: 3, 6, 14	Mechanical -Number of failures during cyclic low load loading: AMB < PR (3, 6 and 14* weeks) -Laxity: AMB > PR (week 3, 6 and 14*)
See 2004 (N) -only assessment of the lower limb functional outcome was blinded)	N=30 rats (surgical transection of right medial portion ofTA)	-AMB (free cage activity) -SWIMMING EX (free cage activity PLUS running) -RUNNING EX (free cage activity PLUS swimming) Note: Running/swimming EX undertaken for 15-19 minutes per day, from day 5-30 post injury.	Day: 30	Mechanical -Tensile strength: EX running > AMB (day 30) -Load relaxation, stiffness,: EX running = EX swimming = AMB (day 30)
Godbout, 2006 (N)	N=180 Rats (collagenase injection into TA)	-AMB (free cage activity) -IMMED EX (free cage activity PLUS immediate exercise on running wheel at approximately 1 km per day over the first week) - DELAY EX (free cage activity PLUS delayed exercise initiated at 7 days post injury	Day: 3, 7, 28	Immunohistochemistry -Neutrophil concentration: IMMED EX > AMB (day 3, 7) -ED1+ macrophage concentration: IMMED EX > AMB (day 3*, 7*) -ED2+ macrophage concentration: IMMED EX >AMB (day 3*) -Proliferative cells: no difference (day 7) Mechanical -Stiffness; force at rupture point: no difference (day 7); DELAY EX > AMB > IMMED EX (day 28*)
Martinez, 2007 (N)	N=60 rats (bilateral MCL resection)	-PR (hind limb unloading) -AMB (unrestricted cage activity)	Week: 3, 7	mRNA expression: -Collagen I and III: AM>PR (3 weeks) -Decorin, TIMP1, lysyl oxidase: AM>PR (3 weeks*) -Collagen I, III, V : AM>PR (week 7*) -MMP2: AM>PR (week 7*) -TIMP1: AM<PR (week 7*) Tissue cellularity (based on DNA content) -AM<PR (week 3* and 7*)

Study Study type (assessor blinding Y/N)	Subject (injury)	Intervention	Time of euthanasia (follow)¶	Summary of results
Elliasson, 2008 (N)	N=40 rats (3mm transverse segment from TA)	-PR (free cage activity however calf muscle on injured TA injected with botulinum toxin) -AMB (free cage activity)	Day: 3, 8, 14, 21	-mRNA expression for BMP proteins Follistatin: AMB<PR (day 3*, 8*, 14*, 21*) OP-1, GDF-5, GDF-6, GDF-7, BMPR-1b, BMPR-2: No differences Noggin was not detected
Andersson, 2009 (Y)	N=70 rats (3 mm full thickness segment surgically removed from TA)	-PR (Full time unloading using tail suspension) -AMB (free cage activity) -EX (tail suspension BUT with intermittent: a) 15 min cage ambulation b) 15 min treadmill c) 30 min treadmill d) 60 min treadmill e) 15 min x 2 treadmill Note: all groups undertook free cage activity for the first 2 days post injury	Day: 12	Mechanical -Ultimate stress: AMB=EX; AMB>PR (day 12*) -Peak force: AMB>EX>PR (day 12*) -Stiffness: AMB>EX >PR (day 12*) -Cross sectional area: AMB > EX=PR (day 12*) -Gap distance (between tendon stumps): AMB > EX=PR (day 12*) -Ultimate stress, Elastic modulus: No difference (day 12)
Bring, 2009 (Y)	N=64 Rats (TA rupture with a blunt instrument)	-PR (plaster cast with free cage activity) -AMB (free cage activity)	Day: 8, 14, 17, 28	mRNA expression -Collagen I and III, versican, decorin and biglycan: AMB=PR (day 8); AMB > control gene; (day 17*); PR=control gene (day 17) -Sensory neuropeptide receptors [SP-(NK1), CRLR, RAMP-1]: AMB = PR (day 8); AMB>PR (day 17*) Histology Generally higher regenerating activity in AMB. Better structural organisation in AMB, particularly at day 28 -Amount of newly formed capillaries, longitudinally organised collagen: AMB > PR (day 14) - Amount of longitudinally organised collagen, fibroblasts number, and number of spool shaped fibroblasts: AMB<PR (day 28) -Amount of mature collagen: PR>AMB (day 28) (notes this was more disorganised)

Study Study type (assessor blinding Y/N)	Subject (injury)	Intervention	Time of euthanasia (follow)¶	Summary of results
Eliasson, 2009 (Y)	N=110 rats (Surgically transacted TA)	- PR (free cage activity however calf muscle on injured TA injected with botulinum toxin) -AMB (free cage activity)	Day: 3, 8, 14, 21	Mechanical -Length, stiffness, displacement at rupture and energy: AMB > PR (day 3, 8*,14* and 21*) -Peak stress: AMB >PR (day 3, 8, 14, 21) mRNA expression: -TNF-alpha, TGF-beta 1, procollagens I and III: AMB < PR (day 3) -IL 1 beta: AMB < PR (day 3*) - Procollagens I and III; LOX, scleraxis: AMB < PR (day 8); - Procollagen I: AMB > PR (day 14*, 21) - Tenomodulin, COMP: AMB > PR (day 14*, 21*) - Tenascin-C, scleraxis: AMB>PR (day 21)

¶: Intervention continued up to these time points
Botox: botulinen toxin injection to calf
ED1+ and ED2+: represent subpopulation of macrophage
BMP: Bone morphogenetic proteins (BMP), two receptors, and two antagonists
FPT: Flexor Profundus Tendon
TA: Achilles Tendon
MCL: Medial collateral ligament of knee
NOTE: in all cases animals were euthanized prior to testing
TIMP1: tissue inhibitor of matrix metalloproteinase 1
MMP-2: matrix metalloproteinase 2
SEM: Scanning electron microscope
WOF: work of flexion
LOX: lysyl oxidase
COMP: cartilage oligomeric matrix protein
In the outcome column, the greater than (>) and less than (<) symbols refer to the absolute differences between groups. NOTE that the effect is always in favour of the intervention listed first. Ie. A>B for outcomes in which higher values are deemed to be more positive, and: A< B; for outcomes where lower values are more positive. * indicates a significant difference between groups at that time point, except in highlighted cases where gene expression is compared to control or housekeeping gene.

Chapter 5
Do the physiological effects of local tissue cooling affect function, sporting performance and injury risk?

What is known in this area: Lowering local soft tissue temperature may affect a number of physiological systems. This may influence: muscle strength, flexibility, range of movement, nerve conduction, and sensori-motor function. There is little evidenced based consensus on the magnitude or clinical relevance of this, particularly in clinical scenarios when ice is applied prior to therapeutic exercise or athletic competition.

Aim: To update the pathophysiological rationale for using PRICE in the management of soft tissue injury.

Clinical question: Do the physiological effects of local tissue cooling affect function, sporting performance and injury risk?

Objective: To review recent literature and summarise the physiological effects of local tissue cooling and determine its clinical relevance. We were particularly interested in environments when ice may be applied immediately prior to therapeutic exercise or athletic competition.

What this review adds: There is evidence to suggest that in healthy human models, cooling can have a depressive effect on a number of physiological systems including: decreased NCV, isometric strength, and rate of force production. Other aspects of physical performance were influenced to varying degrees: proprioception and functional performance were either unaffected or slightly adversely affected after icing, and there is conflicting evidence on the effect of cooling on the visco-elastic properties of soft tissue in terms of stiffness and range of movement. The clinical relevance of many of the observed physiological changes is questionable. Short periods of ice application seem to have minimal impact on basic functional activity such as light exercise, walking or therapeutic rehabilitation. Longer periods of intense cooling negatively influence higher level functional activities (eg. athletic performance), and potentially increase injury risk. The relevance of these changes and the magnitude of risk depend on the level of sporting activity, the time period between completing ice application and returning to activity, and the type of soft tissue cooled. Few relevant studies have been undertaken on injured subjects; applying ice to an acutely injured ankle has a further negative effect on postural control. Of particular interest were trends that isolated joint cooling or short periods of muscle cooling, can have an excitatory effect on muscle activation. This was observed in both healthy and injured (inhibited) models, and seems to align well with the concept of cryokinetics.

Limitations and future study recommendations:
Relevant studies used a wide range of icing protocols, and therefore variable levels of tissue cooling. Some of the outcomes or measuring techniques were of questionable validity and relevance, and none of the studies used blinded outcome assessment. The majority of studies used a randomised cross over design; and in some cases the wash out time between interventions was either minimal or unclear. Few studies have been undertaken on injured subjects. Future research is needed to determine the potential for using cooling as an adjunct to therapeutic exercise (cryokinetics); this should be based on acutely injured muscle or joint models.

Background

The basic premise for applying ice is to induce physiological effects which enhance recovery after injury. The most important of these, are usually considered to be cold induced analgesia, and reduced cellular metabolism. However, local cooling also has potential to produce concomitant effects on many other physiological systems. This may involve changes to: muscle strength, flexibility, range of movement, nerve conduction, and sensori-motor control. Although some of these changes may be subtle, there is little evidenced based consensus on their magnitude or clinical relevance. The proposed benefits of cryotherapy must be balanced with any potential adverse effects, before making recommendations for its use. Ice is often used to treat acute injuries in sport. In situations involving minor trauma, athletes will usually return to a competitive environment, shortly or immediately after the application of cold. Similarly, there is a growing trend of using ice prior to undertaking therapeutic exercise (cryokinetics).

Objective

The objective of this chapter was to update the evidence base for the physiological effects of local cooling, and consider their clinical relevance, in terms of function, sporting performance and injury risk.

Methods

We searched the titles generated from the main search strategy outlined in Appendix Table 1-4. Relevant studies were extracted, with exclusions made based on titles, abstracts or full text versions.

Inclusion criteria

No restrictions were made on study design or participants (injured or healthy). Interventions were any cooling intervention, with no limitations on mode or dosage of application. There were no restrictions made on study comparison; for observational studies, pre and post treatment values were compared. Outcomes could involve any physiological outcome relating to function. Primary outcomes were key correlates of sporting performance such as: muscle strength (and subcomponents of strength); range of movement; sensori-motor control (proprioception, postural/neuromuscular control); and functional performance eg. vertical jump, sprint speed, accuracy and precision of movement. Secondary outcomes of interest were nerve conduction, tissue stiffness, muscle activation patterns, ground reaction force and submaximal strength. Studies measuring strength or force production during evoked muscle contractions were not considered.

Data extraction

Data were extracted for: study type, participant demographics, cooling mode and dosage, and key outcomes (pre vs post; or ice vs other intervention/control). We considered outcomes measured at all time points. As one of our primary objectives was to determine the safety of icing prior physical activity, we were particularly interested in the maximum potential change in outcome.

Risk of bias

All included studies were assessed in terms of design, and methodological quality based on Cochrane risk of bias tool[1] (sequence generation, allocation concealment, assessor blinding, incomplete outcome data).

Results

Excluded studies (with reasons) are listed in Appendix Table 5. Characteristics of included studies[2-42] are summarised in Figure 1. Each included study assessed at least one relevant physiological or clinically based outcome, before (baseline) and after (post test) cryotherapy. In most cases, a control (rest) or comparison (heating) condition was also used, with the majority using a cross over design. The time between conditions varied, from a few hours,[11 13 15] up to two days,[7,10,21,26,36] with the longest being [15,16,20] to 2 weeks.[17] Seven used a randomised controlled methodology to compare across conditions,[4,8,19,35,38-41] of which two4,19 used allocation concealment. No study undertook blinded assessment of outcome. All but three studies[38-41] used healthy participants; the injured models used were acute sprain[40] or induced joint distension at the knee.[38,39,41]

The majority of studies applied cooling for between 20 and 30 minutes. Three used shorter periods of just 3 minutes,[15,16,32] and the longest duration of cooling was 1 hour.[34] In most studies, outcome re-testing was undertaken immediately after cryotherapy removal only; five used multiple follow ups, retesting outcomes up to 15,[7] 20,[40] 30,[21] 60[39] and 90[41] minutes post intervention. Figure 2 provides a summary of the cooling protocols used prior to recording primary outcomes.

Primary outcomes
Maximal strength

Four trials studied the effect of 10-30 minute cryotherapy treatments on isokinetic ankle strength, using comparison with untreated control. In a randomised cross over study,[2] 30 minute CWI at 10°C, did not affect PF peak torque; however it caused a significant increase in muscular endurance, compared to control. An RCT by Hopkins and colleagues[4] which used allocation concealment also found that cold tended to enhance ankle muscle performance. Of note, cooling was with a single ice pack for 30 minutes and restricted to the lateral ankle joint; this intervention significantly increased PF peak torque, compared to control. In contrast, both Borgmeyer et al.[5] and Hatzel et al.[3] using ice massage and CWI respectively, found little effect on ankle muscle strength. Hatzel et al.[3] did not use any randomisation, and there was just 1 day rest, between cooling and control conditions. They recorded a wide spectrum of strength outcomes (concentric and eccentric strength, in ankle plantar flexion, dorsiflexion, eversion and inversion but the only significant difference

difference between interventions was that CWI caused a significant reduction in concentric DF. In a randomised cross over study, Borgmeyer et al.[5] found trends that muscle cooling increased concentric (30 deg/sec) arm strength this change was not significant.

Four studies considered the effects of icing on isometric strength[6-9] however, contrasting results were reported. Two used observational designs[6,7] comparing strength before and after icing. Zhou et al.[6] found reductions in knee extension force when muscle temperatures were cooled below 34°C; and force production was decreased further (25% lower than baseline) when muscle temperatures reached 30°C. Douris et al.[7] demonstrated a significant reduction in grip strength (by 24%) immediately after a 5 minute forearm immersion. This effect diminished with time, and a 5.9 % reduction remained, 15 minutes after immersion. Two randomised studies compared the effects of cooling and heating, prior to isometric testing at the biceps,[8] and triceps surae[9] muscles. Although Nosaka et al.[8] noted a 10°C difference in tissue temperature (at 15-20mm below skin surface) between groups, this did not affect maximal isometric elbow flexion. In contrast, Kubo and colleagues[9] who seemed to use more intense cooling intervention for the entire lower leg (CWI at 5°C), reported cold induced decreases in isometric PF strength.

Range of movement

In two studies, cooling was applied immediately before[35] or during[37] lower limb stretching. 20 minutes of simultaneous cooling (ice pack on hamstrings) and stretching, resulted in significantly larger increases in active SLR compared to heating and stretching, or stretching alone.[37] Burke et al.[35] showed an opposite, but non-significant effect, and cooling was associated with smaller increases hamstring flexibility, in comparison to heating or stretching alone.
Two small studies[9,34] focused on how local temperature influences tissues' passive resistance to movement. Both used a force transducer to determine the resistance of the triceps surae muscle and tendon unit, during either passive knee flexion[34] or ankle PF.9 One of the studies[34] used EMG to ensure that active muscle contraction did not confound the outcomes. In both cases, the passive resistance increased after cooling, whereas heating or control interventions had little effect. In contrast, a cross over study[36] found that temperature did not affect knee joint laxity, based on anterior tibial displacement during arthrometer testing (KT 1000).

Proprioception

Clinical assessment of proprioception involved measurement of: joint positional sense (JPS), or force perception. The effects of cooling on JPS were mixed. Three observational studies noted no effect on single plane JPS at the knee[22] or multi-plane JPS at the shoulder joint.[26,27] In contrast, two studies found that 15 minutes of cooling significantly decreased active JPS at the ankle[23] and knee[25] using randomised cross over and observational designs respectively. One observational24 reported that cooling did not significantly affect participants' ability to discriminate between different levels of weight resistance during open chain knee extension.

Functional performance

A number of studies considered the effect of cooling immediately prior to undertaking various types of functional, or sports specific tasks. One study[42] focused on low level function; 30 minutes of ice pack application on the ankle joint, did not affect lower extremity kinetics and kinematics in the closed chain during a semi-recumbant stepping exercise. Many others have considered the effects of joint cooling prior to higher level functional activity, however the results are variable. Miniello et al.[31] concluded that CWI of the entire lower leg did not impair ankle stabilization following landing from a jump; similarly, others found that ice and compression over the ankle, knee or both, did not alter the vertical ground reaction forces associated with landing from a double[30] or single leg[14] jump. Others have found conflicting evidence based on measures of lower limb power and speed.[28,29,32,33] 3 minute ice treatments[32] had little effect on lower limb functional performance; however increasing the application duration to 10 minutes, decreased performance on vertical jump and shuttle sprint. Using similar methods, but with a longer application time of 20 minutes, others,[28,29,33] also noted cold induced decreases in athletic performance based on vertical jump height;[28,29,33] shuttle sprint times[28,33] and ground reaction forces during landing.[29] There was further evidence from an observational study that 20 minutes of shoulder joint cooling, significantly decreased throwing accuracy.[27]

Secondary outcomes

Sub-maximal strength

Two small cross over studies measured how cooling affected the accuracy and variation of sub-maximal force production [at a predetermined % of subjects' maximum voluntary contraction (MVC)] at the wrist or hand. In each case, force production was measured using a force gauge or hand held dynamometer, with visual feedback.[10,11] In each case, 10-15 minute CWI's were compared to either heat11 or no treatment.[10] Rubley et al.[10] found no differences between groups in the accuracy and variation when reproducing 10%, 25% and 40% of thumb-index pincer MVC. Similarly, Geurts et al.[11] reported that force control at 25% and 50% of first dorsal interossei MVC was unaffected by local temperature. Again limitations across both these studies include a lack of randomisation, and little, to no wash out time between treatment interventions.

Muscle recruitment

The effect of cooling on local muscle recruitment has been studied using various outcome measures. Three studies[4,12,17] focused on the effect of ankle joint cooling on soleus muscle recruitment based on H reflex recordings. There were trends from each study that cooling resulted in increased muscle excitability (based on H-reflex facilitation) in one case a 30 minute treatment resulted in a 15% increase in Hmax/Mmax ratio.[4] Similar findings were noted with knee joint cooling, based on quadriceps central activation ratio (CAR) in healthy subjects; a 20 minute ice pack treatment significantly increased CAR for up to 25 minutes after treatment, compared to control.[18]

A follow up study by Krause et al.[13] used surface EMG to determine the amplitude and frequency of wrist extensor muscle activity at 30%, 50% and 85%, of MVC, at different tissue temperatures. Skin temperature varied between 27°C and 37°C; however this did not affect EMG amplitude. In contrast, EMG frequency decreased with tissue cooling at all levels of force production. Based on normalised EMG readings, CWI significantly decreased peroneus longus activity during a single leg jump landing;[31] this returned to baseline after a 5 minute re-warming period. Others[14] found little change in EMG muscle activity in a number of muscles of the lower limb after 30 minutes of cooling on the knee joint.

Kinugasa's group undertook two similar studies[15,16] but they cooled muscle directly, and measured muscle firing patterns using novel outcome. MRI images of the quadriceps muscles were taken before and after an exercise task. Using a cross over design, exercise was undertaken either with or without short periods of pre-cooling of the vastus lateralis (VL)[15] or vastus medialis (VM).[16] Analysis of T2 weighted MRI scans with imaging software showed that exercise resulted in increased signal in all quadriceps muscle compartments, under control (no pre-cooling) conditions. Similar exercise induced increases were found in the VL, VM and rectus femoris (RF) compartments when pre-cooling was used, but the change in T2 uptake between pre and post exercise images was significantly higher in the vastus intermedialis (VI) compartment. The authors concluded that this related to a cold induced activation of VI, resulting in increased metabolic activity. Of note, the time between conditions ranged from 1 week,[16] to just a few hours.[15]

Nerve conduction velocity (NCV)

Cooling skin temperatures to 10°C, decreased NCV by 33% (to 22m/s), whereas there were no changes within an untreated control group.[19] Two smaller studies[6,9] also found cooling has a similar effect on muscle fibre conduction velocity; cooling increased the time between the onset of quadriceps muscle activity (based on EMG) and force production (extension at the knee joint). The largest detriments were noted at muscle temperatures below 32°C,[6] interestingly one of the studies found similar patterns with heating.[9]

Reflex pathways

In a different approach, two RCT's[20,21] cooled the lateral ankle region, before monitoring the reflex response to sudden ankle perturbation. Interestingly, both found that the magnitude and speed of peroneal muscles' response to sudden joint movement was not affected by ankle joint cooling.

Injured models

Only three studies used an injured model. Kernozek et al.[40] measured postural sway on a force platform, before and after a 20 minute CWI, using a small sample of participants post acute ankle sprain. Cooling significantly increased sway and values remained higher than baseline for up to 20 minutes after treatment cessation. Three others[38,39,41] used models of acute injury based on laboratory induced knee joint effusion. Hopkins et al.[41] measured H Reflex using percutaneous simulation of the femoral nerve, and surface EMG of the VM. H reflex measurements were decreased immediately after joint distension; 20 minutes of knee joint cooling significantly increased H reflex compared to control. Similarly, Rice et al.[38] showed that knee joint distension decreased quadriceps EMG amplitude, muscle fibre conduction velocity (MFCV), and peak torque. Ice application to the knee joint subsequently increased MFCV and peak torque in comparison to untreated controls, and there were further trends that cooling restored EMG amplitude (based on the root mean squares) closer to normal values (90% of baseline), in comparison to controls, which remained at 75% of baseline. A larger study by Hopkins et al.[39] also compared ice to untreated control, but they measured quadriceps peak power, in addition to EMG muscle activity and peak force. Again, peak torque, power and VL activity declined more in untreated knees compared to the cryotherapy group. There were no differences between groups based on integrated EMG outcomes.

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Figure 1

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
MUSCLE STRENGTH (CONCENTRIC / ECCENTRIC)			
Kimura, 1997 (Randomised cross over – 7 to 14 days between conditions)	N=22 healthy 11 male, 11 female Mean age 23.8 (+/- 3.5 yrs)	-Ice 30 min (CWI to mid thigh at 10°C) -Control	Peak torque ankle PF eccentric (5 maximal repetitions at 30 deg/sec and 120 deg/sec) I = C Muscular endurance (total work during 100 maximal reps at 120 deg/sec) I>C* Note: I = 380 Nm INCREASE (muscular endurance over 100 maximal reps)
Hatzel, 2000	N=20 healthy Mean age: 19.6 (+/- 1.3 yrs)	-Ice 20 min (CWI to tibial plateau at 10°C)	Ankle Peak torque -Concentric/Eccentric - PF,INV,EV at 60 deg/sec and 120 deg/sec: no change -Concentric DF (at 60 and 120 deg / sec): decrease post I* Note: I = 6 Nm DECREASE (concentric DF at 60 deg/sec); and 5Nm DECREASE (concentric DF at 120 deg/sec)
Hopkins, 2002a (RCT; allocation concealment)	N=30 healthy 16 male, 14 female Mean age: 21 (+/- 3yrs)	-Ice 30 min (1.5L of crushed ice to lateral ankle, final skin temperature approx. 16°C) -Control	Peak torque ankle PF I>C (30, 60, 90 minutes) Note: I increased peak torque by approximately 2% immediately after Rx, just under 5% 30 minutes post ice, and 2% 90 minutes post ice
Borgmeyer, 2004 (Randomised cross over – 1 week between conditions)	N=11 healthy males Mean age: 20.9 (+/- 1.1 yrs)	-Ice 10 min (ice massage to biceps) -Control	Peak torque elbow flexion concentric (30 deg/sec; 1 rep every 2 minutes for 20 minutes) I= C Note: trend towards increased torque in ice condition

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
MUSCLE STRENGTH (ISOMETRIC)			
Zhou, 1998) (Observational)	N=7 healthy 4 male, 3 female Mean age: 20.3 (+/-1.4 yrs)	-Ice bag applied until thigh IM temperature reached 30°C	Electromechanical delay (time lag between onset of EMG and muscle tension development) Decrease post ice* Peak contraction force Decrease post ice* MFCV Decrease post ice* Note: Decreasing muscle temperature from resting levels (37°C) to 30°C causes: a 125N decrease in peak contraction force, a 0.5 m/s-1decrease in MFCV
Douris, 2003 (Cross Over – 4 days between conditions)	N=16 healthy Mean age: 32 (+/-6.3 yrs), range: 20-42 yrs	-Ice for 5, 10, 15 or 20 minutes (CWI elbow, forearm and hand at 10°C)	Maximal isometric hand grip strength (hand dynamometer, 180 deg of shoulder flexion, dominant arm, 3 second holds, verbal encouragement) I = decrease* at all durations Note: Grip strength was decreased by 24.2% immediately after CWI, and remained 5.5% lower 15 minutes after CWI cessation
Nosaka, 2004 (RCT)	N=20 healthy females Mean age: 19.6 (+/-2.8y)	-Heat 15 min (microwave) -Ice 15 min (biceps; ice cold water bag 10 cm x 15cm at 0°C; towel between ice bag and skin; biceps)	Isometric force at elbow flexors I=H
Kubo, 2005 (Randomised Cross Over – states conditions were on separate days)	N=8 healthy males Mean age 26 (+/-2yrs)	-Ice 30 min (CWI in 5°C, to head of fibula) -Heat 30 min (HWI in 42°C to head of fibula)	MVC PF Post I < Pre I* Note: Ice decreased MVC by approx. 9Nm
SUB-MAXIMAL STRENGTH			
Rubley 2003 (Cross over – 1 day between conditions)	N=15 healthy 8 male, 7 female Mean age 22 (+/-3 yrs)	-Ice 15 min (CWI at 10°C up to medial epicondyle) -Control	Thumb and index finger pinch at 10%, 25% and 40% of MVC (following visual feedback). Maintain for 30 secs (the first 5 secs discounted), 5 reps at each %. Sub-maximal isometric force production of 10%, 25%, 40% of MVC Accuracy (root mean square error of each rep) or variation (SD across 5 reps) of force production was not affected by cooling.

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Geurts, 2004 (Cross over – no time between conditions?)	N=10 6 male, 4 female Aged 23-41y	-Ice 10 min [CWI in 8C, mean skin temp: 17.7 (1.3C)] -Heat [Water perfusion patch and hot pack, mean skin temp: 27.9 (2.3C)]	Sub-maximal force control at 25 and 50% of MVC (1st dorsal interosseous muscle) No change in sub-maximal force control
MUSCLE ACTIVATION PATTERNS			
Krause, 2000 (Observational)	N=10 healthy Aged 23.9 (+/-2.3 yrs)	-Ice 20 min [5.6 L of crushed ice x 2 to medial and lateral ankle] (skin temperature monitored) -Ice 20 min (ice pack, skin temperature reduction to 28°C)	H reflex H Reflex (percutaneous stimulation of tibial nerve, surface EMG of soleus) Inverse correlation between H reflex and skin temperature ie. Increased motoneurone-pool recruitment during and after cooling
Krause, 2001 (Cross over – time between conditions unclear)	N=32 healthy Aged 20-30 yrs Amplitude and frequency in surface EMG from Before and after cooling / heating	-Heat 10 min (hot pack, skin temperature to 45°C) -Control	Surface EMG at hand extensors during 20 second holds at 10%, 30%, 50 and 80% of MVC (dynamometer pressure gauge) EMG Amplitude No differences at any level of muscle contractions EMG Frequency I<C at 30% or more of MVC
Hopkins, 2002a (RCT; allocation concealment)	N=30 healthy 16 male, 14 female Mean age: 21 (+/-3yrs)	-Ice 30 min (1.5L of crushed ice to lateral ankle, final skin temperature approx. 16°C) -Control	H Reflex (percutaneous stimulation of tibial nerve, surface EMG of soleus, normalised to peak M-response) -Change from baseline (H max / M Max ratio) I>C (30*, 60* and 90* min)
Hart, 2005 (Observational)	N=20 healthy 9 male, 11 female Mean age 23.8 (+/-3.6 yrs)	-Ice 20 min (crushed ice to anterior knee with elastic wrap)	Note: Approx. 15% increase in Hmax / Mmax ratio after 30 min cryotherapy treatment. Forward jump with single leg landing EMG activity gluteus medius, biceps femoris, vastus lateralis, medial gastrocnemius Pre I = Post I (immediately, 15 and 30 min post treatment)
Kinugasa, 2005b (Cross over - 1 week between conditions)	7 healthy males Mean age: 24.9 (+/-2.1 yrs)	-Ice 3 mins [ice pack over VM before initiating quads exercise, and applied between each set (60 secs), skin temperature: VM: 10.6 (2.4 C)] -Control	Quad activation patterns assessed by comparing mf MRI (T2 weighted) before and after knee extension exercise (10 reps x 5 sets at 70% of 10 rep max, 1 min rest between sets) % change in T2 value before and after exercise (using imaging software): I=C in RF,VL,VM I>C* in VI

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Kinugasa, 2005a (Randomised cross over – 2 hrs between conditions)	7 healthy males Mean age: 25 (2.0 yrs)	-Ice 3 mins [(2 ice packs over VL before initiating quads exercise, and applied between each set (60 secs), skin temperature ; VL: 15.0 (1.8 C) -Control	Quad activation patterns assessed by comparing mf MRI (T2 weighted) before and after knee extension exercise (10 reps x 5 sets at 60% of 10 rep max, 1 min rest between sets) % change in T2 value before and after exercise (using imaging software I=C VL I>C in RF and Vm I>C*in VI
Palmieri-Smith, 2007 (Cross over- 2 weeks between conditions)	N=22 healthy Mean age: 25 (+/-14 yrs)	-Ice 20 mins (ice bag anterior ankle) - Control	H max, M max, H ratio I>C (10*, 20* mins during Rx and 10*, 20* post Rx) Plasma norepinepherine I>C (10* during Rx)
Pietrosimone, 2009a (Cross over – 3 to 14 days between conditions)	N=11 healthy Mean age: 25 (+/-5yrs)	-Ice 20 mins (knee joint) -Control	Quadriceps CAR -I>C (immed*, 10 and 25* mins post Rx)
NERVE CONDUCTION VELOCITY			
Zhou, 1998) (Observational)	N=7 healthy 4 male, 3 female Mean age: 20.3 (+/-1.4 yrs)	-Ice bag applied until thigh IM temperature reached 30°C	Electromechanical delay (time lag between initiating quads contraction on EMG and force development) Decrease post ice* Peak contraction force Decrease post ice* Muscle fibre conduction velocity Decrease post ice* Note: Decreasing muscle temperature from resting levels (37°C) to 30°C causes: a 125N decrease in peak contraction force, a 0.5 m/s-1decrease in muscle fibre conduction velocity
Kubo, 2005 (Randomised cross over - states conditions were on separate days)	N=8 healthy males Mean age 26 (+/-2yrs)	-Ice 30 min (CWI in 5°C, to head of fibula) -Heat 30 min (HWI in 42°C to head of fibula)	Electromechanical delay [time lag between initiating calf muscle contraction (PF) on EMG and force development] Post I > Pre I* Post H > Pre H* Note: Both ice and heat increased the time between muscle activation (on EMG) and force development, by 25% and 19% respectively

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Algafly, 2007 (RCT with allocation concealment)	N=23 healthy	-Ice (crushed ice applied until skin temperature reduced to 10C foot) -Control	NCV (foot) Decreased* at skin temperatures reductions to 15°C, continued to decreased further at 10°C, no changes in control Note: Cooling from baseline to 10C, decreased NCV by 33% (from approx. 35m/s to 22m/s)
REFLEX PATHWAYS			
Hopkins, 2006a (Randomised cross over -1 week between conditions) Berg, 2007 (Randomised cross over – 24 hrs between conditions)	N=13 healthy Mean age 23 (+/- 4 yrs) N=27 healthy subjects 14 males, 13 females Mean age: 24 (+/- 2.7yrs)	-Ice 30 min (1.5 L crushed ice with elastic wrap; lateral ankle joint) -Control 30 min (sham treatment: 1.5L of dry clay with elastic wrap; lateral ankle joint) -Ice 20 mins (ice bag with compression over lateral ankle joint) -Control	Ankle inversion perturbation (up to 28 degrees) while walking Peroneal reaction time (Surface EMG peroneus longus) I=C Sudden ankle perturbation to 25 degrees of inversion. -Peroneal muscle activity (mV) I=C (immediately, 15 min and 30 min after removal of ice) Peroneal reaction time with surface EMG. I=C (immediately, 15 min and 30 min after removal of ice)
Berg, 2007 (Randomised cross over – 24 hrs between conditions)	N=27 healthy subjects 14 males, 13 females Mean age: 24 (+/- 2.7yrs)	-Ice 20 mins (ice bag with compression over lateral ankle joint) -Control	Sudden ankle perturbation to 25 degrees of inversion. -Peroneal muscle activity (mV) I=C (immediately, 15 min and 30 min after removal of ice) Peroneal reaction time with surface EMG. I=C (immediately, 15 min and 30 min after removal of ice)
PROPRIOCEPTION			
Thieme, 1996 (Randomised cross over – states attended two sessions)	N=37 healthy 16 male, 21 female Mean age 23.4 (+/- 6.3yrs)	-Ice 20 mins (2 ice packs (each 30.5 x 49cm, with 1160 of ice), 1 anteriorly, covering an area 10 cm above and 10 cm below the patella, with the other around the popliteal fossa), -Control	Active JPS error at the knee (30, 60 and 90 degrees) I=C
Hopper, 1997 (Observational)	N=49 healthy 42 female, 7 male Mean age: 19.4 (range: 17-28)	-Ice 15 mins (CWI immersion at<5°C, 5cm above the lateral maleolus, skin temperature 15°C)	Active JPS error at ankle (40% and 80% of maximum inversion angle, at 42 degrees of PF) Post I > Pre I* Note: Ice increased JPS error by 0.5 degrees

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Tremblay, 2001 (Observational)	N=20 healthy 14 male, 6 female Mean age 22.1 (+/- 2.6yrs)	-Ice 20 mins (Crushed ice with moist towel barrier, to quadriceps muscle belly)	Threshold for weight discrimination during open chain leg extension (kg) Pre I = Post I
Uchio, 2003 (Observational)	N=20 healthy 10 male, 10 female Aged: 21-28 yrs	-Ice 15 mins (icing system, cooling pad at 4C, skin temperature: 21.6°C at knee)	Active JPS error at knee (5 and 25 degrees) Immed post I > Pre I* 15 mins post I > Pre I Note: Active JPS error increased by 1.7 deg immediately after cooling (p=0.003), remained 0.9 deg worse than baseline for up to 15 minutes after cessation of ice
Dover, 2004 (Randomised cross over - 48 hrs between conditions)	N=30 healthy 15 male Mean age: 23.7 (+/-5.5) 15 female: Mean age: 20.7 (+/-1.4)	-Ice 30 mins (1kg ice cubes in 20 x 25 cm bag, secured with standardised elastic bandage, centre of bag over the tip of Acromion; skin temperature reduced to 13.3°C) -Control	Active JPS error at shoulder (90% IR and ER) I=C
Wassinger, 2007 (Observational)	N=22 healthy 14 male, 8 female Mean age: 21.6 (+/- 2.4 yrs)	-Ice 20 mins (1.5kg ice cubes in 1.15 L bag, secured with standardised elastic bandage to centre of bag over the tip of Acromion)	Active JPS error at shoulder (20 degrees FL, 90 degrees ABD) Pre I=Post I
FUNCTIONAL / ATHLETIC PERFORMANCE			
Cross, 1996 (RCT)	N= 20 healthy Mean age: 19.3 (+/-1.2 yrs)	-Ice 20 mins (CWI at 13°C up to fibular head, with water turbulence) -Control	Hop test I=C Vertical jump I<C Shuttle run I<C Note: Ice decreased vertical jump by approximately 2 cm, and decreased shuttle run by approximately 0.16 seconds

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Kinzey, 2000 (Observational)	N=15 healthy 7 male, 8 female Mean age: 22.3 (+/- 2.1 yrs)	-Ice 20 min (CWI at 10°C up to patella)	One leg vertical jump (5 jumps x 5 sets) before, immediate after CWI Peak vertical GRF Post I > Pre I* Average GRF Post I =Pre I Vertical impulse Post I<Pre I* Note: a 0.04% difference in vertical GRF was significant
Jameson, 2001 (Cross over - 24hrs between conditions)	N=10 healthy Mean age: 22.4 (+/- 1.26 yrs)	-Ice 20 mins (crushed ice pack to ankle) -Ice 20 mins (crushed ice pack to knee) -Ice 20 mins (crushed ice packs to ankle and knee) -Control (no ice)	Vertical GRF (peak, average, integrated and time to peak during 2 footed jump) Pre=post (all groups) I (ankle) = I (knee) = I (ankle/knee) = C
Hart, 2005 (Observational)	N=20 healthy 9 male, 11 female Mean age 23.8 (+/- 3.6 yrs)	-Ice 20 min (crushed ice to anterior knee with elastic wrap)	Forward jump with single leg landing GRF; knee joint angle Pre I = Post I (immediately, 15 and 30 min post treatment)
Miniello, 2005 (Observational)	N=17 healthy females Mean age: 20.9 (+/- 1.1 yrs)	-Ice 20 mins (CWI at 13-15°C up to tibial tuberosity)	EMG activity (Preparatory and reactive) counter movement jump -Tibialis anterior Preparatory activity increased immediately post I* -Peroneus longus Preparatory and reactive activity decreased immediately post I* Time to stabilisation Pre I = Post I Note: EMG returned to baseline 5 minutes after cooling
Wassinger, 2007 (Observational)	N=22 healthy 14 male, 8 female Mean age: 21.6 (+/- 2.4 yrs)	-Ice 20 mins (1.5kg ice cubes in 1.15 L bag, secured with standardised elastic bandage to centre of bag over the tip of Acromion)	-Functional throwing performance index (number of throws to hit a target and number of throws in 30 secs) Post I < Pre I* -JPS Post I=Pre I

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Fischer, 2009 (Cross over – 1 day between conditions)	N=42 healthy 25 female Mean age 22 (+/- 0.5y) 17 male Mean age 23 (+/- 0.5y)	-Ice 3 min (x2 ice bags (28 x 46cm) with cubed ice, hamstring muscle belly, secured with plastic wrap) -Ice 10 min (x2 ice bags (28 x 46cm) with cubed ice, hamstring muscle belly, secured with plastic wrap) -Control	-Co-contraction (side shuffle test with band resistance) Post control > pre control* (20 minutes post treatment) -Shuttle run Post I 10 min > Pre I 10 min* (at 10 and 20 mins post treatment) -Single leg vertical jump Pre I 10 min > Post I 10 min (immediately post treatment) Note: Ice slowed down shuttle run by approximately 0.2 seconds, and decreased single leg vertical jump by 1cm
Richendollar, 2009 (Randomised cross over - 24 hrs between ice conditions)	N=24 healthy males Mean age: 21.3 (+/- 3.3 yrs)	-No ice followed by 20 minute rest -No ice followed by 20 minute warm up -Ice 20 min (1.4 kg of crushed ice in plastic bag, secured with compression wrap over anterior thigh) followed by 20 minute rest -Ice 20 min (1.4 kg of crushed ice in plastic bag, secured with compression wrap over anterior thigh) followed by 20 minute warm up	Single leg vertical jump No warm up: I < No I* Warm up: I< No I Shuttle run agility No warm up: I>No I* Warm up: I>No I 40 yard sprint No warm up: I>No I* Warm up: I>No I Note: When no warm up is undertaken (after icing), ice produces an approximate decrease of:1.7cm to vertical jump, and an approximate increase of 0.23 seconds onto shuttle run, and 40 yard sprint times.
RANGE OF MOVEMENT / MECHANICAL PROPERTIES			
Muraoka, 2008 (Observational)	N=6 healthy males Mean age: 27 (+/- 4yrs)	-Ice 60 min (CWI at 5-8°C, lower leg, IM temperature decrease by 5.8)	Outcomes monitored during passive knee extension (verified 'passive' with EMG) from 90 to 0 degrees % increase in passive TA force (via force transducer) Post I>Pre I* Gastroc stiffness (via force transducer) Post I > Pre I* Fasicle length (US) Increased in both groups: I=C Note; Ice increased passive TA force by 19%, and increased passive tissue stiffness by 2N/mm; US confirmed no change in the muscle length.

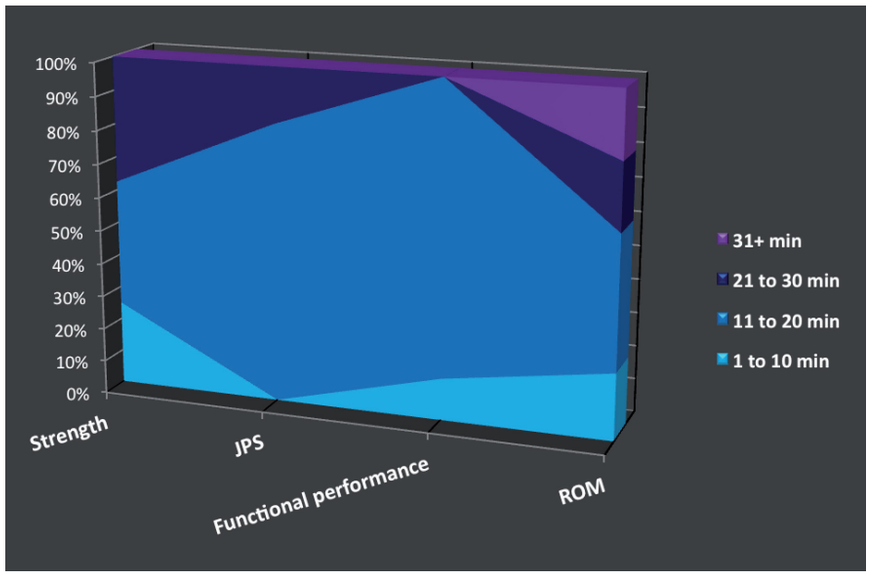
Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
Kubo, 2005 (Randomised cross over - states conditions were on separate days)	N=8 healthy males Mean age 26 (+/- 2yrs)	-Ice 30 min (CWI in 5°C, to head of fibula) -Heat 30 min (HWI in 42°C to head of fibula)	Passive ankle joint movement (5 dg/sec) in prone, from 15 degrees PF to 30 degrees DF Passive torque Post I>Pre I Post H<Pre H* Note: Ice increased passive torque around the ankle joint by 1Nm, whereas with heat there was a decrease of 2.2Nm
Burke, 2001 (RCT)	N=45 healthy 21 female, 24 male Age range: 18-25 yrs	-Ice 10 min (CWI in 8°C up to gluteal fold) then PNF training -Hot 10 min (HWI in 44°C up to gluteal fold) then PNF training -Control 10 min (standing) then PNF training	Conditions were undertaken prior to PNF training (every day for 5 days) Hamstring length (degrees) Day 5 I >Day 1 I Day 5 H > Day 1H Day 5 C > day 1 C No differences between groups Note: 5 days of PNF stretching alone increased hamstring length by 26 degrees; there were no differences when muscle heating was used prior to stretching. When ice was applied prior to PNF stretching, hamstring length was increased by 23.5 degrees over a 5 day period.
Brodowicz, 1996 (RCT)	N=24 healthy athletes Mean age: 20.7 (+/- 1.2 yr)	-Control 20 minutes stretching protocol -Ice during 20 minutes stretching (ice bags secured with an elastic wrap to the posterior thigh) -Heat during 20 minutes stretching (hot packs secured with an elastic wrap to the posterior thigh) All groups: both legs	Increase in active SLR (sum of right and left sides in degrees) I>heat=control* Note: Icing during stretching resulted in a 10 degree greater increase in flexibility, compared to stretching alone and heat and stretching
Benoit, 1996 (Cross over - 1 day between conditions)	N=15 healthy 8 male, 7 female Mean age: 22.8 (+/- 2.5yr)	-Ice 20 min (CWI at 15°C, 4 inches a bove patella) -Heat 20 min (HWI at 40°C, 4 inches above patella) -Control (no immersion)	Anterior tibial displacement (KT 1000 arthrometer at 89N or maximal force) No differences between groups

Author (Study type, Factors lowering risk of bias)	Subject / inclusion criteria	Pre test Intervention	Outcomes / Results
RANGE OF MOVEMENT / MECHANICAL PROPERTIES			
Rice, 2009 (RCT)	N=16 induced injury (Experimental knee joint effusion using saline to 50mmHg intra-articular pressure) 10 male, 6 female I: mean age 36.5 (10.6); C: mean age 34.3 (11.7)	-Ice 20 min (3 plastic bags of crushed ice, around knee joint) -Control	Decrease in quadriceps peak torque post injury (normalised to body mass (nm/kg x 100) I<C* Decrease in MFCV post injury (n=10 only) I<C* Decrease in EMG (RMS) post injury (% of baseline) I<C Note: POST INJURY: -I=26 Nm higher peak torque -I=0.5ms-1 higher MFCV -I=15% higher EMG RMS
Hopkins, 2006b (RCT)	N=45 induced injury (experimental knee joint effusion using 55ml of saline) 26 male, 19 female Mean age: 21 (+/- 2 yrs)	-Ice 30 min (1.5L of crushed ice directly onto the anterior knee, secured with elastic wrap) -Control 30 min (sham ice bag and elastic wrap onto anterior knee)	EMG activity (during recumbent stepping) post injury -VL: I>C at 30 min and 60 min post effusino -No differences in integrated EMG activity DECREASE in peak torque post injury I<C at 30 min post effusion DECREASE in Peak power post injury I<C at 30 and 60 min post effusion
Kernozek, 2008 (Observational)	N= 15 Post grade 1 lateral ankle sprain (past 4-7 days) Aged: mean: 21.3 (=/- 3.54) 18-29 y	Ice 20 minute (CWI; 0-4°C, stirred every few minutes, immersion to 5-7cm below tibial tuberosity)	Postural sway variability (medial to lateral) Pre I<Post I (immediately*, 10 min*, 20 min* post I)
Hopkins, 2002b (RCT)	N=30 induced injury (Experimental knee joint effusion using 60 ml sterile saline) 19 male, 11female Age 21.8 (2.4y)	-Ice 30 mins (1.5 L bag of crushed ice x 2, over anterior and posterior knee) -TENS -Control	H reflex [amplitude / change (pre-post)] I>C (15*,30*,45*,60* mins post injection) I>TENS (45*, 60* mins post injection) Note: I resulted in an increase in H reflex beyond baselines from 15-60 minutes. confirmed no change in the muscle length.

I: Ice
C: Control (note: control = no intervention unless otherwise indicated)
H: Heat
CWI: cold water immersion
HWI: hot water immersion
PF: plantar flexion
MVC: maximum voluntary contraction
H Reflex: Hoffman reflex
VM: Vastus Medialis
VL: Vastus Lateralis
VI: Vastus Intermedialis
RF: Rectus Femoris
mf MRI: muscle functional magnetic resonance imaginge
CAR: Central activation ratio
I/M: Intramuscular
JPS: joint positional sense
TA: tendo Achilles
US: Ultrasound
PNF: Proprioceptive Neuromuscular Facilitation
SLR: Straight Leg Raise
MFCV: Muscle Fibre Conduction Velocity
RMS: Root Mean Squares
GRF: Ground reaction force
In the outcome column, the greater than (>) and less than (<) symbols refer to the absolute differences between groups/conditions (eg. Ice vs Control).
In cases where comparisons were made within groups before and after conditions, Pre I = pre intervention value (before), and post I = post intervention value (after).
* indicates a significant difference between groups (time point is immediately after treatment unless otherwise indicated).

Figure 2

Summary of cooling durations used in studies assessing Primary outcomes (Key correlates of physical performance)



Chapter 6

Which components of PRICE are effective in the clinical management of acute soft tissue injury?

What is known in this area: Protection, rest, ice, compression and elevation (PRICE), is synonymous with acute soft tissue injury management. The original guidelines1 recommended that all components of PRICE should be employed immediately after acute soft tissue injury, and gave specific recommendations for its practical use. Much of the recommendations were based on expert consensus and there was little high quality empirical evidence in this area.

Aim: To update the clinical evidence for using PRICE in the management of acute soft tissue injury.

Clinical question: Which components of PRICE are effective in the clinical management of acute soft tissue injury?

Objective: To review the current literature and determine which components of PRICE are effective in the clinical management of acute soft tissue injury based on an injured human model?

PROTECTION/REST: There is moderate quality evidence that functional treatment is more effective than cast immobilisation after ankle sprain for a range of important outcomes, but there are little long term differences. There is also moderate evidence that this approach is most effective in less severe sprains. There is moderate evidence that semi-rigid supports are more effective than elastic bandages, and low quality evidence that DTG is ineffective in terms of short term recovery. There is conflicting evidence on the most effective form of external support used in conjunction with functional treatment (semi-rigid, taping, lace up or focal compression). There is very low quality evidence that 3 weeks immobilisation after primary shoulder dislocation, is similar to using a period of immobilisation guided by patient discretion and comfort, in terms of long term re-injury rate. There is very low quality evidence that a supervised active treatment intervention is effective an effective approach after closed elbow dislocation in an active population. There is very low quality evidence that 24 hrs of immobilisation in end of range flexion, followed by isometric exercise is an effective approach after quadriceps contusion in an active population.

ICE: Based on a closed soft tissue injury model, there is moderate evidence that cold therapy is effective at decreasing short pain after acute ankle injury and general soft tissue contusion; there is low quality evidence that shorter intermittent applications are sufficient to induce short term analgesia. Based on a post surgical model, there is high quality evidence that cold therapy provides effective short term analgesia, but has little benefit in terms of other critically important outcomes. Evidence from questionnaires and case studies confirm that cold therapy does have the capacity to do harm; most cases involved short term complications with a full recovery. There were isolated cases of permanent scarring and loss of function. There are few reports of adverse events within lab based and clinical studies. The risk of inducing adverse events is low, if clear instructions for practical application are provided and evidence based rationale considered.

COMPRESSION: There is very low quality evidence that compression is ineffective after muscle injury. There is moderate evidence that semi-rigid supports are more effective than elastic bandages, and low quality evidence that DTG is ineffective in terms of short term recovery. There is conflicting evidence on the most effective form of external support used in conjunction with functional treatment.

ELEVATION: There is low quality evidence that elevation alone is marginally better than compression and elevation in terms of decreasing ankle volume. There is also low quality evidence that limb volume returns to baseline levels quickly after returning the extremity to a dependent position. There is also moderate evidence that tissue volume (swelling) will increase after orthopaedic surgery, regardless of the magnitude of home based limb elevation.

Which components of PRICE are effective in the clinical management of acute soft tissue injury based on a human model?

Protection, rest, ice, compression and elevation (PRICE), is synonymous with acute soft tissue injury management. The original guidelines[1] recommended that all components of PRICE should be employed immediately after acute soft tissue injury. There was little high quality empirical evidence in this area eg. meta-analysis (MA), systematic review (SR), randomised controlled trials (RCT), and much of the recommendations were based on expert consensus. The main recommendations from the original guidelines[1] were as follows:

Protection and rest should be used for at least 3 days post injury, with longer periods advised according to injury severity. Only isometric type exercises should be undertaken during the acute stages. Compression should be applied immediately after injury, with continuous use over the first 72 hours post injury only. Compression should be applied with uniform pressure, from proximal to distal, with additional intermittent compression permitted. Elevate for as long as possible in the first 72 hours, but avoid immediate restoration of the injured body part to a gravity dependant position. Compression and elevation should not be undertaken simultaneously. Where possible ice should be applied in the immediate stages post injury; the optimal protocol is chipped ice (with damp barrier) for durations of 20-30 minutes, repeated every 2 hours. This protocol should be altered based on levels of body fat, and the presence of superficial nerve at the application site. Athletes were advised not to return to competition immediately after applying ice.

Our primary aim was to update the original ACPSM guidelines.[1] The objective of this chapter was to review of the current literature to determine which components / or combinations of PRICE are clinically effective in the management of acute soft tissue injury.

Methods

Search strategy

We searched the titles generated from the main search strategy outlined in Appendix Table 1-4. Relevant studies were extracted, with exclusions made based on titles, abstracts or full text versions.

Inclusion criteria

Study type: Systematic review, randomised or observational studies (published since 1996).

Participants: Injured humans with acute soft tissue injury. We did not consider models using complete tendon rupture, however no otehr restrictions were made on the type or severity of injury.

Intervention: Any component or combination or PRICE initiated within the acute phases of injury. Protection and rest were defined as any intervention unloading, immobilising or modifying activity after injury the injured tissue. No restrictions were made on mode, duration or dosage of ice, compression or elevation.

Outcomes: Any clinical based outcome from a study based on injured human participants was considered to be of critical importance.

Comparison: Intervention could have compared with anything other than surgery.

Note: Individual studies were not considered if they were already included within an eligible systematic review or meta-analysis.

Grading of evidence

Five criteria were used to grade the quality of evidence in each sub-group:

- Study design
- Internal validity (Risk of bias)
- Consistency (across studies, in terms of the size and direction of effect estimates)
- Directness (external validity)
- Publication bias

All five criteria were assessed by two independent reviewers. Initially study designs were used to categorise evidence into the following categories: high quality (MA or SR, RCT), moderate (CT) low quality (observational) or very low quality (other study design). Evidence was then upgraded, or downgraded according to the remaining four criteria. Internal validity was assessed using The AMSTAR[3] scoring scale for meta-analyses or systematic reviews (Appendix Table 9). For all original research, internal validity was assessed using the Cochrane risk of bias tool[2] (Appendix Table 10); using the criterion: sequence generation, allocation concealment, assessor blinding, incomplete outcome data, other (adequate detail provided on PRICE intervention AND details of co-interventions). Blinding of participant or caregivers were not considered based on the nature of the interventions. Consistency, directness and publication bias were assessed qualitatively by each reviewer. In the event that evidence was downgraded (or upgraded); the rationale was provided (as detailed overleaf).

Evidence Summary

As we were potentially dealing with a large number of heterogenous studies, we created separate evidence summaries according to the type of soft tissue affected, and treatment comparison. The following definitions were used as a final quality grading:[4]

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

RESULTS

Figure 1 provides a summary of included studies by primary intervention and injury type. Detailed study characteristics are summarised in Figure 2. Risk of bias summary is provided in Figures 3 and 4. Excluded studies (with reasons) are listed in Appendix Table 5. Confidence intervals are 95% unless otherwise stated.

Protection/Rest: Ankle sprain

Four SR's were eligible for inclusion.[5-8] Three compared immobilisation with functional treatment after acute ankle sprain;[5,6,8] one compared various forms of functional management of ankle sprain.[7] All reviews fulfilled at least 85% of criterion on AMSTAR.[3] This included stringent selection criteria, data extraction, and literature searches. All reviews undertook and considered the scientific quality of included studies, and when applicable, an appropriate method of meta-analysis was undertaken. None of the studies used graphical or statistical tests to consider the threat of publication bias. Searching up to 1998, Pijnenburg et al.[5] included 27 randomised and quasi randomised studies of acute ligaments ruptures, with the majority confirming injury severity via arthrogram or stress radiograph. They classified 5 included studies as high quality, and undertook separate sub-group analysis on this data. Note that the authors considered <3 weeks of cast immobilisation to be a functional treatment. Kerkhoffs and colleagues undertook two Cochrane reviews.[6,7] Both reviews included acute injury to the lateral ankle, based on physical examination, stress radiograph or arthrogram. Literature searching was undertaken up to 2000, and a total of 30 RCT's were included. The smallest and most recent review,[8] excluded any studies with >80% drop out, leaving 9 eligible RCTs. All four reviews[5-8] pooled data for MA.
There were 6 relevant RCT's [9-14] (and one related protocol15), published after the search limits on the aforementioned SR's. All undertook adequate sequence generation. In one study, allocation concealment was based on 'a predetermined rotation system',[9] and another was unclear;[10] all others employed either off site concealment, or opaque sealed envelopes. Blinding of outcome assessor was limited to one study.[14] In all cases the intervention was clearly described, and although co-interventions were used, they were deemed to be standardised across groups. Ankle sprain severity differed across RCT's, they included: grade 1 or 2;[9,11] or grades 2 and 3.[10,12] One study[13] which included all severities sub-grouped by injury grade, using stratified randomisation. No formal grading was undertaken in Lamb's study;[14] however, if we consider that their primary inclusion criteria was 'unable weight-bear for at least 3 days post injury', this might have been restricted to more severe sprains.

Cast immobilisation vs Functional
SR

Pooling the results of 10 studies, Pijnenburg et al.[5] found that functional treatment was associated with less time lost from work (15 days (range 12-18) compared with casting (38 days (range 28-48); and significantly lower levels of residual pain (RR: 0.67 CI: 0.5-0.9), and complaints of giving way (RR: 0.7 CI: 0.5-0.9) at 6 weeks. Similarly, Kerkoffs et al.6 found a number of significant effects in favour of functional treatment. These included return to sport (n=5 studies pooled: RR 1.86 (CI 1.2; 1.9); days to return to sport [n=3 studies pooled; WMD: 4.8 days (95% CI: 1.5-8.3)], swelling [n=3 studies pooled; RR: 1.7 (CI: 1.17-2.59)] and patient satisfaction [n=6 studies pooled; RR: 4.25 (CI: 1.17-2.59)]. No differences were found between groups in terms of pain, giving way, re-injury. Jones and Amendola[8] did not find any significant difference based on pooled data, however there were trends that functional treatment was superior in terms of time to return to work, subjective instability and re-injury rate. Notably the two reviews that undertook sub-group analysis on the high quality studies (n=11;[6] n=5[5]) found no significant differences between groups.

RCT

In a large RCT14 10 days of POP immobilisation resulted in significantly better function up to 3 months post injury, compared to DTG. There were similar patterns that casting was also superior to rigid bracing, however, the differences were less pronounced. Beynonn et al.[13] used a stratified approach, randomising by injury grade. They found no differences in outcome between casting for 10 days, and functional treatment with a rigid brace, in participants with grade 3 (severe) injury. However, functional treatment resulted in a significantly faster return to function and sporting activity in participants' with grade 2 ankle sprains. None of the studies found any significant differences between groups at 6-12 month follow up.[13,14]

Evidence summary: There is moderate quality evidence that functional treatment is more effective than cast immobilisation after ankle sprain for a range of important outcomes, but there are little long term differences between the interventions. There is also moderate evidence that this approach is most effective in less severe sprains. [The findings were deemed to be consistent across reviews for the majority of outcomes. Downgraded from high to moderate quality due to: the lack of effect based on sub-group analysis on 'high quality studies' within two of the reviews/inconsistent findings from the large RCT by Lamb et al.[14]] Note: A controlled trial by Samato et al.[48] (high risk of bias) showed very low quality evidence that Cast immobilisation with weight-bearing is less effective in more severe sprains].

Functional vs functional

A number of studies have evaluated the effect of using different methods of external support, to accompany early mobilisation after sprain. Kerkhoffs et al.[7] included two RCT's comparing functional treatment with elastic bandaging or semi rigid support. Pooled results found a faster return to work in favour of semi-rigid based on dichotomous (RR: 4.3 CI: 2.4-6); and continuous scales (WMD: 9.6 days (6.3;12.9) and less complaints of giving way (RR: 8; CI: 1.03-62), all in favour of the semi rigid bracing. Lace up braces were associated with less swelling when compared to elastic bandaging (n=1; RR: 5.5 CI 1.7; 17.8), taping (n=2; RR: 4.07, CI 1.2; 13.7), and semi rigid braces (n=1; RR: 4.19; CI: 1.3; 13.98). No differences were noted between taping and semi-rigid bracing (n=2 studies).

Three related RCT's[10,12,14] found further trends that semi rigid bracing is superior to elastic bandaging. Lamb et al.[14] found that semi-rigid supports resulted in higher levels of subjective function at 3 months compared to DTG. A small study by Boyce et al.[12] found no differences between groups in terms of pain or swelling, however, rigid bracing did result in higher levels of function at 10 days post injury. Leanderson et al.[10] recorded a range of outcomes; however, the only significant difference was that braced participants completed a figure of eight running test faster at 10 weeks. Furthermore, Watts and Armstrong[11] found that adding DTG to standard advice was of little additional benefit during recovery after grade 1 and 2 sprains. Follow up at 10 days also found that DTG was associated with higher levels of analgesic consumption. A critical limitation was the 60% loss to follow up reported in this study. One small study[9] compared two different methods of focal compression, with a semi rigid support. No short term differences were found in pain, swelling or function.

Evidence summary: There is moderate evidence that semi-rigid supports are more effective than elastic bandages [downgraded based on consistency of results across all outcomes], and low quality evidence that DTG is ineffective in terms of short term recovery [downgraded due to risk of bias[11]]. There is conflicting evidence on the most effective form of external support used in conjunction with functional treatment (semi-rigid vs taping vs lace up vs focal compression). There is very low quality evidence (controlled study[49], high risk of bias) that weight-bearing mobilisation with semi-rigid support is superior to a walking cast.

Elevation vs elevation and compression

Tsang and colleagues16 measured the changes in ankle volume associated with 30 minutes of elevation, or combined elevation and compression treatment, in twelve student subjects with acute ankle sprain. Both interventions significantly decreased limb volume, with trends towards larger changes (10mL difference) in the elevation only group. Interestingly, they also considered the effect of an immediate return to a gravity dependent position after treatment. In both groups, limb volume returned to pre treatment values after 5 minutes of sitting.

Evidence summary: There is low quality evidence that elevation alone is marginally better than compression and elevation in terms of decreasing ankle volume. There is also low quality evidence that limb volume returns to baseline levels quickly after returning the extremity to a dependent position. [Downgraded based on risk of bias and small number of studies (unable to judge for consistency)]

Soft tissue injury

Ice and compression

Much of the clinical literature on the effectiveness of ice and compression is based on postsurgical models. In a SR,17 only 6 out of 24 included RCT's used subjects with closed soft tissue injury. These studies generally had a number of methodological limitations (mean PEDro score 4.3; range 3-8) and sample size ranged from 30-143. This review found evidence from single, small RCT's that cold therapy is more effective that heat, contrast therapy and no treatment, in terms of reducing swelling and pain after ankle sprain; but there is no evidence to suggest enhanced function or long term outcome. Of note, the authors found wide variation in the mode and treatment dosage of cooling used across studies; they note that often this was limited to between 20 and 90 minutes of cooling which may not be sufficient to achieve a worthwhile clinical effect.

Two further RCT's have been added to the evidence base recently. A large RCT by Airaksinen and colleagues18 found that 4 daily applications of a topical cooling gel, reduced pain in comparison to placebo gel. These results were based on general minor soft tissue injuries and cannot be generalised to more moderate or severe injuries. Bleakley et al19 compared the effectiveness of two different cooling doses in a group of 89 participants with acute ankle sprain. An intermittent 10 minute application was associated with lower levels of pain at week 1, in comparison to a standard 20 minute application. There were no differences between groups at 3 month follow up. One SR20 considered the effects of compression after soft tissue injury; the included studies were all previously included within other reviews.6,7

Evidence summary: There is moderate evidence that cryotherapy is effective at decreasing short pain after acute ankle injury and general soft tissue contusion. [Downgraded based small number of studies (unable to judge consistency)]. There is low quality evidence that shorter intermittent applications are sufficient to induce short term analgesia. [Downgraded based on risk of bias, and small number of studies (unable to judge consistency)]

Post surgery

The remainder of recent RCT's have focused on the effectiveness of various combinations of cooling and compression after post orthopaedic surgery (eg. ACL reconstruction, TKA, THA, CTR). Comparison across studies is greatly limited by clinical heterogeneity. Bleakley et al.[17] focused on a wide range of treatment comparisons, however few definitive conclusions were found. Much of this related to the wide variations in terms of the injury type, treatment intervention and comparison group. In addition, the internal validity of studies was low (3.4/10), based on PEDro. There was evidence from a single RCT's that cold therapy is effective in terms of short term analgesia after minor knee surgery, but had no effect on function, swelling or range of movement. The majority of orthopaedic studies compared ice and compression against, compression only. The compression interventions normally consisted of a compressive cooling device filled with room temperature water. Six out of eight studies found that ice and compression was no more effective than compression alone; two found significantly larger decreases in short pain with ice and compression. The limitations of using an orthopaedic setting to assess the effectiveness of cooling were noted by the authors; of particular concern is the use of post surgical dressing or socks which risk mitigating the cooling effect. Only one study in this review included a measure of skin temperature under the barriers, which was reported to be a modest 28°C.

A related review[21] focused on the effectiveness of cryotherapy after ACL reconstruction only. Using similar comparisons, they pooled data from six studies using random effects modelling. They found cryotherapy had a significant effect over placebo in terms of pain relief, but there were no overall differences for drainage or range of motion.

Further studies have been undertaken in this area since the publication of these SR's. Holmström and Härdin[22] compared 48 hours of basic analgesia (paracetamol), epidural anaesthesia or cryocuff after Uni-compartmental knee arthroplasty. Sequence generation and allocation concealment were not described and blinding was not undertaken. Results found no difference between groups in wound drainage, subjective pain, swelling, ROM and function. Both the epidural and cryocuff groups needed significantly less additional pain relief (morphine) during the first 24 hours post surgery, compared to the control. In a randomised controlled design, Smith et al.[23] found little differences in swelling, ROM, bleeding or pain, when using a commercial cooling systems, or a compression bandage over the first 24 hrs after TKR. There was no allocation concealment or blinding of outcome assessment. A further limitation was that management of both groups was similar after 24hrs, with both receiving cooling with an ice bag for up to 72 hrs post surgery. Using a similar population, a controlled trial[50] found significant differences in favour of a cooling group compared to compression only, in terms of short term pain, ROM and post operative swelling.

There are few clinical studies of elevation after injury. We found one RCT24 measuring the effect of post operative hand elevation, based on a population of n=43 participants after carpal tunnel decompression. One group received a normal sling (arm by side with elbow flexed to 90 deg), and the other undertook high elevation with the hand above the heart. Water volumetry found that both groups had increases in hand volume at five days post operatively. There were few meaningful differences between groups, and the mean increase in the high elevation group was approximately 2 ml less than in the sling control.

Evidence summary: There is high quality evidence that cold therapy provides effective short term analgesia, but has little benefit in terms of other important clinical outcomes. There is also low quality evidence that tissue volume (swelling) will increase after orthopaedic surgery, regardless of the magnitude of home based limb elevation (Downgraded based on risk of bias, and small number of studies (unable to judge consistency). [Note: Post surgical dressings could prevent adequate tissue cooling, and consequently, it is difficult to extrapolate some of this evidence to a closed soft tissue injury model].

Other Evidence

Ankle sprain

A single case study[47] on a female athlete with a grade 2 ankle sprain (clinical diagnosis) employed a range of PRICE interventions coupled with progressive active rehabilitation and strengthening exercise. This approach resulted in a fast return to sports (2 weeds) with excellent long term functional outcome at approximately 1 year.

Shoulder dislocation

Hovellius et al.[25] focused on long term outcomes after primary shoulder dislocation. A fixed sling immobilisation time of 21 days, was compared with a control using immobilisation for any time up to 21 days. The duration of immobilisation in the control was made at patients' discretion and comfort; 87/104 patients in this group, continued with a sling for just 7 days. Of note, there were a number of protocol violators in the fixed time group ie. individuals who removed their sling prior to the recommended 21 days. The primary outcome, injury reoccurrence, was recorded over a 25 year period. The duration of immobilisation did not seem to a factor in the risk of re-injury, or requirement for surgical intervention. Of note this was a mixed methods study, with only some of the recruitment centres using randomisation. In addition, allocation concealment and intention to treat were not undertaken.

Elbow dislocation

In a case series design,[26] 20 military personnel with closed (simple) posterior elbow dislocation (reduced within 1 hour) were treated with a supervised active treatment intervention, without slings or immobilisation. Co-interventions included: compression, icing, elevation, electrical stimulation, active elbow and hand exercises were undertaken from day one, with resistance added from day 2, and swimming from day 3. Maximum range of movement was achieved within 19 days (range 3-30) post injury, with all subjects reaching extension to within 5° of their injured side. No patients were lost to follow up, and long term outcome was described as excellent, with minor subjective complaints. One re-dislocation occurred during contact sports at 15 months.

Quadriceps contusion

Another prospective case series[27] was undertaken on a military population, with acute quadriceps contusion. Inclusion criteria which were, inability to continue participation in sport, and lack of pain free straight leg raise. Each of the 47 participants were braced in 120 degrees of knee flexion for 24 hours, followed by progressive isometric exercises. The mean time for return to athletic activity was 3.5 days (range 2-5). Follow up between 3 and 6 months found 1 case of

Muscle injury

In a non randomised, controlled design,[28] 40 participants with acute muscle injury were treated with either immediate compression (80mm/Hg), or control. The control group received rest and ice or in certain cases moderate compression (40 mm/Hg) after 10-30 minutes post injury. There were no differences between groups in terms of subjective recovery, range of movement, serum CK levels or ultrasonic findings.

Evidence summary: There is very low quality evidence that 3 weeks immobilisation after primary shoulder dislocation, is similar to using a period of immobilisation guided by patient discretion and comfort, in terms of long term re-injury rate. There is very low quality evidence that a supervised active treatment intervention is effective an effective approach after closed elbow dislocation and ankle sprain in an active population. There is very low quality evidence that 24 hrs of immobilisation in end of range flexion, followed by isometric exercise is an effective approach after quadriceps contusion in an active population. There is very low quality evidence that compression is ineffective after muscle injury [Very low quality based on observational design; risk of bias and small number of studies (unable to judge consistency)]

Adverse effects

Characteristics of studies reporting adverse effects are provided in Figure 5. Two recent surveys focused on practitioners' experiences of adverse events relating to electrophysical agents, with a primary focus on cryotherapy. The target populations were athletic trainers[29] and physiotherapists[30] with respective response rates of 30% to 72%. One report estimated that cryotherapy accounted for a larger number of complications than heat, electrical stimulation and therapeutic exercise.[29] The severity of these events varied but included skin burns, frostbite, intolerance or allergy. A smaller survey of private practitioners estimated that on average one physiotherapist observed a cold related adverse incident every 5 years.[30]

In conjunction, we found a number of case reports of adverse events associated with cryotherapy; the most common was skin burn/damage,[30-36] with others reporting nerve damage,[37,38] cold urticaria[39] and a compartment syndrome.[40] It is difficult to determine definitive risk factors for such adverse events based on case study evidence. Notwithstanding this, there were a number of common clinical circumstances across reports which merit further investigation. Perhaps the most frequent trend was that cryotherapy was usually applied continuously or for prolonged periods,[33-35,38] and there was one report of a patient falling asleep during treatment.[32] Another common event was patients' compressing the cooling modality between their lower leg and a table; indeed this resulted in severe skin damage or nerve palsy with short application times of 20-30 minutes.[30,31,37] In conjunction with previous reports, both incidences of nerve palsy occurred after cooling around a superficial nerve eg. common peroneal[37] or around foot and ankle.[38] In both cases symptoms were still present for between 6 and 12 months. One survey noted that cold allergy was the most commonly observed adverse event associated with cryotherapy.[29] We found just one report of a cold allergy which occurred during an experimental study;[39] this was consistent with cold urticaria (wheal formation and skin discolouration), but symptoms had fully resolved within 48 hours.

Cooling was applied directly to the skin in three cases,[31,37,38] and two [33,34] did not specify if a barrier was used at the cooling interface. Previous surveys highlight that in clinical practice it is common to use a barrier between the cooling surface and the skin.[1] Much of the rationale is to minimise the risk of adverse effects, and in particular, preventing excessive tissue cooling. Dry or thick dressings are associated with excessive skin insulation, and can limit skin temperatures to just 27°C[41] even after applications of up to one hour. In contrast, damp barriers may do little to affect cooling efficiency when compared to direct application onto the skin.[42,43] We have previously discussed that optimal skin temperature reductions can be achieved if our primary objective is to achieve analgesia. Furthermore, there is considerable evidence that shorter applications times are sufficient. We must also consider that skin burns result from excessive cooling; cell death can occur at a threshold of around minus 10°C.44 Based on Chapter 2[45] such excessive tissue temperatures seem unlikely with crushed ice, particularly in cases where it is melting during treatment and the skin/cooling interface remains at a constant temperature of around 0°C. Perhaps the mechanism for producing excessively skin temperature reductions relate to concomitant mechanical compression and reduction in superficial blood flow. Pragmatically this is also more likely with prolonged or uncontrolled treatment durations, or in circumstances of patient or practitioner error.

Note: Evidence from questionnaires and case studies confirm that cold therapy does have the capacity to do harm. In most cases this was short term and a full recovery was made; there were isolated cases of permanent scarring and loss of function. There are few reports of adverse events within lab based and clinical studies. The risk of inducing adverse events is low, if clear instructions for practical application are provided and evidence based rationale considered.

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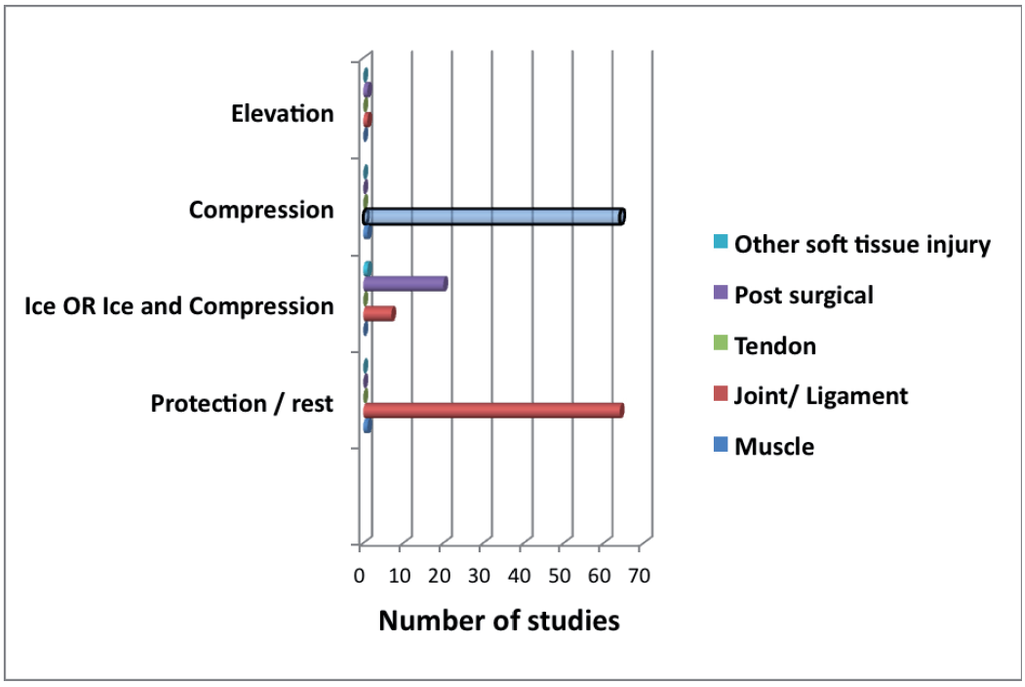
Figure 1

Summary of the evidence base by primary intervention and injury type



NOTE: In some cases external supports/bandaging could have been used for dual purpose (protection/ rest and compression) this depicted by the translucent compression bar; this figure includes the individual studies within eligible SR

Figure 2
Characteristics of included

Study	Inclusion criteria	Intervention	Results (follow up)
ANKLE SPRAIN			
Pijnenburg, 2000 SR (1966-1998)	N=27 RCT -Injury: Acute ruptures of ankle (in most trials an arthrogram or stress radiographs or both were used) -Excluded: Recurrent ankle injury; chronic instability; follow up <60% or unclear or follow up exclusively with questionnaire -Stats: Relative risks, data pooling with random effects modelling -Follow up: 6/12 - 3.8 y	F vs CAST F vs Min / no Rx (eg. elastic bandage; note 3/52 in cast immobilisation was defined as functional)	**-Time lost from work:** F < CAST (15 days; range: 12-18 vs 38 days; range: 28-48) [n=10 RCT] **-Residual pain:** F<CAST (6/52*) (RR: 0.67 CI: 0.5 to 0.9) [n=10 RCT]; F< min/no Rx (6/52*) (RR: 0.53 CI: 0.27 to 1.02) [n=3 RCT] **-Giving way:** F<CAST (6/52*) (RR: 0.69 CI: 0.5 to 0.94) [n=10 RCT]; F< min/no Rx (6/52*) (RR: 0.34 CI: 0.17 to 0.71) [n=3 RCT] **-SUBGROUP ANALYSIS:** No differences based on 'high quality' studies (n=5 RCT)
Kerkhoffs, 2002a SR (up to-2002) (Includes Karlsson 1996)	N=9 RCT -Injury: Acute injury to lateral ankle ligaments (diagnosed by physical examination, stress radiograph or arthrogram)	F vs F (F= early mobilisation with any of the following: Elast, Semi-R; Tape; Lace up)	**- Return to work:** Semi-R>Elast; (RR 4.3; CI 2.4-6) [n=2 RCT] **-Time to return to work:** Semi rigid<Elast (WMD 9.6 days; CI: 6.3-12.9) [n=1 RCT] **-Giving way:** Semi-R<Elast (RR 8; CI: 1.03-62) [n=1 RCT] **-Swelling:** Lace up<Elast (short term*) (RR 5.5; CI: 1.7-17.8)[n=1 RCT]; Lace up<Tape (RR 4.07; CI: 1.2-13.7) [n=2 RCT]; Lace up<Semi-R (RR 4.19; CI: 1.26-13.98) [n=1 RCT] **-All outcomes:** Tape =semi rigid [n=2 RCT]; Elast=tape Note: higher levels of complications with tape
Kerkhoffs, 2002b SR (up to -2000)	N=21 RCT / quasi RCT -Injury: Acute injury to lateral ankle ligaments (diagnosed by physical examination, stress radiograph or arthrogram)	Immob vs functional Mean validity score: 9.1 – 10 / 18	**-Number returning to sports: F >Immob** (RR 1.86; CI: 1.2 - 1.9) [n=5 RCT] **-Days to return to sport** F<IMM (WMD: 4.8 days (95% CI: 1.5-8.3) [n=3RCT] **-Time to return to work** F<IMM (WMD: 8 days (95% CI 6.3-10.1) **-Swelling (short term):** F<IMM (RR: 1.7; CI 1.17-2.59) [n=3 RCT] **-Patient satisfaction:** F>IMM (RR 1.8; CI 1.09-3.07) [n=6 RCT] **No significant differences in:** Pain, giving way (subjective instability), recurrent sprain, swelling **-SUBGROUP ANALYSIS:** Based on 'high quality' studies (n=11 RCT), differences noted for return to work only

Study	Inclusion criteria	Intervention	Results (follow up)
Jones, 2007 SR (up to December 2005)	N=9 RCT -Injury: Ankle sprains Exclusion: <80% patients available for follow up, non randomised -Stats: Relative risk, data pooling Follow up: 3/12 – 3.8 y	Immobilisation vs some form of early functional treatment (early motion, bandage, tape, brace, airstirrup, aircast, wrap and airstirrup)	**-% return to work** (RR: 1.06; CI 0.98-1.150) [n=414 patients] **-Days to return to work/sport:** F<Immob [4/5 RCT] -Patient satisfaction: Immob>F [n=2] (RR 0.6 CI 0.3-1.2) [n=598 patients] **-C/o Subjective instability:** F<Immob [3/5 RCT], (RR; 1.01 CI 0.72-1.42) [n=414 patients] **-Re-injury rate:** F<Immob [5/6 RCT], (RR 0.81 CI 0.58-1.12) Note: Pooled data was not significant for any outcome, however aside from patient satisfaction, there were trends in favour of functional Rx
Lamb, 2009 RCT	N=584 -Injury: Severe ankle sprain (unable to WB at least 3/7 after injury -Excluded: >7days since injury, <16 yrs, fractures (not including flake fractures), contraindication to immobilisation,	-ELAST (DTG) - CAST -Semi-R (Aircast) -Semi-R (Bledsoe) All groups: elevated and immobilised in tubular compression for 2-3 days; and 10 days, crutches, advise on elevation, and pain relieving medications	**-FAOS** (subscales function, pain, symptoms, and activity): CAST > Tubi (1/12*; 3/12*); Aircast >tubi (3/12* – for function subscale only) **-SF12:** CAST>Tubi (3/12*); Aircast > Tubi (4/12*) **FAOS, SF, Functional limitation profile:** Tubi=CAST=Aircast=Bledsoe (9/12) Note: At 3/12, subjective function was 8-9% higher with CAST or Semi rigid support compared with DTG
Beynnon, 2006 RCT	N=172 -Injury: First time ankle ligament injury <72 hrs (Stratified by Grade 1,2 and 3 (Bergfield, 1986) -Excluded: Previous sprain, previous abnormal gait, fracture current or within previous 12 months, syndesmosis injury, burns laceration, 16 yr, pregnant, chronic illnesses	-Elastic wrap (G1 and 2) -Air-stirrup (all grades) -Air-stirrup and elastic wrap (Grade 1 and 2) -CAST (with WB) (Grade 2 and 3) All groups: Week 1: Crutches as needed, ice, elevation, mobility, and non impact C/V, progressing to Stage 2: contrast therapy, progressive dynamic exs, strength, and finally Stage 3: agility, sports specific drills.	**-Time to normal walking (days / subjective)** Grade 1: Elast and Air < Elast=Air* Grade 2: Elast and Air =Elast=Air < CAST* Grade 3: CAST=Air **-Time to normal stair climbing** Grade 1: Elast and Air < Elast=Air* Grade 2 : Elast and Air =Elast=Air < CAST* Grade 3: Air<CAST (not sig) **-Time to full athletic / recreational activity** Grade 1: Elast and Air < Elast* Grade 2:Elastic=Air and Elast < CAST* Grade 3: CAST=Air **Function (Karlsson), re-injury, jump, toe raise, ROM** No differences between groups (6/12)

Study	Inclusion criteria	Intervention	Results (follow up)
Bleakley, 2006 RCT	N=89 -Injury: Grade 1 and 2 ankle sprain, 50% sporting population -Excluded: Grade 3, >72 hours	-I : Standard (20 min, x 3 per day) -I: Intermittent (10 min on, 10 min off, 10 min on, x 3 per day) All groups: standardised rehab and mode of I	**-Pain** Intermittent<Standard (1 week*) Intermittent=standard (1-4/52) **-Function** Intermittent=standard (1-4/52) **-Swelling** Intermittent=standard (1-4/52)
Boyce, 2005 RCT	N=50 -Injury: Mean 3-4 hr old ankle sprain (moderate/severe), 38% sports related -Excluded: <16 y, fracture	-Elastic -Semi-R (Aircast) All groups: standardised advise sheet on RICE	**-Function (modified Karlsson)** Semi-R>Elastic (10/7*; 1/12*) **-Pain, swelling** No differences (10/7, 1/12)
Watts, 2001 RCT	N=400 (197) -Injury: Grade 1 and 2 ankle sprains, 24 hrs -Excluded: <16 yrs, mental illness, bony injury, multiple injury, >24 hrs, no telephone, patients whom the treating physician felt would benefit from cast immobilisation N=73	-DTG -No DTG All groups: Advice sheet on exercises and analgesia	**-Analgesic consumption** No DTG<DTG (7/7*) **-Pain (sleep disturbance), mobility, return to work** No differences(7/7) Note: 24% more patients took painkillers during the first week when using DTF
Leanderson, 1999 RCT	-Injury: Grade 2 / 3 ankle sprains (Gordon, 1968)(<24 hrs) N=30	-Compression bandage -Semi-R (Aircast) All groups: early mobilisation and WB'ing, no physiotherapy	**-Time of figure of 8 run** Semi-R<Bandage (10/52*) **Clinical exam, JPS, Isokinetic strength** No differences: Bandage v sSemi-R (1,3,5/7; 2,4,10/52)
Guskiewicz, 1999 RCT	-Injury: Grade 1 or 2 ankle sprain (clinical exam), <24 hrs post injury	-Rigid support (in built focal compression) -Semi-R (Aircast: alternating compression pressures) - Elastic bandage (with felt horseshoe) All groups: standardised rehab from day 1. Crutches, rehab, cryo, abstinence from NSAID's. Progressed according to functional level attained.	**-Pain, swelling (volumetric analysis), function** No differences between groups (day 1,2,3,5,7)

Study	Inclusion criteria	Intervention	Results (follow up)
Samoto, 2007 CT	N=55 injuries (54 participants) (grouped by injury severity) -Injury: Acute lateral ankle ligament injury; diagnosis by clinical assessment, stress X-Ray, and arthrography (mean 3.5 days post injury)	-Isolated ATFL injury -Combined ATFL and CFL injury Both groups: 1 week IMM with WB, followed by 1 week in functional brace with WB and physical therapy, jogging permitted after 6 weeks, return to sport after 10 weeks	**-Function/Pain/Alignment (AOFAS)** ATFL>combined (month 6*, 1 year*, final* (mean 5 years) **-Joint laxity** ATFL>combined (month 6*, 1 year*, final* (mean 5 years)
Nyska, 1999 CT	N=36 -Injury: Acute Grade 3 ankle sprains	-CAST and WB'ing: 3 weeks in short leg walking cast -Semi-R and WB'ing: 3 weeks early walking, aircast external support All groups: WB'ing as soon as pain allowed	**-Walking ability** Semi>CAST (week 3*) Semi=CAST (day 3, month 6) **-Function / Return to work** Semi>Immob (week 3*) Semi=CAST (day 3, month 6) **-Clinical assessment (swelling, ROM, balance, tenderness)** Semi<CAST (week 3*) Semi=CAST (day 3, month 6) Physiotherapy sought Semi<CAST (month 6*)
Glasoe, 1999 Case study	N=1 female athlete, aged 17y -Injury: L ankle inversion injury, grade 2 based on clinical assessment, no history of previous sprain	Immediate care: I/C immediately after injury, 20 min every 2 hours, NWB'ing Up to 1 week: Immobilised in boot with WB'ing (1 week), active ROM, IC post exercise 1 week onwards: resistive exercise, bracing, progressive rehab	Participation in sport 2 weeks post injury, limited clinical problems (4 weeks), no re-injury at approximately 1 year follow up.
GENERAL SOFT TISSUE INJURY			
Airaksinen, 2003 RCT	N=74 -Injury: sports related soft tissue injury	-cold gel -placebo get All groups: 4 times/day for 14 days	**-Pain** Cold<P (week 1*, 2*, 4*) **-Function (disability)** Cold<P (week 1*, 2*, 4*) **-Patient satisfaction** Cold>P (week 4*)

Study	Inclusion criteria	Intervention	Results (follow up)
Tsang, 2003 RCT	N=12 -Injury: Inversion ankle sprain, 2-4 days old	-Elevation (vertical) -Elevation and intermittent compression (max inflation to diastolic BP, 45s inflation;15s deflation) All groups: 30 minutes Rx	**-Change in ankle volume between pre and post (volumetric analysis)** Both groups ankle volume decreased after Rx; E > E and C (immediate), No significant difference between groups 5 minutes post Rx, volume returned to baseline levels in both groups Note: 10 mL greater decreases in volume with E alone
SHOULDER DISLOCATION			
Hovellius, 08 OB	N=257 shoulders -Injury: primary shoulder dislocation (verified radiologically), reduction performed/verified by an experienced surgeon	-Immobilisation (sling 21 days – 28 weeks) -Partial immobilisation (sling until patient was comfortable) (n=37 for <5/7, n=50 for 7/7, n=16 for 2/52, n=1 for 3/52) Protocol violators were analysed in a separate group (n=41)	**-Re-injury** Sub-grouped into age at time of dislocation (yrs) and analysed Treatment group was not a factor in the risk of re-dislocation at 25 y follow up
ELBOW DISLOCATION			
Ross, 1999 Case series	N=20 (age: 18-24 y) -injury: closed posterior elbow dislocation -excluded: fracture (aside from small avulsion fracture), non posterior dislocation, spontaneous reduction	-Reduction within 1hr post injury, next day active ROM exs under supervision, progressing to strengthening, supplemental treatments: E-stim, cryotherapy, compression	**-Mean final elbow ROM** 4 deg through to 139 deg **-Time to final ROM** 19 days **-Final extension within 5 deg of un-injured side** All patients **-Re-dislocation (1 y follow up)** 1/20
MUSCLE INJURY			
Thorsson, 97 CT	N=40 athletes with contusion or distension injuries (thigh or calf)	-C (30 minutes of compression bandage on maximum stretch = 40-80mmHg, within 5 minutes of injury. Moderate compression (40mmHg) after 30 minutes, rest and elevation -Rest and elevation (in some cases, non maximal compression after 10-30 minutes)	**-ROM, Serum CK, Ultrasonography (echostructure normal Y/N, type), Time to subjective recovery, isometric strength:** No significant difference between groups Note: Maximum compression group reached full subjective recovery approximately 5/7 faster than control
Aronen, 06 Case Series	N=47 (mean age 19.2; range 18-22 yrs) -Injury: quadriceps contusion during sport, unable to continue sport, unable to perform SLR	-Knee braced in 120 deg flex continuously for 24 hrs, crutch walking, followed by pain-free stretching and isometrics. Thigh padding for remainder of athletic season.	**-Time to full active flexion** All subjects: 72 hrs **-Time to unrestricted activities** 3.5 days (range: 2-5 days) **-Myositis ossificans (X-Ray)** 1/46

Study	Inclusion criteria	Intervention	Results (follow up)
SURGICAL			
Bleakley, 2003; 2007 SR (up to April 2005)	N=24 RCT/CT -Injury: acute STI, recovery post orthopaedic surgical procedure, pain, swelling, function, ROM -Inclusion: English language Stats: Effect sizes, no data pooling Follow up: 1/7 to 1/12	I vs H, contrast, E-stim, No Rx, placebo I and ex vs ex alone I/C vs I I/C vs C	**-Swelling** I<H=C (day 5*) [n=1] **-Pain** I ex < ex alone (week 1*) [n=1] I/C <C (week 1*) [n=2] I<placebo (week 1*) [n=1] **All outcomes** I/C=C [n=6] I/C=no intervention [n=4] Note: Few definitive conclusions due to heterogeneous data, wide variations in intervention mode dosage, treatment comparison
Raynor, 2005 SR (up to November 2002)	N=7 RCT -Injury: recovery post ACL Inclusion: srthroscopically assisted ACL reconstruction treated post operatively with cold therapy, comparison to no cold therapy or room temperature device Stats: effect size estimates and data pooling using random effects modelling Follow up: Short term	I vs No I (control) I vs Room temperature (compression)	**-Pain** I<placebo* [n=6 RCT] **-Post operative drainage** I=control / room temperature [n=4 RCT] **-ROM** I=control / room temperature [n=4 RCT]
Fagan, 2004 RCT	N=43 -Injury: recovery post carpal tunnel decompression -Excluded: Revision surgery, concurrent disease, post traumatic CTS, unable to use sling or understand its use	-E (high sling, above heart, 45 deg – full elevation) -E (simple sling, shoulder neutral, elbow at 90 deg)	**-Swelling (volumetric analysis)** Both groups increased post surgery E (high) = E(simple) (day 5) Note: 11-13mL increase in volume over 5/7 post surgery
Holmstrom, 2005 RCT	N=60 -Injury: recovery post Unicondylar knee arthroscopy	-I/C (cryocuff, gauze barrier, automated cooling device, 48 hrs) -EDA (2.5-5 mg/mL bupivacaine) -Analgesics and standardised rehabilitation only (as below) All groups: paracetamol, supplementary morphine when required, standardised rehabilitation	**Morphine consumption** EDA=I/C<Control (day 1*) **Pain, bleeding, swelling, ROM, function** No differences between groups (day 1-7, six weeks)

Study	Inclusion criteria	Intervention	Results (follow up)
Smith, 2002 RCT	N=84 -Injury: recovery post unilateral TKR	-C (Robert Jones for 24 hrs, followed by ice bags in linen towel for 24-48 hrs) -I (Robert Jones for 6 hrs; cryopad technology for 18 hrs; followed by ice bags in linen towel for 24-48 hrs)	**Length of hospital stay, blood loss, swelling, ROM (flexion), pain** C=I
Morsi, 2002	N=60 (30 patients bilateral) -Injury: Bilateral TKR, 6 weeks between surgery	-I/C (continuous cold flow cooling device, immediately post op, over post surgical dressing, C from crepe bandage, skin temperature maintained at 2°C for first 2 h post surgery, then 12°C continuously for 6 days) -C (crepe bandage)	**Pain** -VAS:I<C (mean over day 1-6*) -Analgesic consumption: I<C (mean over day1-6*) **ROM** I>C (week 1*,2*) I=C (week 6) **Swelling/Blood loss** I<C (day 6*)

Y: years; F: Functional treatment; Rx: treatment; TKR: Total knee replacement; CAST: Cast immobilisation; Elast: Elastic bandaging; Semi-R: Semi Rigid support; WB: weight-bearing ; C/V: Cardiovascular training; Ex: exercise; Sx: Subjective; I: Ice; H: Heat; E-Stim: Electrical Stimulation; FAOS: Foot and ankle score; AOFAS: American orthopaedic and foot society; SF-12: Short form 12 (mental and quality of life scoring scale); FLP: Functional limitation profile (UK version of the Sickness Impact Profile); DTG: Double tubigrip; Bergfeld J, Cox J, Drez D et al. Symposium: management of acute ankle sprains. Contemp Orthop 1986;13:83-116. ; Gordon BL (1968). Standard nomenclature of athletic injuries. American Association of Orthopaedic Surgeons, Chicago, pg. 7.

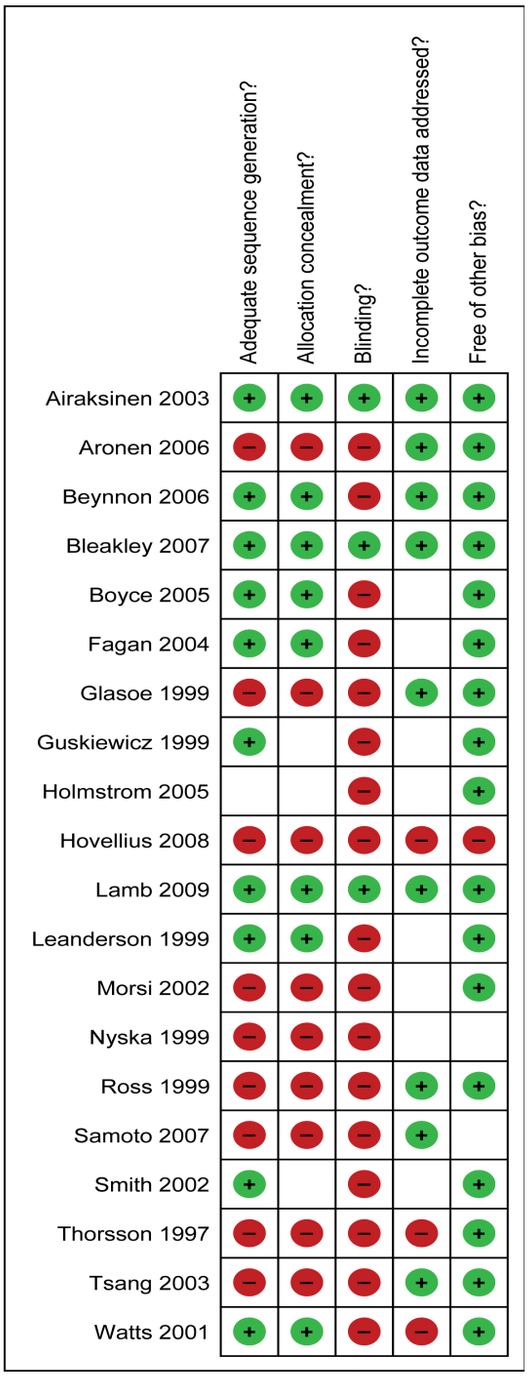
Figure 3
Review authors' judgements on AMSTAR criterion item for each included SR

	AMSTAR CRITERION										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Pijnenburg, 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	•	Y
Kerkhoffs, 2002a	Y	Y	Y	Y	Y	Y	Y	Y	Y	•	Y
Kerkhoffs, 2002b	Y	Y	Y	Y	Y	Y	Y	Y	Y	•	Y
Jones, 2007	Y	Y	Y	•	Y	Y	Y	Y	•	•	•
Bleakley 2003, 2007	Y	Y	Y	•	•	Y	Y	Y	•	•	•
Raynor, 2005	Y	Y	Y	Y	•	Y	Y	•	Y	•	•

Y: AMSTAR criterions fulfilled; • : AMSTAR criterion not fulfilled[3]

Figure 4

Risk of bias summary: review authors' judgements about each risk of bias item[2] for each included clinical study



Details of Cochrane risk of bias tool2 provided in Appendix Table 10

Figure 5
Characteristics of studies

SKIN BURN			
Study	**Subject / inclusion criteria**	**Details of intervention**	**Details of adverse outcomes**
Selfe, 2007 (case report)	N=1 healthy male, aged 43 years, recruited into a research study	Lab based experiment Mode: Commercial gel pack (Surface of gel pack = -17°C at start of treatment) Barrier: None Duration: 20 min	Blanched skin over patella with a surrounding zone of erythema immediately after pack removal. Area became red and hot over next 3 hours, with discomfort in bed later that night. Skin colour and sensation returned to normal the next day, no long term problems.
Lee, 2007 (case report)	N=1 male post bilateral patellar tendon repair	3 days post operative cryotherapy, 2 weeks of home cryotherapy Mode: Cooling pad (water and ice circulated through the cooling pad) Barrier: Dressing and paper towel interface Duration: continuous?	-At 2 weeks noted skin changes -Admitted for debridement and dressing (two occasions), final treatment involved further debridement and rectus abdominus microvascular transplants on both knees.
Maquire, 2006 (case series) (data extracted from abstract only)	N=4 cases of frostbite during post operative care	Mode: Cold cuff device Barrier? Duration?	-Frostbite at top of patella. -Speculation that the area of frostbite in all four cases corresponded with an area of the cooling cuff that was modified for care ACL surgery, of note, none of the cases had ACL surgery.
Cuthill, 2006 (case study)	N=1 female with soft tissue injury to left gastrocnemius	Mode: Commercial cold pack, leg resting on chair, with cold pack between. Barrier: dishcloth Duration: approximately 30 minutes,	-On removal of pack, a large hard and dusky purple area noted with blanching of skin. -After 1 hr this became painful with erythema. -Next day calf was swollen with blistering (3% of body surface area) = superficial and deep partial thickness burns treated conservatively. -14 days off work, with full skin coverage taking 12 days.
Keskin, 2005 (case study)	N=1female with acute synovial arthritis at knee	Mode: Cold pack Barrier:Direct? Duration: approximately 2 hrs to knee	-Grade 2 and 3 frostbite on medial aspect of knee -Treated with minor debridement and daily dressings for 10 days. Full recovery reported.

Study	Subject / inclusion criteria	Details of intervention	Details of adverse outcomes
Graham, 2000 (Case study)	N=1 female age 42 yrs; 4 week history of vague discomfort in foot. Previous treatment was NSAID; and 3 days previously icing.	Mode: Bag of frozen chips, Barrier: Towel Duration: fell asleep, at least 40 minutes?	-Erythema on removal of chips, developing into to discolouration and pain the next day. -Paraesthesia of index and middle toes. -At three days there was 4 x 3 cm area of skin necrosis (third degree frostbite – deep dermal layer) on the dorsum of the foot, surrounded by erythema and blistering. -Debridement under anaesthetic, and treatment with a split thickness skin graft, with wound healing satisfactorily. -Destruction of the superficial and deep peroneal nerves to 2 and 3rd toes.
O'Toole, 1999 (Case study)	N=1 female aged 59 yrs, calf strain	Mode: ice pack placed between a foot stool and the patients elevated leg Barrier: direct application Duration: 20 minutes.	-Over 24 hrs large blistered area developed. -Presented to casualty 4 days later, where a diagnosis of a superficial partial thickness burn (1% of body) was made. -Treated conservatively, with healing after 10 days.
NERVE DAMAGE			
Hoiness, 1998 (Case study)	N=1 female; 59 yrs; closed dislocated bimalleolar fracture left ankle ; clinical trial, use of continusous cryocompression for preoperative swelling	Mode: Cryocuff with elevation and immobilisation Barrier: directly to the skin, removed once per day to check skin Duration: Continuous cryocompression for 5-7 days before surgery.	-On the 6th day pre surery, patient c/o coldness and numbness on foot. -On assessment the foot was cold anaesthetic and glassy looking, with reduced microcirculation. -No sign of thromboembolism, and doral pedis and posterior tibial blood flow were normal on Doppler. -Blistering and epidermolysis developed in next few days. -Patient underwent surgery – external fixation for bony injury. -6 months: Clawing of toes and marked dystrophy of the foot, with discoloration and slight hyperaemia of the skin. Dorsal skin on foot was anaesthetic. Neurograph showing damage to all major nerves in the foot. Severe stiffness of T/C joint, and subchondral fracture of talus.
Moeller, 1997 (Case study)	N=1 with hamstring soreness; aged: 22 yrs	Mode: Ice pack compressed between table and distal hamstring. Barrier: direct to skin Duration: 20 minutes	-Unable to move foot after removal of ice pack -Grade 3 muscle activity (dorsiflexion, toe extension and eversion), and deep tendon reflexes were 1 / 4 at Achilles and 2 / 4 at knee after 24hrs and numbness over the anterolateral aspect of the left leg. -Symptoms persisted for 1 week. Nerve conduction studies at common peroneal nerve found axonotmesis with 50-70% axonal loss compared to the opposite leg. -Minimal strength improvements at 4 months. -Full recovery noted at 12 months.

Study	Subject / inclusion criteria	Details of intervention	Details of adverse outcomes
COMPARTMENT SYNDROME			
Khajavi, 2004 (Case study)	N=1 male aged 35 years; Osteoarticular transfer system (OATS) surgery knee; discharged with cryotherapy instructions	Mode: Electronic cooling pad, 33F, Barrier: Dressing between cooling unit and skin, aside from at day 4 (direct contact at posteriomedial calf). Duration: continuous, refilled with ice every 3 hrs, and once during the night.	Day 5 post operatively pain was noted in the calf, mild to moderate calf swelling, and large degree of erythema on posteromedial calf. -No evidence of DVT on ultrasound examination. High compartment pressures of 53mmHg in anterior and lateral compartments of leg, and 37mmHg and 20 mmHg in superficial and deep posterior compartments respectively. -Emergency fasciotomy performed, no muscle debridement necessary initially (small portion of muscle debrided in superficial compartment 2 days later). -Full recovery at 33 month follow up. -Full recovery noted at 12 months.
ALLERGY			
Dover, 2004 (case study)	N=1 male college student, 19 yr; 9.7 % body fat; participating in a research study Had previously used ice for a knee injury in the past	Mode: 1 kg ice to shoulder, air removed secured with an elastic bandage Barrier: direct? Duration: 30 minute duration	-After 10 minutes of icing: subjective complaint of headache, feeling woozy, dehydrated. -Skin temperature did not attenuate as per other subjects with in the study. -Lowest temperature reported was 23.4C, in comparison to 12C in other subjects. -Unusually skin temperature began to increase after 10 minutes of treatment (total increase of 4.2C) -After removal of the ice pack (30 minutes): wheal formation and discoloration around the shoulder consistent with cold urticaria. Similar to previous reaction at knee after icing. -Resolved within 48 hrs.
QUESTIONNAIRE			
Cuthill, 2006 (questionnaire)	N=111 physiotherapists in Scotland (private practice)	72 % response rate	% of therapists with experience of witnessing cold induced injury 49%: 0 injuries 20%: 1 injury 23%: 1-5 injuries 9%: 5-10 injuries Total years of practice from physiotherapists responding to questionnaires = 725 yrs Incidence rate of cold induced injury estimated at 1 per physiotherapist every 5 yrs.

Study	Subject / inclusion criteria	Details of intervention	Details of adverse outcomes
QUESTIONNAIRE			
Nadler, 2003 (Questionnaire)	N=3012 certified athletic trainers	Descriptive questionnaire on the frequency and types of complications associated with therapeutic modalities No details on the circumstances of the complications eg. duration, mode etc.	-30% response rate: of which 26% reported a complication. -Cryotherapy accounted for the highest percentage of complications (43%) -Other types of modalities listed were heat, electrical stimulation, therapeutic exercise and other N=86 allergy N=16 pain or intolerance N= 23 burn N=6 frostbite N=2 Raynauds N=11 skin rash N=3 Diaphoresis N=1 unspecified
Wilke, 2003 (Questionnaire)	110 podiatrists	Survey on the use of continuous cold flow units, and the incidences of complications	-29 responses -More than half used continuous cold flow units. -No serious complications noted with ice bags, several minor complications noted with ice bags and continuous flow units -5 serious complications noted with continuous flow units: (Erythema and blistering – avascular necrosis of talus; cyanotic forefoot – full recovery; erythema, oedema – full recovery; cyanotic forth toe – amputation 4th toe; cyanotic forefoot – amputation of 4th and 5th digits)

Executive Summary:
Methods, Clinical Recommendations and Implications

Background

Soft tissue injury is a common problem in sport, recreational and physical activities. The quality of acute stage management of a soft tissue injury is thought to be an important determinant for short and long term recovery. In the early stages, soft tissue injuries are characterised by an acute inflammatory response. This is manifested clinically by the presence of pain, redness, swelling and loss of function. Traditionally, the clinical management of soft tissue injury has placed most emphasis on minimising or controlling acute inflammation. Protection, Rest, Ice, Compression and Elevation (PRICE) remains one of the most popular approaches for the management of acute injuries and in particular the control of inflammation. Some or all components of PRICE continue to be combined, based on the type or severity of soft tissue injury.

Original ACPSM guidelines

Soft tissue injury is a common problem in sport, recreational and physical activities. The quality of acute stage management of a soft tissue injury is thought to be an important determinant for short and long term recovery. In the early stages, soft tissue injuries are characterised by an acute inflammatory response. This is manifested clinically by the presence of pain, redness, swelling and loss of function. Traditionally, the clinical management of soft tissue injury has placed most emphasis on minimising or controlling acute inflammation. Protection, Rest, Ice, Compression and Elevation (PRICE) remains one of the most popular approaches for the management of acute injuries and in particular the control of inflammation. Some or all components of PRICE continue to be combined, based on the type or severity of soft tissue injury.

Aim

Our aim was to review the pathophysiological rationale and clinical effectiveness for using PRICE in acute soft tissue injury management, and produce clinical guidelines for its use.

Methods

In January 2009, ACPSM members from a range of disciplines volunteered to form a working group responsible for guideline development. The guideline development process followed the ´Grading of Recommendations, Assessment, Development, and Evaluation´ (GRADE) approach.[2] The following milestones were made and addressed in order: 1) develop specific clinical questions; 2) literature searching; 3) address importance of outcomes (critical; important but not critical, not important); 4) extract data/grade quality of evidence; 5) develop final recommendations.

Group consensus in January 2009 produced 5 clinical questions relating to using PRICE, or its individual components to treat acute soft tissue injury (Figure 1). Extensive literature searching (electronic, hand searching) was undertaken by at least two researchers, and was completed in October 2009. Evidence relevant to each clinical question was extracted, graded, summarised and reviewed by the working group, and external experts. Data from over 250 relevant studies were extracted and summarised.

Final guideline recommendations and relevant clinical implications were made by consensus discussion in September 2010. The strength of the recommendation (for or against the intervention) was graded as **strong** (definitely do); **weak** (probably do), or **uncertain** (indicating that the panel made no specific recommendation for or against interventions). Factors that influenced decisions on the strength of recommendations were: quality of evidence, balance between desirable and undesirable effects based on the values and preferences in terms of health outcome benefits, burden and expense.

Figure 1

Key for Figure 1

Clinically relevant questions:

1. What is the magnitude and depth of cooling associated with ice?
2. Can PRICE decrease the inflammatory response after acute soft tissue injury?
3. What effect does mechanical loading have on inflammation and soft tissue healing after acute injury?
4. Do the physiological effects of local tissue cooling affect function, sporting performance and injury risk?
5. Which components of PRICE are effective in the clinical management of acute soft tissue injury?

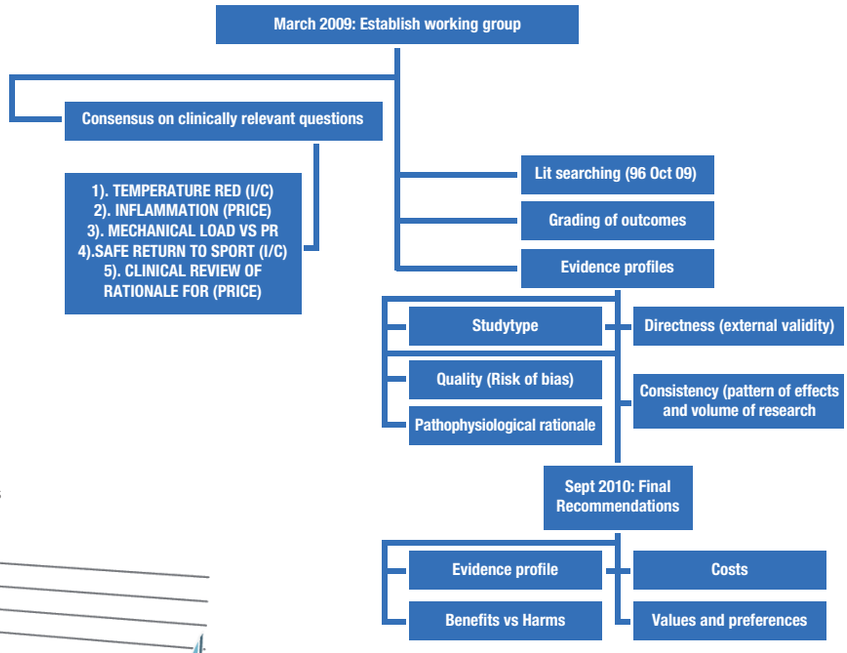
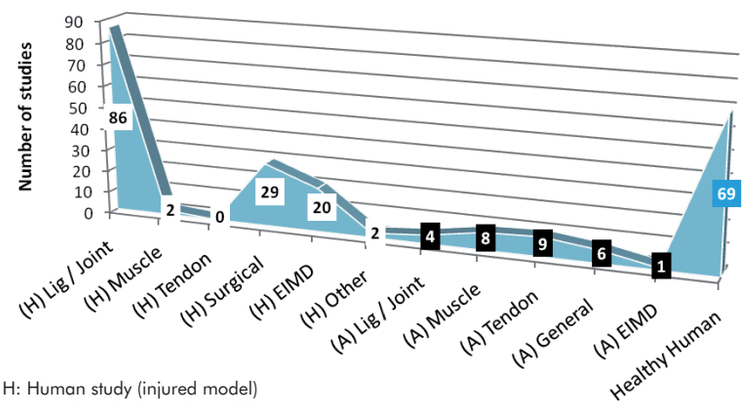


Figure 2

Overview of relevant studies used to inform panel consensus



H: Human study (injured model)
A: Animal study (injured model)
EIMD: exercise induced muscle damage

Summary of Evidence and Clinical Implications

Protection And Rest

Unloading injured tissue

The rationale for protection and rest after an acute soft tissue injury is to minimise bleeding, and prevent excessive distension or re-rupture at the injury site. Animal models confirm that periods of protection/rest (tissue unloading) are required in the acute stages after soft tissue injury and that aggressive ambulation or exercise should be avoided.[3] Previous guidelines suggested isometric exercise can be undertaken in the immediate stages after injury; [1] we found very low quality clinical evidence to support this.[4]

Loading injured tissue and stress induction

There is moderate quality clinical evidence that functional treatment, which incorporates early mobilisation and weight-bearing, is more effective than cast immobilisation after ankle sprain (particularly less severe sprains), for a range of important short term outcomes. There is a dearth of evidence in this area for other types of soft tissue injury. Evidence from basic science models concur that progressive mechanical loading (in comparison to immobilisation and/or unloading) in animals is more likely to restore the strength and morphological characteristics of collagenous tissue after injury.[3] The mechanism may be that mechanical loading upregulates gene expression for key proteins associated with tendon tissue healing.[3] It is not clear whether this is consistent for all other soft tissue, particularly in human models. Notwithstanding this, exercise or 'tissue loading' should perhaps be more formally recognised as an essential component of soft tissue injury management. Although functional exercise already plays a key role in rehabilitation, much of its rationale relates to maintenance of mobility and strength during recovery. We would suggest that progressive mechanical loading could also play an important role in tissue healing, and restoration of tissue morphology and biomechanics after injury. Developing evidence based guidance on the optimal timing, dosage and nature of initiating loading after injury is important, and we must ascertain whether this should vary according to the type of soft tissue affected (eg. muscle vs tendon vs ligament).

Clinical relevance

The optimal nature and duration of protection/rest is not clear and ultimately depends on injury severity. We would suggest that for the majority of soft tissue injuries, as a minimum, movements replicating the injuring force are avoided in the acute phases. There is potential that excessive protection/rest (tissue unloading) will do harm. Animal models confirm that 2-3 weeks of protection/rest result in adverse changes to tissue biomechanics and morphology.[3] This threshold may not be clinically applicable however, and the changes may be reversible.

Mechanical loading after injury may be reparative or damaging. Clinically, practitioners should be aware of the importance of making a safe transition from protection/rest to tissue loading after injury. Until further evidence is forthcoming, we would suggest that the transition should continue to be made carefully, within the limits of pain, with full consideration of the injury severity and nature of damage (tensile vs compression) and affected tissue (ligament vs muscle vs tendon). When applicable, therapeutic exercises should provide progressive loading on the injured structures, based on speed, range and number of repetitions.

ICE

The basic premise for cooling after injury is to extract heat from the body tissue to attain various clinical benefits. These include: limiting the extent of injury by decreasing tissue metabolism thereby reducing secondary cell death, providing analgesia, and facilitating rehabilitation.[5,6]

Cold induced analgesia

We found most evidence that ice can provide adequate pain relief after injury. There is moderate clinical evidence that cold therapy is effective at decreasing short term pain after acute ankle injury and general soft tissue contusion, and low quality clinical evidence that shorter intermittent applications are sufficient to induce short term analgesia.[4] Based on a post surgical model, there is high quality evidence that cold therapy provides effective short term analgesia.[4] These clinical findings are supported by basic scientific evidence; and we found numerous laboratory based studies confirming that skin temperature is reduced to less than 13°C after 5-15 minutes of cooling.[5] This is the currently accepted threshold for inducing effective local analgesia. Importantly, not all modes of cryotherapy cool equally or at the same rate.[5] We would suggest that in most clinical scenarios, crushed ice (ice cubes in a plastic bag) should be the mode of choice. Primarily, this is the most widely researched mode of cooling. Furthermore, it is assured that crushed ice (when melting) will be close to 0°C throughout treatment; in contrast the surface temperature of commercial gel packs is more difficult to estimate which risks ineffective cooling or extreme temperature gradients. Finally, crushed ice reaches threshold temperatures for analgesia faster than other modes of cooling.[5]

Ice and inflammation

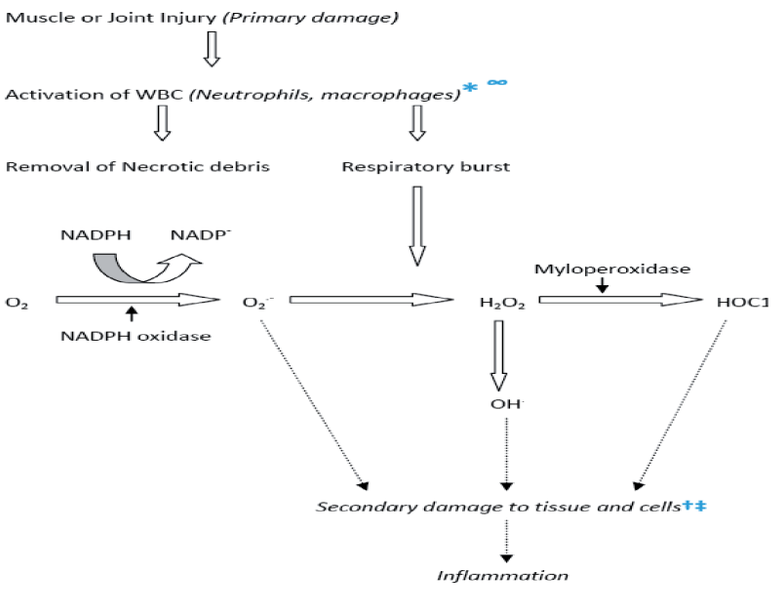
There is moderate clinical evidence that ice has little effect on other clinical outcomes including recovery time, function, and swelling (limb girth). There may be many reasons for this lack of effect. Primarily, the majority of studies in this area have used post surgical models; few have used closed soft tissue injury. We must also acknowledge that it can be difficult to induce clinically significant temperature reductions on deep muscle and joints after injury; and currently accepted threshold temperatures for reducing cellular metabolism (5°C-15°C) seem unattainable.[5] There is very low quality evidence from human studies that ice may reduce metabolism or aspects of the inflammatory response;[6] the effect that ice has on biomarkers of inflammation and muscle damage after EIMD in humans is inconsistent.[6]

There is evidence from animal models to suggest that ice can have a consistent effect on some important cellular and physiological events associated with inflammation after injury. This includes cell metabolism, white blood cell activity within the vasculature, and potentially apoptosis (all reduced[6]). The relative benefits of these effects have yet to be fully elucidated and it is difficult to contextualize within a human model. A key factor to consider is that large temperature reductions can be readily induced at the site of injury in an animal model.

Another important mechanism associated with cooling in the immediate stages after injury is the vasoconstrictive effect it may have on the vasculature. The original PRICE guidelines found consistent evidence that various modes of cooling decreased blood flow in human models. We found further evidence that cooling reduced blood flow in healthy human tissue, with no evidence of cold induced vasodilation.[6] Other cold induced effects included reduced oxygen saturation, and facilitated venous capillary outflow in healthy tendon models.[6] There is a dearth of related studies on injured humans; and the effect of ice on microcirculation in injured animal models is inconsistent.[6]

Figure 3

Summary of the effects of PRICE on white blood cell activation and secondary damage



*Animal model (n=3 studies) found cooling decreased % of adherent and rolling WBC's based on intravital microscopy; [4] animal models found lower levels of WBC's after cooling based on histological analysis of excised tissue, one found increased numbers of macrophages after cooling[6]

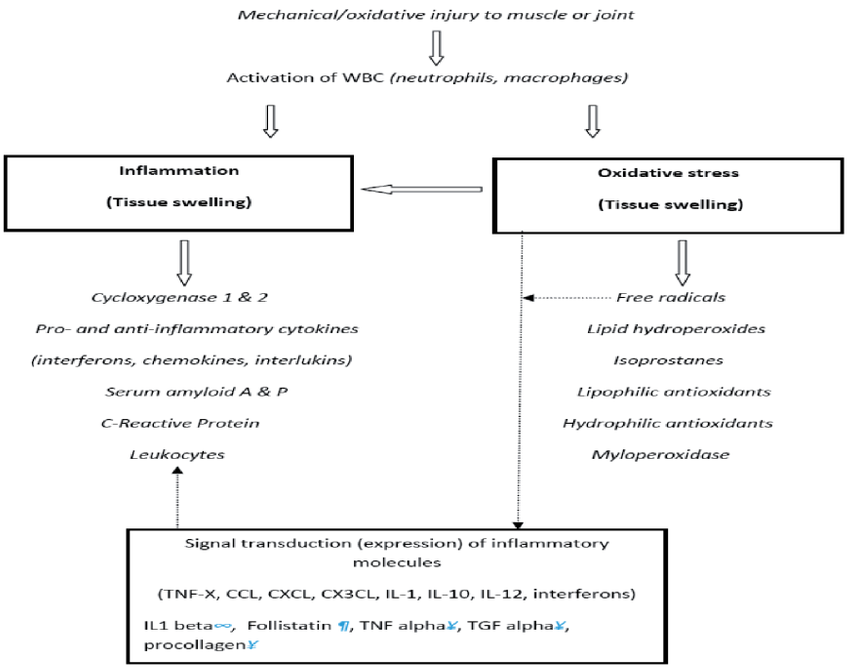
∞ Animal model (n=1 study) found immediate exercise increased neutrophils and macrophages (ED1+ and ED2+) based on histological analysis of excised tissue[3]

† Animal model (n=1 study) found cooling inhibited the loss of mitochondrial oxidative function[6]

‡ Animal model (n=1 study) found cooling decreased number of apoptotic muscle cells[6]

Figure 4

Summary of the effects of PRICE on biochemical markers of inflammation and oxidative stress



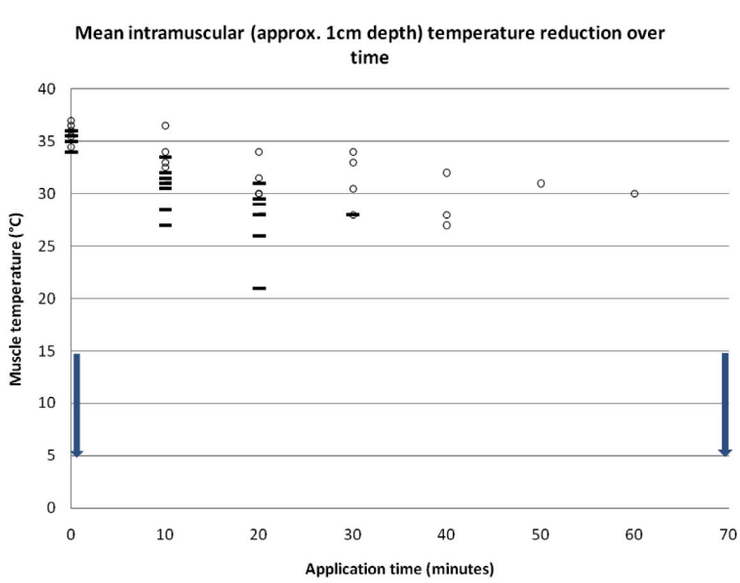
∞ Animal model (n=1 study) found immediate exercise increased neutrophils and macrophages (ED1+ and ED2+) based on histological analysis of excised tissue [3]
∞ Animal model (n=1 study) found that mechanical loading significantly increased expression compared to unloaded [3]
¥ Animal model (n=1 study) found trends that mechanical loading decreased expression compared to unloaded [3]
¶ Animal model (n=1 study) found trends that mechanical loading decreased expression compared to unloaded [3]

Targeting deep tissue injury

Based on basic scientific and clinical evidence, we would suggest that in some clinical scenarios, cold induced benefits may be limited to analgesia; particularly in situations associated with higher levels of body fat, deep soft tissue injury or when insulating barriers are necessitated (eg. post surgical models) at the cooling interface. We do however acknowledge that the current threshold temperatures for achieving analgesia (skin temperature of <13°C) or metabolic reduction (reduction to 5-15°C at the injury site) are not definitive and may be subject to change based on emerging understanding of the biochemical and physiological events surrounding acute injury and inflammation.[7] We can also not discount the clinical value of inducing modest deep temperature reductions, or using ice to prevent injured tissue from heating up above baseline levels.[5]

The previous guidelines[1] recommended applying ice every 2 hours during the acute phases. For certain injuries, it may be more effective to increase the cooling dose by decreasing the time between applications. This will maximise the potential to lower deep tissue temperature. However, we must consider that prolonged continuous ice applications risk side effects; potentially the safest balance is to apply more regular intermittent applications. Lab based evidence shows that short periods of ice pack removal allow skin temperatures to re-warm (thereby avoiding extreme skin or nerve temperature reductions), without re-warming deep tissue temperatures.[5]

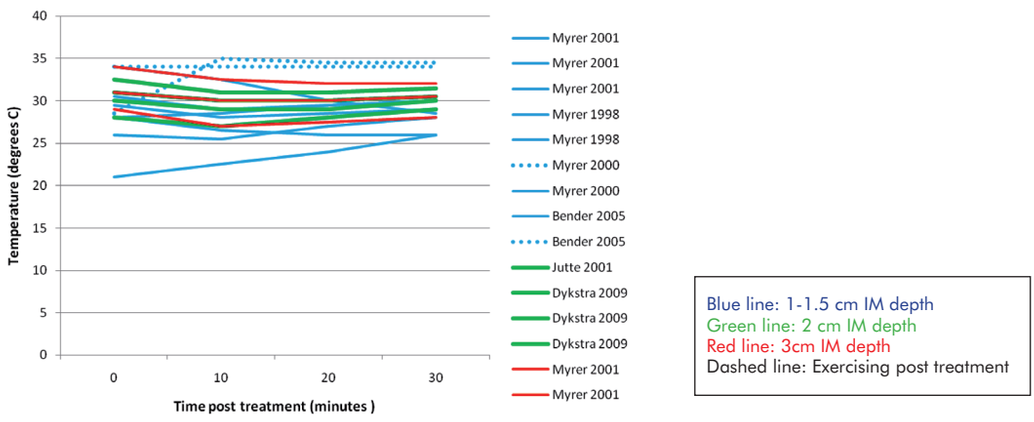
Figure 5



-Circles represent values from participants with 21-40mm skin-fold at the point of cryotherapy application
-Lines represent values from participants with <20 mm skin-fold at the point of cryotherapy application
-Arrows overlap the area representing potentially optimal INTRA-MUSCULAR temperature reduction of 5-15°C.
-All data is based on crushed ice, applied directly onto the skin surface [5]
-Three studies applied additional external compression [5]

Figure 6

Mean Re-warming rates in Muscle (Intramuscular depths 1-3cm)



Combining ice and exercise

Cryokinetics is a technique which uses ice to facilitate therapeutic exercise after injury. This practice may be gaining popularity within the UK, and was not fully discussed within the previous guidelines.[1] There remains a dearth of related clinical evidence for cryokinetics; however there are patterns from basic scientific reports which align well with its general concept. Both healthy and injured models show isolated joint cooling or short periods of muscle cooling can have an excitatory effect on muscle activation.[8] Certain soft tissue injuries are associated with varying degrees of muscle inhibition, and cooling may allow patients to access motor neurones that may be otherwise unattainable after injury. There is no evidence to suggest that cryokinetics is safe in the acute phases of injury. The risk is that cooling is erroneously used to extensively anaesthetise an injured area to facilitate aggressive rehabilitation. Most recommendations concur that cryokinetics is most appropriate after the acute phases. We would suggest that the exercises included in a cryokinetics treatment package should be relevant to the stage of tissue healing.

Pitch-side management and return to play

There are many occasions, particularly in sport when ice is applied prior to physical activity. Often this involves very brief applications during a break in play, where the cold sensation is used as a counter irritant for pain. This technique is usually effective, and is associated with minimal tissue cooling. Other scenarios involve longer duration icing (eg. half time, rolling substitutions or between events), and more significant levels of cooling can result prior to initiating or returning to sporting activity. It is important that clinicians consider the effect that this may have on local tissue physiology. We found a large number of studies relevant to this area (n=46); the corollary was that although cooling induced a number of changes to various physiological systems relevant to athletic performance, some of which were statistically significant, their clinical relevance was generally questionable.[8] However, we would suggest that longer periods of intense cooling (>10 minutes) may negatively influence some correlates of athletic performance (eg. vertical jump, sprinting speed), and consequently affect injury risk.[8] Cooling of the hands, feet, or other areas that typically have less body fat may be most at risk. The effect that cold has on other important correlates of functional performance such as precision and sporting performance per se is not clear. It is likely that any risks are negated with a progressive warm up prior to returning to activity.

Adverse effects

Based on evidence from case reports and questionnaires, it is clear that cold therapy does have the capacity to do harm. A small number of reports described isolated cases of permanent scarring on the skin and temporary and permanent loss of muscle function.[4] There are few reports of adverse events within laboratory controlled and clinical studies. We feel that the risk of inducing adverse events with cooling is low, provided contraindications are fully checked, and clear instructions for practical application and dosage are given.

Compression And Elevation

Acute injury and oedema

Healthy tissue maintains a dynamic balance of fluid movement between the vascular system and interstitial tissue space. Much of this resides in the fine interaction between hydrostatic and osmotic forces at the capillary bed. Acute soft tissue injury and the ensuing inflammatory response can affect hydrostatic and osmotic pressures, disrupting this balance. Around the injury site, changes in blood viscosity and flow tend to increase the hydrostatic pressure within the blood vessel; and macromolecules accumulate within the interstitial space reversing the osmotic gradient. The net effect is increased fluid movement from the blood vessel, into the surrounding interstitial space resulting in oedema formation.

Elevation

One of the primary reasons for using elevation or compression after injury is to try to restore the pressure gradients within the affected tissue. This is done through external mechanical pressure (compression) or gravity (elevation). The physics and physiology underpinning the rationale for elevation are perhaps more clear-cut. Elevating an acutely injured ankle decreases the gravitational force exerted on the column of blood between the heart and foot, thereby decreasing the hydrostatic pressure within the vasculature, minimising oedema and the resistance to venous and lymphatic flow around the injured tissue.

Despite clear rationale, the optimal duration or angle of elevation remains contentious. If our primary clinical goal is to limit tissue oedema and avoid the pain and discomfort relating to increased tissue pressures, it seems logical to elevate as much as possible, for as long as possible. Clinical evidence for elevation is poor however; we found one relevant post surgical model showing no effect.[4] Other models found foot and ankle volumes cannot be decreased for a prolonged period of time with elevation, as volumes quickly return to baseline on returning to sitting or standing.[4] This has been termed, the 'rebound effect'. Intermittent return to a gravity dependent position is inevitable in most body parts after injury, particularly at distal body segments (eg. ankles). Clinically, a graduated return to standing after elevation is perhaps most likely to minimise rebound swelling and discomfort. This is in accordance with the previous guidelines.[1]

Compression pressures

Despite a relatively large number of studies into the effectiveness of external supports and bandages, much of the evidence for compression is conflicting.[4] The exact physiological rationale has yet to be fully explicated, and there is little evidence for an optimal compressive force. The rationale for using high levels of compression pressure is to minimise initial tissue haemorrhage after injury. We found very low quality evidence that this approach is ineffective after muscle injury. This was based on one controlled study comparing immediate compression (bandaging) at 80mmHg, with rest/ice.[4] A related rationale for compressing is to prevent oedematous fluid from accumulating within the interstitial space. The external mechanical pressure is thought to increase the hydrostatic pressure of the interstitial fluid thereby forcing fluid from the injury site towards the capillary, lymph vessels, or tissue spaces away from the traumatised area. Smaller external forces may achieve this effect; many standard protocols recommend pressures between 15 and 35mm/Hg.[9,10]

Limb shape

Double tubigrip (DTG) provides external pressures of around 15-25 mmHg, but has no clinical benefit after ankle sprain.[4] Some have expressed concern that as DTG does not conform to the shape of the ankle its compressive force is mitigated, and may even encourage swelling to accumulate. Indeed it is well accepted that compression devices/stockings used in other areas of health care must be properly fitted and graduated, to work effectively eg. in prevention of deep venous thrombosis (DVT). Notwithstanding this, soft tissue injuries can affect most body parts, and it is difficult to design a bandage which conforms to all bony prominences and allows for anatomical variation. A number of commercial supports have been designed to provide focal compression around the ankle, similarly felt padding can be used to fill in gaps around body prominences, and focus compression at certain tissues. This approach seems pragmatic; horseshoe shaped felt around the ankle malleolus may prevent pressure peaks around the bony prominences[11] at the ankle, and may prevent oedematous accumulation around the more pain sensitive injured ligaments. Currently, there is little supporting clinical evidence for focal compression.[4]

Compression, body position and ambulation

Elevation and compression are commonly applied together in clinical practice; the rationale is usually to achieve an enhanced effect on local tissue pressure gradients. The previous guidelines[1] found some evidence that elevation alone reduced ankle volume more effectively, than a combination of elevation and compression post sprain. There was low quality evidence that both elevation alone, and concomitant compression and elevation significantly decreased limb volume after acute ankle sprain, however there were trends towards larger decreases with elevation only.[4] Some[12] have suggested that combining elevation and compression induces too great a change in interstitial pressure which collapses some of the finer lymphatic capillaries, adversely affecting their drainage function. Clearly, pressure profiles within the venous and lymphatic system will vary according to body position. Compressive force may therefore need to be reduced in a lying or elevated position.
There is both retrospective and prospective evidence that intermittent compression is most effective at resolving oedema post foot fracture.[13,14] Clinical evidence shows moderate evidence that semi-rigid supports are more effective than elastic bandages after ankle sprain;[4] the physiological reasons for this are not clear. Some semi-rigid ankle supports are designed that their external pressure increases on weight-bearing which creates an oscillating force (from proximal to distal) on the vasculature and lymphatic systems during ambulation. It is an interesting concept that walking and movement may be needed to maximise the effectiveness of some compression devices.

Blood flow velocity and shunting

Compression is used effectively in many areas of health care to treat venous insufficiency, prevention of ulcer recurrence and DVT.[15] The most popular mode is graduated stockings (GCS) which increase blood flow velocity, and shunt blood from the superficial to the deep venous system.[16] The mechanical pressures generated with GCS range from 14-17mmHg (Class 1) up to 25 to 35 mmHg (Class 3);[16] these values are quite similar to those currently used and recommended after acute soft tissue injury. Increased blood flow velocity and venous shunting may only be warranted at certain times after acute injury. Clinically related evidence in this area is limited to EIMD; in these models, the immediate use of graduated compression garments (10-15 mmHg) had an inconsistent effect on biomarkers of muscle damage and inflammation.[6] Note we did not consider their effects on sports 'recovery' per se within the scope of these review guidelines.

Optimal compression

There is little evidence to suggest an optimal level of compression pressure, or whether a constant or intermittent approach is preferable. This perhaps depends on our desired physiological rationale which may include: stopping or minimising the initial tissue haemorrhage; preventing / reversing the accumulation of oedema within the interstitial space; or enhancing venous and lymphatic return. In all cases, too little compression may not have the desired effect whereas too much could be deleterious. Perhaps ideally, the level of compression should be guided by the tissue pressures within the injured tissue.[12] It is unlikely that one approach (mode, dosage) will be equally effective across the soft tissue injury spectrum. It is most likely that factors such as: distance of the injured body part from the heart; injury severity and depth; time after injury; tissue vascularity and depth of the injured tissue, should influence our choice and dosage of compression, and elevation.

We have already discussed the effects that compression can have on blood flow velocity. Intermittent or sequential compression pressures may maximise this effect, with increases in flow of up to 200%.[17] Such large changes can induce a number of effects at a tissue level including: increased shear stress, arteriovenous pressure gradient and peripheral resistance, with subsequent increases in proteins, nutrients, and growth factors to the injury site. Shear stresses on the endothelial walls also stimulate nitric oxide production, causing further vasodilatation. Again, the optimal time after injury for inducing these effects should be considered.

The importance of introducing controlled mechanical loading during rehabilitation has already been discussed. There is potential that compression (particularly intermittent compression) may provide another medium for inducing cyclic loading during recovery.[17] Related animal models have found that early cyclic compression is effective for recovery and reduces certain aspects of the inflammatory response after EIMD.[6] In other clinical populations, compressive garments have been used to assist or re-establish motor functioning;[18] the mechanism is thought to relate to a combination of biomechanical or neurophysiological effects. Currently there is preliminary evidence that compression garments can improve motor function after EIMD.[19] Although supervised rehabilitation is regarded as the primary method of re-training motor control and sporting technique after injury, compressive supports may be a useful adjunct; based on their biomechanical support, and potential to enhance cutaneous stimulation, sensory awareness and joint positional sense.

Swelling and joint effusion adversely affect sensori-motor control, joint function and range of movement after injury. These factors can prevent progression of rehabilitation, particularly therapeutic exercise.[8] Recent evidence suggests that compression and/or elevation have little long term effect on tissue swelling, particularly in gravity dependent positions.[4] Nonetheless, there could still be potential to use elevation or compression to produce short term reductions in swelling/effusion, providing a therapeutic window to maximise the effect of rehabilitation exercises.

In recent years, various kinesiology taping techniques have become a popular method of managing oedema after acute soft tissue injury. The application of tape usually follows the lymphatic anatomy; the rationale is to lift superficial tissue, creating space for optimal lymphatic function. This seems to contradict the traditional approach of applying an external compressive force on an injury. It is unclear which of the approaches is superior, or whether they can be used interchangeably or simultaneously.

The clinical effectiveness of other methods of equilibrating tissue pressures, and enhancing venous or lymphatic flow should also be considered. Exercise (either systemic or isolated movement of a body part), creates intra-thoracic pressure changes and induces the skeletal muscle pump which may enhance venous haemodynamics and lymphatic function after injury. The success of this approach may again be time dependent (after injury), but aligns well with functional treatment, and the graduated transition to controlled tissue loading.

GENERAL RECOMMENDATIONS FROM PANEL CONSENSUS

-Definitely unload (Protection/Rest) soft tissue in the acute phases after injury. As a minimum, unloading should **definitely** include avoiding movements in the plane of injury during the acute phases after injury. (1)

-Progressive mechanical loading should **definitely** be initiated **after** the acute phases. For the majority of soft tissue injuries, **complete** tissue unloading (Protection and Rest) beyond the acute phases after injury should **definitely** be avoided. (2)

-Definitely apply ice after an acute soft tissue injury (3). In the absence of acute injury, it is probably safe to apply brief applications of ice for pain relief before returning to exercise/sporting activity, without increased risk of injury or performance detriment (4).

-Probably use elevation after an acute soft tissue injury. After any elevation **definitely** return the body part to a gravity dependent position gradually. (5)

-Probably use compression after an acute soft tissue injury. **Probably DON'T** use high levels of compression with simultaneous elevation. (6)

Specific Recommendations And Key Clinical Implications

1) The duration of unloading (Protection/Rest) definitely depends on the severity of the injury. We suggest that sustained or repetitive low level loads into the injuring plane should probably be avoided, and that external supports or bracing will help compliance with this.
2) We recommend that the details of mechanical loading and speed of progression are guided by: the severity of the injury, the injuring mechanism (excessive tensile vs compressive forces), and the type of soft tissue injury (ligament vs tendon vs muscle). This approach should definitely be supervised by a Chartered Physiotherapist.
3) We suggest that the primary clinical effect is a reduction in pain; 'reducing' inflammation, swelling or secondary injury is not guaranteed, and depends on the depth of injury, body part and % of overlying body fat. We recommend using crushed ice for at least 10 minutes to reduce pain. A thin damp barrier at the cooling interface will definitely not mitigate the cooling effect. Dry thick bandaging will definitively mitigate the cooling effect and clinical effectiveness. We recommend avoiding continuous application for longer than 20-30 minutes; we suggest that the optimal time between ice applications should be guided by pain and discomfort levels and can be less than 2 hours. It is difficult to give specific recommendations on an optimal cooling dosage for effectively inducing deep tissue temperature reduction; we suggest intermittent applications are the safest approach.
4) In most sporting environments, it is best practice to undertake a game related warm up prior to initiating or returning to physical activity or sport. We would recommend that a short game related warm up is undertaken between completing a short period of icing (<10 minutes), and returning to return to physical activity / sport.
5) There is no optimal duration of elevation; we suggest that distal body segments require longer periods. During periods of elevation patients will probably feel less pain and discomfort as a result of lower tissue pressures. Tissue/limb girth will probably return to its pre elevation girth even with a gradual return to a dependant position.
6) If the clinical aim is to reduce the net fluid loss from the vascular system after injury, then the compressive force of the bandage/ compressive modality should exceed interstitial fluid pressure. This value will definitely depend on the type of injury and affected body part, and it is difficult to provide specific recommendations on an optimal pressure. We suggest using focal compression around bony protuberances, and we recommend that the compressive modality configures to the shape of the body part, and provides a graduated compressive force. Compression bandages and external supports could contribute to recovery through a combination of physiological and therapeutic pathways. We suggest that most modes of compression provide additional benefits in terms of biomechanical support, controlling range of movement, and reassurance after injury. In some cases, external support may simply be needed to corroborate the severity of an injury to a patient, particularly in environments where they might risk an aggressive return to function.

Strong recommendation: 'We recommend' or 'definitely'
Weak recommendation: 'We suggest' or 'probably'
Values and preferences relevant to each recommendation are summarised in Figure 8.
We acknowledge that these recommendations are subject to change based on further research (Figure 8)

Figure 7

Summary of clinical evidence profiles by type of soft tissue injury (The effect of PRICE on critically important outcomes)

EVIDENCE PROFILE	PROTECTION / REST / LOADING			ICE			COMPRESSION			ELEVATION		
	M	**Lig/Jt**	**T**	**M**	**Lig/Jt**	**T**	**M**	**Lig/Jt**	**T**	**M**	**Lig/Jt**	**T**
High	-		-	-	**Effective analgesia post op (2) (4) (+)**	-			-			-
Mod	-	Functional >IMM (1) (+)	-	-	Effective analgesia post ankle sprain (2) (3)	-		Semi Rigid>Elastic (-)	-	-		-
Low	-		-	-		-		No effect DTG (-)	-	-		-
V. Low	-	Short IMM = Long IMM	-	-		-	No effect with 80mmHg		-	-	Elev > Comp (5) Elev does not prevent limb swelling (4) (5)	-

M: Muscle injury; Lig/Jt; ligament or joint injury; T: Tendon injury
A > B: Treatment A is more effective than treatment B; A=B: Treatment B is equally as effective as treatment B; - (dash): No relevant clinical evidence
1). No differences in long term function; 2). No effect on other important clinical outcomes; 3). Immediate return to sport after cooling (>5 minutes) decreases performance in some correlates of sporting performance ; 4) Post surgical model; 5) Based on Limb girth outcome
(+) Supporting evidence from basic science research; (-) Potential conflicting evidence from basic science research

EVIDENCE PROFILE:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 8

PRICE and soft tissue injury: Risks, burdens and costs, what we know and what we don't know

	PROTECTION / REST / TISSUE LOADING	ICE	COMPRESSION	ELEVATION
BASIC SCIENCE What we know	-A period of protection and rest is required after the majority of soft tissue injuries. Excessive protection/rest and unloading will do harm (A). -Mechanical loading / ambulation after injury helps restore strength and morphological characteristics of collagenous tissue after tendon injury (A). -Mechanical loading can upregulate gene expression for some proteins associated with tendon tissue healing (A). -Excessive loading in the early stages after injury will do harm (A). -Exercise (either systemic or isolated movement of a body part), creates intra-thoracic pressure changes and induces the skeletal muscle pump which enhances venous haemodynamics and lymphatic function.	-Skin temperature can be reduced to <13°C within 5-15 minutes. Not all modes of cooling are equally effective; crushed ice provides effective cooling and is probably safest. (HH, CCS) -A damp barrier will not mitigate the cooling effect on the skin; however a thick, dry barrier will mitigate excessively and limit clinical effectiveness. (HH) -Excessive skin / tissue cooling results in harm (CCS). -Muscle and joint temperature reductions are much smaller compared to those obtained at the skin. The lowest temperature recorded at a 1cm intra-muscular (I/M) depth was approximately 20°C; this was in a very lean population (around <10mm skin fold), after 20 minutes of cooling (HH). Few studies have reduced I/M temperature below 25°C. (HH) Fat creates an insulating effect and limits deep tissue temperature reductions (HH). Deep tissue temperature remains the same or continues to cool for up to 10 minutes after ice pack removal (HH). Ice reduces blood flow, reduces oxygen saturation and facilitates capillary outflow in healthy tendons (HH). It has an inconsistent effect on microcirculation in injured animals (A). Ice has a consistent effect on cellular and physiological events associated with inflammation (A) Short periods of cooling can have an excitatory effect on muscle activation (HH, IH).	-Provides support and confidence for many patients. Also exerts an external force on the tissue which could decrease bleeding; and/or prevent accumulation of oedema within the interstitial space. -Commonly used compression bandages exert pressures between 15 and 60mmHg. -In other areas of health care, graduated compression stockings, exerting pressures between 5 and 30mmHg; are used to increase local blood flow, and shunt blood from the superficial to deep venous system. -Cyclic loading (massage) reduces aspects of inflammation and is effective for recovery after EIMD (A). -Light compression garments have an inconsistent effect on markers of muscle damage, and some markers of inflammation after EIMD (IH).	-Elevating a body part decreases the gravitational force on the column of blood between that body part and the heart, thereby decreasing hydrostatic pressure, and facilitating venous and lymphatic flow.

CLINICAL WHAT WE KNOW	-Protection/rest is a non specific term which is interpreted as casting (with or without weight-bearing), partial weight-bearing, activity modification, external support, bracing, bandaging or taping. -Functional treatment (early mobilisation/ambulation with a support) is more effective than immobilisation/ non weight-bearing after acute ankle sprain (Mod). -Semi-rigid supports are more effective than elastic bandages when used as an adjunct to functional treatment (Mod).	-Ice application can effectively decrease pain after surgery (High) and acute ankle sprain (Mod). -Removal for an ice pack for a short period of time is safe and effective (Low). -Ice has little effect on recovery time, function, swelling (Mod), but there are few studies on closed soft tissue injuries. -Short periods of cooling can safely precede physical activity; longer periods (>5-15 minutes), particularly over areas with little body fat, could risk re-injury and affect sporting performance (HH).	-Light tubular bandaging is ineffective after ankle sprain (Low). -Maximal compression bandaging is ineffective after muscle contusion (V. Low). -Semi-rigid supports are more effective than elastic bandaging (Mod). -Compression and elevation is less effective than compression alone in terms of reducing swelling (Low).	-Elevation had no effect on upper limb swelling after surgery (Low). It decreased lower limb swelling after ankle sprain (Low); this quickly returns to baseline (pre-elevation volumes) on return to a gravity dependent position (Low).
RISKS, BURDENS AND COST	**Risks:** Excessive or inadequate PR; misunderstanding of what PR should entail; currently non-specific terminology relating to different advice from practitioner, patient misinterpretation; difficulty progressing into the active rehabilitation stage, potential loss of general fitness **Burdens:** Potential lack of independence, loss of earnings, patient discipline, boredom, safe progression into active loading/rehabilitation requires increased therapist input/time **Cost:** Variable: high relating to bracing, crutches, casting; low relating to slings, bandages, lower relating to unloading/ avoidance	**Risks:** Direct side effects: skin burn/ nerve palsy, non-specific advice from practitioner, unable to tolerate cold sensation, difficulty targeting deeper injuries, premature return to activity/sport after excessive cooling, wide range of treatment modes **Burdens:** Patient compliance required, crushed ice requires preparation for home use, repetitive removal/reapplication, melting ice can be messy, tolerating cold sensation, **Cost:** Variable: higher relating to commercial ice machine, gel packs have a lower cost, crushed ice is minimal.	**Risks:** Excessive or inadequate compression; non-specific advice from practitioner; wide range of treatment options and associated pressures **Burdens:** potential discomfort during wear, repetitive removal/reapplication; pain with removal/reapplication, in some cases application skill is important for ensuring effectiveness and patient education or increased therapist input/time is required **Cost:** Variable: high relating to pneumatic devices; low relating to bandaging, however potential for a high cumulative cost (eg. within a department)	**Risks:** Potential rebound, may encourage excessive unloading, potential difficulty progressing into the active rehabilitation stage, potential loss of general fitness **Burdens:** Potential lack of independence, loss of earnings, patient discipline, boredom **Cost:** No direct cost

WHAT WE DON'T KNOW	-The majority of basic science research is based on injured tendon models (surgical resection). -How to make a safe transition from protection/rest to progressive loading? -The most effective form of external support to compliment functional management? -The optimal timing, dosage, nature and speed of induced load? And whether this should vary according to muscle, tendon or ligament tissue?	-The effect of cooling on key events associated with inflammation eg. oxidative stress? -Whether the current threshold temperatures for achieving analgesia (skin temperature of <13°C) or metabolic reduction (reduction to 5-15°C at the injury site) will change based on emerging understanding of inflammation? -The magnitude or depth of temperature reductions obtainable in smaller joints with less surrounding adipose tissue (eg. wrist, elbow, ankle), in the absence of tourniquet and post operative dressings? -The clinical relevance of inducing small or moderate temperature reductions on deep tissue in terms of inflammation, / local cellular metabolism? -The benefits and safety of using higher dosages of cooling (eg. longer durations, but with regular short periods of removal) to target deep injuries? -If ice can 'decrease' the magnitude of the inflammatory response or selectively influence aspects of inflammation enough, to have a clinical benefit after a significant injury across all soft tissue types?	-Optimal mode of compression, its associated force, and if this should be constant or intermittent? Clear physiological goal eg. preventing bleeding, increasing interstitial pressure, increasing venous return or venous shunting? Whether this should vary according to time from injury, type of tissue injured? -The clinical relevance of other potential mechanisms of effect including: limiting movement, enhancing adherence with advice (rest), enhanced sensori-motor function, cyclic loading? -If a temporary reduction in swelling could provide a therapeutic window for exercise?	-If elevation improves patient comfort? Or decreases the risk of adverse effects? -How a temporary reduction in tissue girth relates to actual joint effusion? -Optimal duration or angle of elevation? Whether this should vary according to the type of tissue injured, or the body part? -If a temporary reduction in swelling could provide a therapeutic window for exercise?

NOTE:

-THERE IS A PARTICULAR DEARTH OF RELEVANT RESEARCH BASED ON ACUTELY INFLAMED TENDONS, AND MUSCLE STRAINS OR CONTUSION.
-WE ACKNOWLEDGE THAT OUR CURRENT RECOMMENDATIONS ARE SUBJECT TO CHANGE BASED ON FURTHER RESEARCH IN ANY OF THESE OUTLINED AREAS

A: Based on evidence derived from animal models; **HH:** Based on evidence derived from un-injured human models; **IH:** Based on evidence derived from lab induced injury human
V. Low: Based on Very low quality evidence from injured human model; **Low:** Based on low quality evidence from injured human; **Mod:** Based on moderate quality evidence from injured human; **High:** Based on high quality evidence from injured human; **CCS:** Clinical case study; **EIMD:** exercise induced muscle damage

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Appendix Table 1:
Search Strategy 1

1. *Cryotherapy/
2. cold compress.mp.
3. ice bath$.mp.
4. ice pack.mp.
5. exp Cold Temperature/th, mt, et, ae, me [Therapy, Methods, Etiology, Adverse Effects, Metabolism] (3068)
6. cryokinetic.mp.
7. cold pack$.mp.
8. exp Ice/
9. rice.mp.
10. PRICE.mp.
11. OR/ 1-10
12. H-Reflex/ or arthrogenic muscle response.mp.
13. exp Proprioception/ph, cl [Physiology, Classification]
14. Kinesthesis/ or joint positional sense.mp.
15. Blood Circulation/ or Blood Flow Velocity/ or blood flow.mp.
16. Edema/ or swelling.mp.
17. Metabolism/ph [Physiology]
18. Lymphatic System/ph, pp, in, pa [Physiology, Physiopathology, Injuries, Pathology]
19. limb girth.mp.
20. range of movement.mp.
21. Muscle Strength/ph [Physiology]
22. Neural Conduction/ph [Physiology]
23. Hemodynamics/ph [Physiology]
24. Skin Temperature/ph [Physiology]
25. Body Temperature/ or Oxygen Consumption/ or muscle temperature.mp.
26. joint temperature.mp.
27. OR/12-26
28. and 11 (1482)
29. from 28 keep 208

MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial s (Ovid)

Appendix Table 2:
Search Strategy 2

1. exp Casts, Surgical/ or exp Immobilization/ or immobilisation.mp.
2. exp Bandages/
3. compression.mp. or Intermittent Pneumatic Compression Devices/ or Stockings, Compression/
4. pop.mp.
5. tubigrip.mp.
6. exp "Sprains and Strains"/
7. exp Ligaments/
8. exp Contusions/
9. exp Tendon Injuries/
10. exp Tendinopathy/
11. exp Soft Tissue Injuries/
12. exp Weight-Bearing/
13. elevation.mp.
14. Athletic Injuries/
15. Rest/
16. OR/1-5
17. OR/6-14
18. 16 and 17
19. limit 18 to (english language and yr="1996 - 2009") (2947)
20. from 19 keep (131)

MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial s (Ovid)

Appendix Table 3:
Search Strategy 3

1. exp Cryotherapy/
2. cold compress.mp.
3. ice pack.mp.
4. Cold Temperature/
5. exp Ice/
6. PRICE.mp.
7. exp "Sprains and Strains"/
8. exp Contusions/
9. exp Tendon Injuries/
10. exp Soft Tissue Injuries/
11. exp Athletic Injuries/
12. OR/1-6
13. OR 7-11
14. 12 and 13
15. limit 14 to (english language and humans and yr="1996 -Current") (139)
16. from 15 keep (11)

MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial s (Ovid)

Appendix Table 2:
Search Strategy 2

Related articles search on Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/)	
Reference	**Number of related titles read**
Pollard (2005)	145
Tsang (2003)	96
Agalfy (2007)	183
Hopper (1997)	190
Wassinger (2007)	119
Hopkins (2002)	225
Kubo (2005)	472
De Ruiter (2001)	202
Kimura (1997)	120
Yanagisawa (2007)	816
Glenn (2004)	146
Karunakara (1999)	244
Knobloch (2008)	94
Weston (1994)	116
Schaser (2007)	321
Howatson (2003)	184
Davies (2009)	291
Kraemer (2001)	468
Citation tracking	
Undertaken on all incoming primary and review articles n=350	

Appendix 4b

Literature searches from related reviews, previously completed by the authors

1. MeSH descriptor Cryotherapy, this term only
2. MeSH descriptor Cold Temperature, this term only
3. MeSH descriptor Immersion, this term only
4. #2 AND #3
5. #1 OR #4
6. ((cold or ice or contrast) NEAR/3 (immers* or bath or therapy)):ti,ab,kw
7. (cryotherapy):ti,ab,kw
8. (#5 OR #6 OR #7
9. MeSH descriptor Exercise, this term only
10. MeSH descriptor Muscle, Skeletal, this term only
11. MeSH descriptor Athletic Injuries, this term only
12. MeSH descriptor Soft Tissue Injuries, this term only
13. MeSH descriptor Creatine Kinase explode all trees
14. MeSH descriptor Physical Exertion, this term only
15. MeSH descriptor Muscle Fatigue, this term only
16. MeSH descriptor Muscle Cramp, this term only
17. MeSH descriptor Spasm, this term only
18. MeSH descriptor Muscle Rigidity, this term only
19. MeSh descriptor Sprains and Strains, this term only
20. MeSH descriptor Muscle Weakness, this term only
21. (sore* NEAR/3 musc*):ti,ab,kw
22. (DOMS):ti,ab,kw
23. (exercise induced and (muscle* NEAR/2 (damage* or injur*))):ti,ab,kw
24. MeSH descriptor Lactic Acid, this term only
25. (lactate* or lactic):ti,ab,kw
26. (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR#21 OR #22 OR #23 OR #24 OR #25)
27. (#8 AND #26)

Undertaken on Cochrane Central Register of Controlled Trials (Wiley InterScience interface), and modified for Medline, EMBASE (Ovid)

Appendix Table 5:
List of excluded studies with reasons

Chapter 3: What is the magnitude and depth of cooling associated with ice/ice and compression?	
Study	**Reason for exclusion***
Akgun K, et al. Temperature changes in superficial and deep tissue layers with respect to time of cold gel pack application in dogs. Yonsei Medical Journal 2004;45(4):711-8. Barlas D, et al. In vivo tissue temperature comparison of cryotherapy with and without external compression. Annals of Emergency Medicine 1996;28(4):436-9. Kim YH, et al. The effect of cold air application on intra-articular and skin temperatures in the knee. Yonsei Medical Journal 2002;43(5):621-6. Pollitt C, et al. Prolonged, continuous distal limb cryotherapy in the horse. Equine Veterinary Journal 2004; 36(3):216-20.	Animal subjects
Daanen HA, et al. The effect of body temperature on the hunting response of the middle finger skin temperature. Eur J Appl Physiol Occup Physiol 1997;76(6): 538-43. Rubley MD, et al. Time course of habituation after repeated ice bath immersion of the ankle. Journal of Sports Rehab 2003. Singh H, et al. The efficacy of continuous cryotherapy on the postoperative shoulder. J Shoulder Elbow Surg 2001;10: 522-25. Speer KP, et al. The efficacy of cryotherapy in the post operative shoulder. J Shoulder Elbow Surg, 1996;5: 62-8.	No measure of temperature / insufficient outcome measure
Anvari B, et al. A comparative study of human skin thermal response to sapphire contact and cryogen spray cooling. IEEE Transactions on Biomedical Engineering 1998;45(7):934-41. Jay O, et al. Skin cooling on contact with cold materials: the effect of blood flow during short-term exposures. Annals of Occupational Hygiene 2004;48(2):129-37.	Cold therapy intervention not clinically relevant
Enwemeka CS, et al. Soft tissue thermodynamics before, during and after cold pack therapy. Med Sci Sports Exerc 2002;34(1):45-50. Muraoka T, et al. Effects of muscle cooling on the stiffness of the human gastrocnemius muscle in vivo. Cells Tissues Organs. 2008;187(2):152-60. Epub 2007 Oct 15. Nosaka K, et al. Influence of pre-exercise muscle temperature on responses to eccentric exercise. J Athl Train 2004;39(2):132-137. Yanagisawa O, et al. Effects of cooling on human skin and skeletal muscle. Eur J Appl Physiol 2007;100(6):737-45. Epub 2007 May 4.	Unable to determine the depth at which temperature was recorded
Lindsell C, et al. Interpretation of the finger skin temperature response to cold provocation. International Archives of Occupational & Environmental Health 2001;74(5):325-35.	Hand immersion, and finger tip temperature recorded only
Holcomb WR, et al. The effect of icing with the pro stim edema management system on cutaneous cooling. J Athl Train 1996;31(2): 126-9	Concomitant electrical stimulation

Chapter 4: What effect does PRICE have on the inflammatory response after acute soft tissue injury?	
Study	**Reason for exclusion***
Fu FH, et al. The effects of cryotherapy on muscle damage in rats subjected to endurance training. Scand J Med Sci Sports 1997;7(6):358-62. Jia J, et al. Cold nerve injury is enhanced by intermittent cooling. Muscle Nerve 1999;22(12):1644-52. Locke M, et al. Cold stress does not induce stress proteins SP 25 and SP 72 in rat skeletal muscle. Cryobiology 2001;43(1):54-62. Nemeth N, et al. Systemic and regional hemorheological consequences of warm and cold hind limb ischemia-reperfusion in a canine model. Clinical Hemorheology & Microcirculation 2004;30(2):133-45. Thorlacius H, et al. Effects of local cooling on microvascular hemodynamics and leukocyte adhesion in the striated muscle of hamsters. J Trauma 1998;45(4):715-19.* Wladis A, et al. Effects of induced hypothermia after soft tissue injury. Arch Orthop Trauma Surg 2004;124(4):243-9. Epub 2003 Oct 7.	Injury model not relevant (animal)
Bailey DM, Erith SJ, Griffin PJ, Dowson A, Brewer DS, Gant N, Williams C. Influence of cold water immersion on indices of muscle damage following prolonged intermittent shuttle running. Journal of Sports Sciences 2007;25(11):1163-1170. Halson SL, Quod MJ, Martin DT, Gardner AS, Ebert TR, Laursen PB. Physiological responses to cold water immersion following cycling in the heat. International Journal of Sports Physiology and Performance 2008;3:331-346 Ingram J, Dawson B, Goodman C, Wallman K, Beilby J. Effect of water immersion methods on post-exercise recovery from simulated team sport exercise. Journal of Science and Medicine in Sport 2009;12(3):417-421. King M, Duffield R. The effects of recovery interventions on consecutive days of intermittent sprint exercise. Journal of Strength and Conditioning Research 2009;23(6):1795-1802. Nemet D, Meckel Y, Bar-Sela S, Zaldivar F, Cooper DM, Eliakim A. Effect of local cold-pack application on systemic anabolic and inflammatory response to sprint-interval training: a prospective comparative trial. Eur J Appl Physiol. 2009 Nov;107(4):411-7. Epub 2009 Aug 4. Peake J, Peiffer JJ, Abbiss CR, Nosaka K, Okutsu M, Laursen PB, Suzuki K. Body temperature and its effect on leukocyte mobilisation, cytokines and markers of neutrophil activation during and after exercise. European Journal of Applied Physiology 2008;102(4):391-401 Robey E, Dawson B, Goodman C, Beilby J. Effect of postexercise recovery procedures following strenuous stair-climb running. Research in Sports Medicine 2009; 17: 245-259. Rowsell GJ, Coutts AJ, Reaburn P, Hill-Haas S. Effects of cold-water immersion on physical performance between successive matches in high-performance junior male soccer players. Journal of Sports Sciences 2009:1-9. Ali A, Creasy RH, Edge JA. Physiological effects of wearing graduated compression stockings during running. European Journal of Applied Physiology 2010; 109: 1017-1025. Trenell MI, Rooney KB, Sue CM, Thompson CH. Compression garments and recovery from eccentric exercise: A 31P-MRS study. Journal of Sports Science and Medicine 2006; 5: 106-114.	Injury / exercise model not relevant (human)

Chapter 4: What effect does PRICE have on the inflammatory response after acute soft tissue injury?	
Study	**Reason for exclusion***
Duffield R, Portus M. Comparison of three types of full body compression garments on throwing and repeat sprint performance in cricket players. British Journal of Sports Medicine 2007; 41: 409-414 Kraemer WJ, Volek JS, Bush JA, Gotshalk LA, Wagner PR, Gómez AL, Zatsiorsky VM, Duarte M, Ratamess NA, Mazzetti SA, Selle BJ. Influence of compression hosiery on physiological responses to standing fatigue in women. Med Sci Sports Exerc. 2000 Nov;32(11):1849-58. Duffield R, Edge J, Merrells R, Hawke E, Barnes M, Simcock D, Gill N. The effects of compression garments on intermittent exercise performance and recovery on consecutive days. International Journal of Sports Physiology and Performance 2008;3(4):454-68.	Injury / exercise model not relevant (human)
Crowe MJ, O'Connor D, Rudd D. Cold water recovery reduces anaerobic performance. International Journal of Sports Medicine 2007;28(12):994-998. Heyman E, De Geus B, Mertens I, Meeusen R. Effects of four recovery methods on repeated maximal rock climbing performance. Medicine & Science in Sports and Exercise 2009;41(6):1303-1310. Kuligowski LA, Lephart SM, Giannantonio FP, Blanc RO. Effect of whirlpool therapy on the signs and symptoms of delayed onset muscle soreness. Journal of Athletic Training 1998;33(3):222-228. Yamane M, Teruya H, Nakano M, Ogai R, Ohnishi N, Kosaka M. Post-exercise leg and forearm flexor muscle cooling in humans attenuates endurance and resistance training effects on muscle performance and on circulatory adaptation. Eur J Appl Physiol. 2006 Mar;96(5):572-80. Kraemer WJ, Bush JA, Triplett-McBride NT, Koziris LP, Mangino LC et al. Compression garments: Influence on muscle fatigue. Journal of Strength and Conditioning Research, 1998; 12(4): 211-215. Kraemer WJ, Bush JA, Newton RU, Duncan ND, Volek JS, Denegar CR et al. Influence of a compression garment on repetitive power output production before and after different types of muscle fatigue. Sports Medicine, Training and Rehabilitation 1998; 82(2): 163-184.	Outcomes not relevant
Schaser, et al. In vivo analysis of micro circulation following closed soft tissue injury. J Orthop Research 1999;17: 678-85.	No cold therapy intervention
Chapter 6: What other physiological effects are associated with tissue cooling, and do they affect sporting performance and injury risk?	
Bornmyr S, et al. Effect of local cold provocation on systolic blood pressure and skin blood flow in the finger. Clin Physiol 2001;21(5):570-5. Oksa et al. Combined effect of repetitive work and cold on muscle function and fatigue. J Appl Physiol 2002; 92:354-361. Petrofsky J. Muscle temperature and EMG amplitude and frequency during isometric exercise. Aviat Space Environ Med 2005;76(11):1024-30. Shibahara N, et al. The responses of skin blood flow, mean arterial pressure and R-R interval induced by cold stimulation with cold wind and ice water. Journal of the Autonomic Nervous System 1996;61(2):109-15. Yona et al. Effects of cold stimulation of human skin on motor unit activity. Jpn J Physiol 1997; 47:341- 8	Cold therapy intervention no relevant

Bandrivskyy A, et al. Wavelet phase coherence analysis: Application to skin temperature and blood flow. Cardiovascular Engineering 2004;4(1):89-93. Doering TJ, et al. Cerebral hemodynamics and cerebral metabolism during cold and warm stress. American Journal of Physical Medicine & Rehabilitation 1996;75(6):408-15. Yanagisawa O, et al. The use of resonance imaging to evaluate the effects of cooling on skeletal muscle after strenuous exercise. European Journal of Applied Physiology 2003;89(1):53-62.	Outcomes not relevant
Bergersen, et al. Blood velocity and skin temperature during cold induced vasodilatation. Journal of Physiology 1998;509. [Bergersen, 1999]	Double data publication
De Ruiter CJ, et al. Similar effects of cooling and fatigue on eccentric and concentric force-velocity relationships in human muscle. J Appl Physiol 2001;90(6):2109-16. De Ruiter CJ, et al. Temperature effect of the force/velocity relationship of the fresh and fatigued human adductor pollicis muscle. Pflugers Arch 2000;440(1):163-70. De Ruiter CJ, et al. Temperature effect on the rates of isometric force development and relaxation in the fresh and fatigued. Exp Physiol 1999; 84:1137-50. Gossen ER. Effect of temperature on post-tetanic potentiation in human dorsiflexor muscles. Can J Physiol Pharmacol 2001;79(1): 49-58.	Twitch contraction on muscle strength outcome
Yanagisawa O, et al. Evaluations of cooling exercised muscle with MR imaging and 31MR spectroscopy. Med Sci Sports Ex 2003;35(9):1517-23.	DOMS study
Mutungi et al. Temperature dependent changes in the viscoelasticity of intact resting mammalian (rat) fast and slow twitch muscle fibres. J Physiol 1998;508: 253-65. Jia, J et al. Cold nerve injury is enhanced by intermittent cooling. Muscle & Nerve 1999; 22(12):1644-52. Zhou L et al. Mechanism research of cryoanalgesia. Neurological Research 1995;17(4):307-11.	In vitro
Gao et al. 2000. Mechanism of cryoinjury in living cells	Induced injury at cellular level using cold therapy
Gallen KG et al. Medicine & Science in Sports & Exercise 1999; 31(5):S295. Marvar PJ et al. Medicine & Science in Sports & Exercise 2002; 34(5):S100. McCrory JL et al.Medicine & Science in Sports & Exercise 2005; 37(5):S278-S279. Ransone, J. W. Medicine & Science in Sports & Exercise 1999; 31(5):S145. Rogers J T, et al. Medicine & Science in Sports & Exercise 2003; 35(5):S265. Wang HE et al. Medicine & Science in Sports & Exercise 2008; 40(5):S215. doi: 10.1249/01.mss.0000322385.57749.b3 Weimar W et al. Medicine & Science in Sports & Exercise 2004; 36(5):S187. Wells B L et al. Medicine & Science in Sports & Exercise 2002; 34(5):S101. Wilson SM et al. Medicine & Science in Sports & Exercise 2006; 38(5):S375.	Platform presentation

Chapter 5: What effect does mechanical loading have on inflammation and healing after acute soft tissue injury?	
Study	**Reason for exclusion***
Demirhan M, et al. Tensile strength of ligaments after thermal shrinkage depending on time and immobilization: in vivo study in the rabbit. J Shoulder Elbow Surg 2005;14(2):193-200.	Not soft tissue injury
Eliasson P, et al. Unloaded rat Achilles tendons continue to grow but lose viscoelasticity. J Appl Physiol 2007;103(2):459-63. Epub 2007 Apr 5. Kanda K, et al. Adverse effect on rabbit anterior cruciate ligament after knee immobilisation: changes in permeability of horseradish peroxidise. Arch Orthop Trauma Surg 1998;117:307-311. Matsumoto F, et al. Mechanical effects of immobilisation on the achilles' tendon. Arch Phys Med Rehabil 2003;84(5):662-7. Narmoneva DA, et al. Altered swelling behaviour of femoral cartilage following joint immobilisation in a canine model. J Orthop Res 2002;20(1):83-91. Thornton GM, et al. Ligament creep recruits fibres at low stresses and can lead to modulus-reducing fibre damage at higher creep stresses: a study in rabbit medial collateral ligament model. J Orthop Res 2002;20(5):967-74.	Animal study not injured
Gelberman RH, et al. The effect of gap formation at the repair site on the strength and excursion of intrasynovial flexor tendons. J Bone Joint Surg Am 1999;81(7):975-82. Palmes D, et al. Achilles tendon healing: long term biomechanical effects of post operative mobilisation and immobilisation in a new mouse model. Journal of Orthopaedic Research 2002;20: 939-946.	Animal study – surgical repair
Green DM, et al. Effect of early full weight bearing after joint injury on inflammation and cartilage degradation. J Bone Joint Surg Am 2006;88(10):2201-9.	Osteochondral lesion
Hurschler C, et al. Scanning electron microscopic characterisation of healing and normal rat ligament microstructure under slack and loaded conditions. Connect Tissue Res 2003;44(2):59-68. Provenzano PP, et al. Healing of subfailure ligament injury: comparison between immature and mature ligaments in a rat model. J Orthop Res 2002;20(5):975-83. Yasunda T, et al. Unfavourable effect of knee immobilization on Achilles tendon healing in rabbits. Acta Orthop Scand 2000; 71(1): 69-73.	No or inadequate control group
Chapter 7. Clinical effectiveness of PRICE	
Guillodo Y, et al. Treatment of muscle trauma in sports people (from injury on the field to resumption of the sport). Ann Phys Rehabil Med. 2009;52(3):246-55. Epub 2009 Feb 23. Kullenberg B, et al. Post operative cryotherapy after total knee arthroplasty: a prospective study of 86 patients. J Arthroplasty 2006;21(8):1175-9.	No relevant outcomes
Kerkhoffs GM, et al. Functional treatments for acute ruptures of the lateral ankle ligament. Acta Orthop Scand. 2003;74(1):69-77. Kerkhoffs GM et al. -Immobilisation of acute ankle sprain. Arch Orthop Trauma Surg 2001;121(8):462-71 Malone TR, et al. Nerve injury in athletes caused by cryotherapy J Athl Train 1992;27(3):235-37. [Bassett, 1991]	Double data publication

Ardèvol J, et al. Treatment of complete rupture of the lateral ligaments of the ankle: a randomised clinical trial comparing cast immobilisation with functional treatment. Knee Surg Sports Traumatol Arthrosc. 2002;10(6):371-7. [Jones et al. 2007] Karlsson J, et al. Early functional treatment of acute ligament injuries of the ankle joint. Scand J Med Sci Sports 1996;6(6):341-5. [Kerkhoffs et al. 2002]	Study included as part of a relevant systematic review article
Costa et al. Randomised controlled trials of immediate weight-bearing mobilisation for rupture of the tendo Achillis. Journal of Bone and Joint Surgery 2006;88:69-77. Josey RA, et al. Immediate, full weightbearing cast treatment of acute Achilles tendon ruptures: a long term follow up study. Foot Ankle Int 2003;24(10):775-9. Jung YB, et al. Active non operative treatment of acute isolated posterior cruciate ligament injury with cylinder cast immobilisation. Knee Surg Sports Traumatol Arthrosc 2008;16(8):729-33. Epub 2008 Apr 17 Saeki Y et al. Effect of local application of cold or heat for relief of pricking pain. Nursing and Health Sciences 2002;4(3):97-105. Stevens et al. Frostbite due to improper use of frozen ice pack.	Healthy subjects / injury model not relevant

*excluded from full text

Appendix Table 6:
Skin temperature

Study	Methods	Body part	Mode	Duration	Factors lowering risk of bias (Cochrane tool)
Selfe, 2009 Randomised cross over	N=11 healthy	Knee	-Crushed Ice (300 gm in plastic bag) -Gel pack -Commercial cooling 1 -Commercial cooling 2	20 min	-
Kennet, 2007 Repeated measures (24 hr wash out)	N=9 healthy	Ankle	- Crushed Ice (1 litre in terrycloth) - Gel pack (direct) - Frozen peas (plastic packaging in terrycloth) - CWI (6L cold water with 1L crushed ice)	20 min	-
Kanlayanaphotporn, 2005 Repeated measures (24 hr wash out)	N=50 healthy	Thigh	- Ice pack (damp towelling barrier) - Gel pack (damp towelling barrier) - Frozen peas (damp towelling barrier) - Mixture of water/alcohol (damp towelling barrier)	20 min	-
Janwantanakul, 2004 Repeated measures (24 hr wash out)	N= 30 healthy	Thigh	- Ice bag (chipped ice in plastic bag) - Ice bag with damp towel wrap (100% cotton towel single layer) - Room temperature water bag	20 min	-
Merrick, 2003 Repeated measures (48hr wash out)	N=15 healthy	Thigh	- Ice bag (crushed ice, 1kg, 4L) - Wet ice (terry towelling inbuilt to allow melting water to contact skin) - Flex-i-cold (Frozen gel pack with no phase change) - Control (no treatment) All ice groups: Elastic wrap to secure pack in place at 45mmHg.	30 min	-
Chesterton, 2002 Repeated measures (3 day wash out)	N=20 healthy	Thigh	- Frozen gel pack (single layer damp towelling barrier) - Frozen peas (single layer damp towelling barrier) - Room temperature gel pack	20 min	Allocation concealment
Palmer, 1996 Repeated measures (48 hr wash out)	N=12 healthy	Ankle and Thigh	Exercise (15 mins) then ice pack secured with elastic wrap, then simulated showering, then reapplication of ice pack (as above)	- 20 min - 30 min - 40 min	-

Study	Methods	Body part	Mode	Duration	Factors lowering risk of bias (Cochrane tool)
Okcu, 2006 RCT	N=32 healthy N=12 acute inversion injury	Ankle	200 ml frozen ice pack x2 applied over: - Robert Jones bandage - Elastic support wrap - Below knee plaster - Synthetic below knee cast	2 hrs?	Sequence generation Allocation concealment
Ibrahim, 2005 RCT	N=18 healthy	Knee	Cryocuff (with autochill) applied over: -No dressing -Thin adhesive dressing (Tegaderm) - Bulky dressing (wool and crepe)	2 hrs	Sequence generation Allocation concealment
Tsang, 1997 Repeated measures (24 hr wash out)	N=9 healthy	Forearm	0.68kg of cubed ice applied over: -Bare skin -Dry towelling -Dry elastic bandage	30 min	-
Metzman, 1996	?	-Synthetic cast -Plaster cast	Crushed ice		

Appendix Table 7:
Muscle temperature

Study	Methods	Body part (mean skin fold mm)	Mode	Duration	Factors lowering risk of bias (Cochrane tool)
Dykstra, 2009 Repeated measures (4 day wash out)	N=12 healthy Depth of measurement: ½ skin fold thickness plus 2 cm	Calf (male: 12.8 +/-4.1; female: 17.3 +/-3.4mm)	-Cubed -Crushed -Wetted. All groups no elastic wrap	20 min	
Bender, 2005 Repeated measures (2 day wash out)	N=16 healthy Depth of measurement: ½ skinfold measurement plus 1.5 cm	Calf (21.1 +/-9.3mm)	Ice bag secured with plastic wrap (62 +/-6.8mm/Hg)	30 min	
Long, 2005 Repeated measures (2 day wash out)	N=6 healthy Depth of measurement: 1 and 2 cm subadipose	Thigh (25.4 +/-2.7 mm)	Ice bag with compression wrap at 42-48mm Hg	Up to 54 min	
Merrick, 2003 Repeated measures (2 day wash out)	N=15 healthy Depth of measurement: 1 and 2 cm subadipose	Thigh (19.3 +/-4.1mm)	-Ice bag -Wet ice -Flex-i-cold All groups compression at 45-50mm/Hg)	32 min	
Otte, 2002 Observational	N=47 healthy Depth of measurement: 1 cm deep to adipose layer	Thigh (sub-grouped into: 0-10mm; 11-20mm; 21-30mm; 31-40mm)	Crushed ice	Up to 58.6 min	
Jutte, 2001 Observational	N=15 healthy Depth of measurement: 2cm below adipose layer	Thigh (21.2 +/-8.6mm)	Ice cubes with 5 inch elastic wrap	30 min	
Myrer, 2001 Observational	N= 30 healthy Depth of measurement: ½ skinfold measurement plus 1cm or 3cm	Calf (overall mean: 15.5+/-8.7mm); sub-grouped into: <8mm (6.5 +/-1.4mm); 10-18 mm (14.1 +/-2.6); >20 mm (25.7+/-5.4)	Crushed ice	20 min	

Study	Methods	Body part (mean skin fold mm)	Mode	Duration	Factors lowering risk of bias (Cochrane tool)
Myrer, 2000 RCT	N=28 healthy Depth of measurement: 1cm below subcutaneous fat	Calf (16.6 +/-7.4mm)	Crushed ice	20 min	Sequence generation
Myrer, 1998 RCT	N=32 healthy Depth of measurement: 1 cm below subcutaneous fat	Calf	-Crushed ice -CWI	20 min	Sequence generation
Zemke, 1998 RCT	N=14 healthy Depth of measurement: ½ skinfold measurement plus 1cm	Calf (ice massage: 0.78 +/-0.25 cm; ice bag: 0.59 +/-0.36cm)	-Ice massage -Ice bag	15 min	Sequence generation
Myrer, 1997 RCT	N=16 healthy Depth of measurement: 1 cm below subcutaneous fat	Calf (male: 17.2 +/-7.5mm; female: 20.9 +/-8mm)	Crushed ice	20 min	Sequence generation

Appendix Table 8:
Joint temperature reduction

Study	Methods	Body part (Barrier)	Mode	Duration (hours)	Factors lowering risk of bias (Cochrane tool)
Levy, 1997 RCT	N=15 Shoulder arthroscopy and debridement of the subacromial spaces	Shoulder: glenohumeral and subacromial spaces (Double thickness 4x4 gauze pad and silk tape)	- Cryocuff rechilled every 15,30,45 minutes - Control (dressing only)	1.5	Sequence generation Allocation concealment
Zaffagnini, 1998 RCT	N=30 Arthroscopic knee surgery (medial or lateral meniscectomy)	Knee (Sterile gauze pads and a layer of sterile webril)	- Cryocuff automatic pump re-chilling every 30 secs - Control (dressing only)	1	Sequence generation Allocation concealment
Ohkoshi, 1999 RCT	N=21 ACL reconstruction (bone tendon bone patellar graft; single incision technique)	Knee: Suprapatellar pouch / intracondylar notch (5 sheets 20x30 gauze, wrapped in elastic bandage)	-Commercial icing machine set to 5°C; -Commercial icing machine set to 10°C -Control (dressing only)	48	Sequence generation
Martin, 2001 CT	N=17 Knee arthroscopy (meniscal tears, OA, loose bodies, plica, chondromalacia)	Knee: lateral gutter (Two layer bandaging)	- Cryocuff immediately post surgery - Cryocuff 1 hour post surgery Both groups water changed every 30 minutes	1-2	
Osbahr, 2002 RCT	N=20 subjects with full thickness rotator cuff tears repaired with a corkscrew open repair	Shoulder joint / AC joint (Large bulky dressing)	- Polar care continuous cooling replenished every 4-6 hrs - Control (dressing only)	23	Sequence generation Allocation concealment Blinded outcome assessment
Martin, 2002 CT	N=12 Knee arthroscopy (meniscal tears, OA, loose bodies, plica, chondromalacia)	Knee: medial gutter and supra-patellar pouch (Two layer bandaging)	-Cryocuff immediately post surgery - Cryocuff 1 hour post surgery Both groups water changed every 30 minutes	1	
Glenn, 2004 CT	N=16 ACL reconstruction (middle third patellar graft; standard two incision technique, metal interface screws)	Knee: medial gutter and supra-patellar pouch (Two layer bandaging)	-Cryocuff for first hour post surgery - Cryocuff for second hour post surgery Both groups water changed every 30 minutes	1	
Sanchez-Inchausti, 2005 Observational/RM	N=23 Knee arthroscopy	Knee: suprapatellar pouch (Round cotton bandage)	Ice bag	1	

Appendix Table 9: AMSTAR Scale

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Appendix Table 10: Cochrane Risk of bias tool

1. Sequence generation Was the allocation sequence adequately generated? (Yes / No / Unclear)
2. Allocation concealment Was allocation adequately concealed? (Yes / No / Unclear)
3. Blinding ‖ Was knowledge of the allocated intervention adequately prevented during the study? Assessments will be made for: a. Outcome assessors: primary outcomes: (Yes / No / Unclear)
4. Were incomplete outcome data adequately addressed? (Yes / No / Unclear)
5. Free of other bias **a. Is the PRICE protocol clear and consistent between groups?** (Yes / No / Unclear) **b. Were no co-interventions used, or if present, were they standardised across groups?** (Yes / No / Unclear)

‖ blinding of participant or caregivers were not considered based on the nature of the interventions.