Cryotherapy for treating soft tissue injuries in sport medicine: a critical review

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ABSTRACT

Sports medicine physicians and physiotherapists commonly use cryotherapy (eg, ice application) postinjury to decrease tissue temperature with the objective of reducing pain, limiting secondary injury and inflammation, and supporting healing. However, besides the analgesic effect of cryotherapy, a literature search revealed no evidence from human studies that cryotherapy limits secondary injury or has positive effects on tissue regeneration. Thus, our current understanding of the potential mechanisms and applications of cryotherapy largely relies on the results from animal studies. Importantly, treatment should not aim at obliterating the inflammatory and regeneration processes but instead aim to restore an adapted/normal regulation of these processes to improve function and recovery. However, some animal studies suggest that cryotherapy may delay or impair tissue regeneration. With the translation of laboratory animal studies to human sport medicine being limited by different injury and muscle characteristics, the effect of cryotherapy in patients with musculoskeletal injuries is uncertain. Thus, pending the results of human studies, cryotherapy may be recommended in the first 6 hours following an injury to reduce pain (and possibly haematoma), but it should be used with caution beyond 12 hours postinjury as animal studies suggest it may interfere with tissue healing and regeneration.

WHAT IS ALREADY KNOWN

⇒ Cryotherapy is one of the basic principles of the RICE protocol (Rest, Ice, Compression, Elevation) and similar iterations (PRICE (Protect+RICE) and Protect, Optimal Loading instead of Rest) taught and applied as a sport medicine standard.
⇒ Ice and cryotherapy in general are currently used by the vast majority of athletes following an injury.

WHAT ARE THE NEW FINDINGS

⇒ There is no human study demonstrating the healing effect of cryotherapy for soft tissue injury.
⇒ Simulated injuries in animal models may differ from human sport injuries.
⇒ Recognising the limitation of applying animal data to human patients, animal studies suggest that cryotherapy may impair and delay muscle regeneration following a severe muscle injury but may be potentially useful for minor muscle injury.
⇒ Animal studies suggest that cryotherapy may compromise long-term tendon healing and mechanical integrity.
⇒ Cryotherapy offers short-term pain relief (eg, postacute injury and postoperative) and may have other clinical benefits (although not scientifically demonstrated) in the initial hours following an injury.
⇒ Thereafter, cryotherapy provides a potential modality to reduce pain following acute injury but continued use should be done with caution to avoid potential interference with the regeneration processes as suggested by animal studies.

INTRODUCTION

Cryotherapy is generally defined as an intervention which assists in the removal of heat from the tissue. Local cryotherapy is widely used in the treatment of acute soft tissue injuries. It can be applied using various modalities such as ice packs, cold water immersion or cooling garments and ice with compression among the most popular.[1] There is an urban myth that ice treatment became popular following the case of Everett Knowles, a 12-year-old American who severed his arm jumping onto a freight train on May 23, 1962. The case attracted attention as the first successful reattachment of a major limb and, with the surgery details being too technical, the press focused on the application of ice to preserve the severed arm.[2 3] However, it is unlikely it was a turning point in medical practice as ice has been used since antiquity, and ice usage was already documented in the scientific literature with the Medline database notably referencing an article titled 'Injury, Ice and Compression' in 1957.[4] Although the title of this article may be seen as the origin of the concept of ice and compression in athletes, it only discussed burn patients after an explosion and the anaesthetic effect of cold for field amputation but did not mention sport-related injury or treatment. Instead, the modern use of cryotherapy for soft tissue injury treatment can be dated from 1978 and the introduction of the RICE protocol (Rest, Ice, Compression, Elevation) by *The Sports Medicine Book*.[5] The RICE protocol later evolved to PRICE (Protect+RICE) and then POLICE (Optimal Loading instead of Rest) where ice constitutes one of the basic principles, largely contributed to popularise the use of cryotherapy for

soft tissue injury treatment.[6] Cryotherapy is advised by about 80% of emergency department consultants in the management of acute ankle sprains.[7] In a recent survey, 88% of the athletes reported using cryotherapy after an acute sport-related injury.[8] Cryotherapy is primarily used to reduce pain perception after a muscle, tendon or ligament injury while it is also largely assumed to be beneficial in decreasing tissue metabolism and limiting secondary injury, inflammation, swelling and haematoma.[1 5 8 9] However, despite its popularity and suggested benefits, recent controversies have emerged around the use of cryotherapy. In fact, very limited evidence supports the benefits of cryotherapy in the treatment of soft tissue injuries. Along with the recent controversies and the lack of evidence, a new acronym PEACE & LOVE (Protection, Elevation, Avoid anti-inflammatories, Compression, Education—for immediate care—then Load, Optimism, Vascularisation and Exercise—for subsequent management) was recently proposed.[10] It is important to note that this latest protocol does not include the I for Ice anymore. Indeed, even Dr Mirkin himself, who proposed the RICE protocol in 1978 for pain relief, stated in 2015 that '*coaches have used my 'RICE' guideline for decades, but now it appears that both Ice and complete Rest may delay healing, instead of helping*'.[11] Conversely, other authors have highlighted that the lack of current evidence is valid both ways, and some benefits such as pain management should not be ignored.[12]

A systematic literature search was performed on cryotherapy's effect on tissue healing but revealed a lack of human studies (figure 1). With an absence of evidence not being evidence of absence, the current document is a critical review challenging the common beliefs surrounding cryotherapy for musculotendinous injuries by evaluating the direct and indirect effects of localised cryotherapy for injury management.

METHODS

452 studies were screened (figure 1) but only 1 human study and 26 animal studies (table 1) matched the below criteria.

Search strategy

The following words and their combinations were used to perform the literature search on Medline and Web of Science databases, without using any automatic filter: "cryotherapy" OR "cryotherapies" OR "ice" OR "icing" OR "cooling" OR "cold" and "skeletal muscle" OR "skeletal muscles" OR "muscle" OR "muscles" OR "tendon" OR "tendons" OR "ligament" OR "ligaments" and "muscle injury" OR "muscle injuries" OR "muscle regeneration" OR "secondary injury" OR "tendon injury" OR "tendon injuries" OR "tendon rupture" OR "ligament tear" OR "ligament injury" OR "ligament injuries" OR "tendon repair"

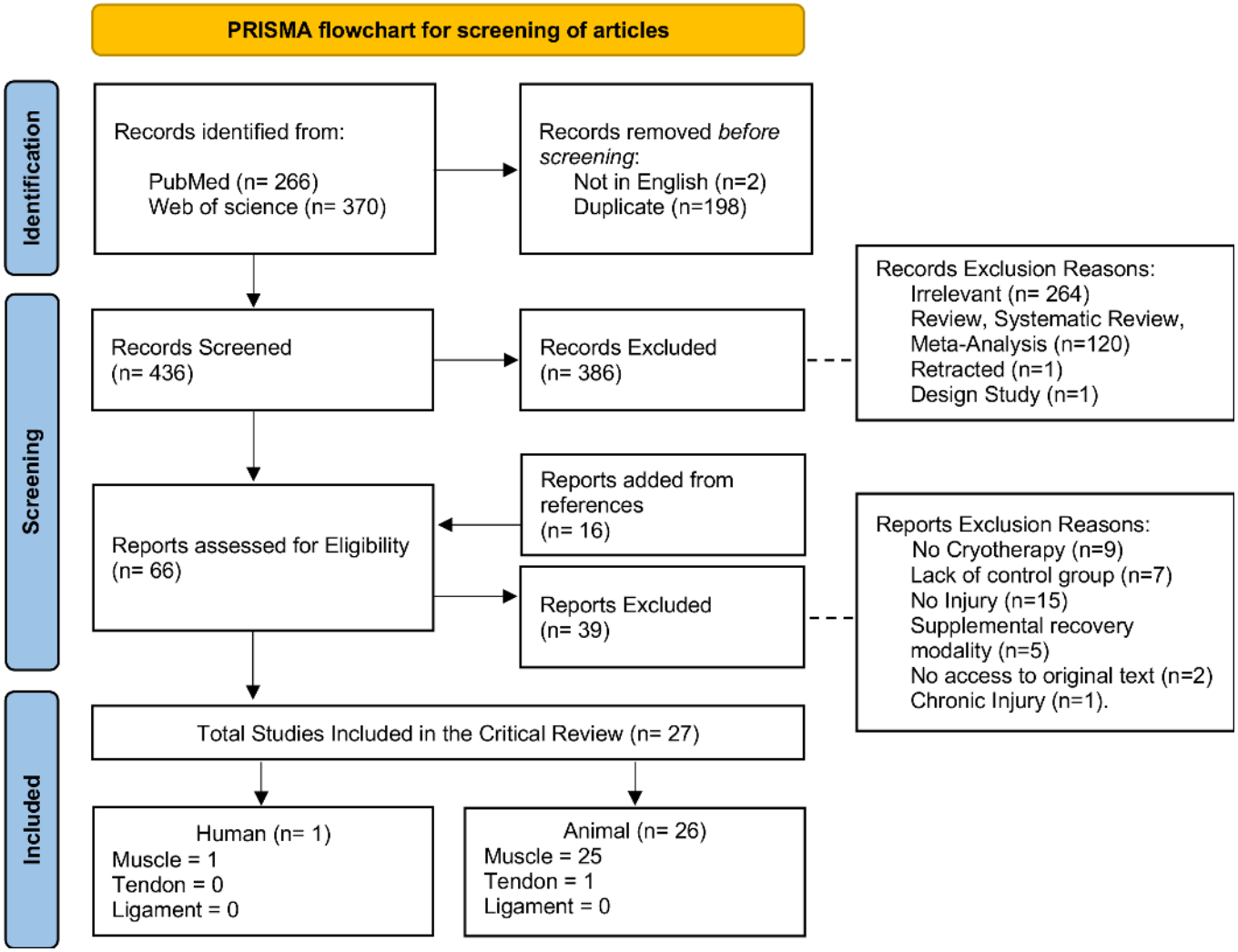

Figure 1 PRISMA flow chart of the articles screened. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Outcome of the literature review

Study	Injury model	Cryotherapy	Measures	Effects	
Animal muscle injury					
Carvalho *et al*[48]	Strain	Ice	Muscle and blood oxidative stress markers, damage markers @ days 1, 5, 10, 15 postinjury	Decreased CK activity @ 1, 5 and 10 days—decreased stress markers levels	+
De Almeida *et al*[72]	Single trauma	Ice pack	Il-1β - IL-6 - TNFα at+6 hour from injury @ 6 hours post	ND with injury control	=
Deal *et al*[26]	Contusion	Ice	Microvascular permeability @ 300 min	Decreased microvascular permeability	+
Dolan *et al*[24]	Contusion	Cold water	Limb volume @ 240 min postinjury	Smaller limb volume up to 240 min postinjury	+
Dos Santos Haupenthal *et al*[73]	Laceration	Ice pack	Muscle mechanical properties, inflammation and oxydative stress markers @ 48 hours and 7 days postinjury	ND on muscle mechanical properties—reduced increase of TNF-α, IFN-γ, IL1β—increase in IL4, IL6, IL10—SOD and GSH limited to control levels	+
Kawashima *et al*[32]	Stretching+electrical stimulation	Ice pack	Macrophage typology, infiltrated cells, Inflammation markers, Myogenic markers, CSA @ days 1, 3, 5, 7 and 14	Smaller regenerative fibres CSA—delayed necrotic fibre removal, M1 infiltration, M1/M2 shift—delayed TNF-α, IL10, IGF-1 levels—delayed emergence of Pax7+SC	—
Kenjo *et al*[25]	Injection	Cold water	Fos-labelled cells, paw volume @ 1, 2, 4, 6, 12 and 24 hours	Decreased paw volume—decreased Fos-labelled cells, number @ 1–2 hours and delayed peak expression.	+
Hurme *et al*[74]	Contusion	Ice pack	Muscle temperature, neutrophils, macrophages, desmin stainings, collagen typology @ 1, 2 and 6 hours and days 1, 2, 5 and 7	No numbers and statistics reported: Smaller haematoma—lower number of inflammatory cells—delayed SC appearance	—
Lee *et al*[23]	Contusion	Cold perfusion	Venule internal diameter, blood flow and erythrocyte velocity, number of rolling/adhering leucocytes @ Before, immediately after contusion and after cooling	3°C: Decreased venule diameter—decreased blood flow rate and erythrocyte velocity—decreased rolling and adhering leucocyte number 27°C: No decrease in blood flow rate—increased erythrocyte velocity—limited decrease in rolling and adhering leucocytes	— +
McMaster and Liddle[75]	Crush	Cold water	Limb swelling @ 2, 4, 6 and 24 hours postinjury	No statistics: Acute cryotherapy: lower limb swelling @ 30°C Multiple cryotherapy: Residual swelling @ 24 hours	—
Merrick *et al*[45]	Crush	Ice pack	Triphenyltetrazolium chloride (TTC) @ 5 hours	Higher reduction in TTC	+
Miyakawa *et al*[34]	Crush	Ice pack	Neutrophils, macrophages (CD68), MCP1 @ 3, 6, 9 and 12 hours postinjury	Delayed neutrophil appearance—limited macrophages and MCP1+cells number	—
Miyazaki *et al*[31]	Crush	Ice pack	Regenerative fibres, M1, M2, iNOS+, Pax7+cell number, TNFα and IGF1 expression @ 6 hour, 12 hours and days 1, 2, 3, 4, 5, 6, 7 postinjury	Smaller regenerative fibres CSA—decreased number of M1, iNOS+cells and TNFα expression—ND for M2—decreased Pax7+cell number	—
Nagata *et al*[42]	Crush	Ice pack	Regenerative fibres, neutrophils, macrophages typology, iNOS+, arginine1, myogenic factors expression, Pax7 and eMyHC+cell number @ days 1, 2, 3, 5, 7, 14 postinjury	Higher CSA of regenerative fibres—lower iNOS+cells number—ND for M2—earlier increase in Pax7+myoD+ SC—earlier increase in eMyHC+cells	+
Oliveira *et al*[46]	Freezing	Ice pack	Muscle weight and injury area @ 4 hours 30 min postinjury	Smaller injury area @ 4 hours 30 min	+
Puntel *et al*[76]	Contusion	Ice	Muscle and blood oxidative stress markers, damage markers @ Before and 24 hours	Limited oxidative stress increase	+
Schaser *et al*[27]	Impact	Cold perfusion	Microvascular diameters, density and permeability red blood cell velocity, leucocytes, neutrophils, macrophages number @ 90 min post-trauma	Maintained functional capillary density—decreased rolling leucocyte percentage and neutrophilic granulocytes number	+
Schaser *et al*[28]	Impact	Cold perfusion	Microvascular parameters—inflammatory cells number, desmin cells @ 24 hours postinjury	Reduced intramuscular pressure—maintained capillary density—decreased adhering leucocytes, neutrophilic granulocytes, macrophages number—lower desmin—ratio	+

Continued

Table 1 Continued

Study	Injury model	Cryotherapy	Measures	Effects	
Shibaguchi *et al*[33]	Injection	Ice pack	Muscle weight, protein content, CSA, collagen area, pax7+cells, TGFβ, HSP72, CD68 expression @ days 3, 7, 15, 28 postinjury	Larger collagen area @ 7 and 15D—ND in protein content, muscle weight, CSA—ND in protein expressions and SC number	—
Shibaguchi *et al*[77]	Injection	Ice pack	Muscle weight, Myosin typology, PGC1α, HSP72 expression @ 1, 2, 4 weeks postinjury	ND in myosin typology, PGC1-α, HSP72	=
Singh *et al*[29]	Contusion	Ice block	Neutrophils, macrophages number, vascular area, CD34, vWF, VEGF, nestin expression, vessel volume, regenerative fibres @ days 1, 3, 7 and 28 postinjury	Delayed/attenuated neutrophils and macrophages number—decreased vWF, VEGF and nestin expression—smaller vessel volume—higher number of immature fibres @ 28 days	—
Siqueira *et al*[47]	Freezing	Ice pack	Oxydative stress markers (DCF-RS, TBARS, MTT, CAT, SOD, SH) @ days 3, 7 and 14 postinjury	Lower levels of DCF-RS, SOD, TBARS and CAT	+
Smith *et al*[78]	Contusion	Ice	Arterioles/venules diameter with laser Doppler into dorsal microcirculatory chamber @ 24 hours post	ND in arteriolar diameter—higher venular diameter	+
Takagi *et al*[30]	Crush	Ice pack	CSA, centrally nucleated fibres %, ED1 macrophage, collagen fibre area @ 6 hours, 12 hours and days 1, 2, 3, 4, 5, 6, 7, 14 and 28 postinjury	Higher centrally nucleated fibre proportion @ 14D for ice—smaller CSA—larger collagen fibre area	—
Vieira Ramos *et al*[71]	Freezing	Ice pack	Muscle weight, regeneration markers mRNA and staining @ days 3, 7 and 14 postinjury	ND in muscle weight—lower proportion of CD68+and TNF-α+ cells—lower NF-κB and TGF-β mRNA level	+
Human muscle injury					
Prins *et al*[20]	Calf muscle rupture	Ice pack	Pain, functional capacity, reconvalescence time	ND in pain, functional capacity and reconvalescence time—high exclusion rate for late diagnostic (>6 hours)—calculated N for significance: 396 patients	=
Animal tendon injury					
Zhang *et al*[62]	Needle	Refrigerant gel	PGE2 levels from 0 hours to 3.5 hours postinjury (every 0.5 hour)	Reduced PGE2 levels by 46.3% in patellar tendon and 50.85% in Achilles tendons.	—

CAT, catalase; CD34, cluster of differentiation 34; CD68, cluster of differentiation 68; CK, creatine kinase; CSA, cross sectional area; DCF-RS, dichlorofluorescein reactive substances; ED1, Pan macrophage marker ED1; eMyHC, embryonic myosin heavy chain; GSH, glutathione; HSP72, Heat shock protein 72; IFNγ, interferon γ; IGF-1, insulin-like growth factor; IL-4, interleukin 4; IL-6, interleukin 6; IL-1β, interleukin 1β; iNOS, inducible nitric oxide synthase; M1, proinflammatory macrophage; M2, anti-inflammatory macrophage; MCP1, monocyte chemottractant protein 1; mRNA, messenger ribonucleic acid; MTT, methyl thiazol tetrazolium; myoD, myogenic differentiation; ND, no difference; NF-κB, nuclear-factor κ-light-chain-enhancer of activated B cells; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PGE2, prostaglandin E2; SC, satellite cell; SH, nonprotein thiol; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor; TNF-α, tumour necrosis factor α; VEGF, vascular endothelial growth factor; vWF, von Willebrand's factor.

OR "ligament repair" OR "muscle repair" OR "tendon healing" OR "muscle healing" OR "ligament healing" OR "sprain".

Searches were performed on titles, abstract and key words. Following the search, article duplicates were removed, and the remaining articles were screened for their eligibility using predefined eligibility criterion (see below). The reference lists of the articles were examined to identify potential additional eligible studies, and additional references cited in previous literature reviews and/or suggested during the reviewing process were also included for assessment (figure 1).

Eligibility

The identified studies were screened for eligibility by two independent authors (VD and YR) using the below inclusion criteria. In case of disagreement on a decision, consensus was sought between the two researchers during re-examination of the study. Eligible results were divided a posteriori depending on the related injured tissue (muscle, tendon and ligament) and the study population (human and animal).

Inclusion criteria were (1) a cryotherapy modality was used in the treatment of an acute injured muscle, tendon or ligament, (2) the treated soft tissue (muscle, tendon or ligament) suffered an acute strain injury, rupture, sprain, contusion, laceration, tear or presented a confirmed state of myofibre degeneration or myofibre regeneration, defined as a situation where myofibre necrosis has occurred,[13] (3) the cryotherapy condition was compared with a control condition, (4) the cryotherapeutic modality was applied only after the injury event and was not in combination with any other treatment modality, (5) original research article and (6) English language.

Equity, diversity and inclusion statement

The author group consists of junior, mid-career and senior researchers and clinicians from different disciplines including physiotherapy, sports medicine and orthopaedic surgery. The authors come from six countries, four in Europe, one in the Middle East and one in the Far East but include only one woman. While this review assessed existing data published in

English, cryotherapy is used worldwide in sports medicine, from high-profile sports events to resource-limited settings.

Current knowledge of cryotherapy for muscle injury treatment

Acute skeletal muscle injuries are one of the most frequent injuries in sport, representing up to 49% of total injuries.[14 15] The use of cryotherapy has been largely advised as an acute treatment, applied immediately postinjury and during the following ~6 hours to decrease pain and limit secondary injury, inflammation, swelling and haematoma.[1 16] But it is not uncommon to see athletes using cryotherapy for longer durations. However, as highlighted in previous reviews, there is no randomised controlled trial (RCT) investigating cryotherapy in the treatment of acute soft tissue injuries.[17–19] Indeed, only one article examining the effects of cryotherapy on human muscle injury was eligible in the current review; a pilot study examining the feasibility of an RCT on cryotherapy to treat gastrocnemius tears.[20] The small sample size of this study did not demonstrate a difference between the cryotherapy and the control condition on pain perception, functional capacity recovery and convalescence time. The authors concluded that a larger trial would be feasible[20] but highlighted the difficulty to recruit patients in a short time frame after an injury vs the necessity to recruit a large cohort of patients to detect small differences. For example, to detect a 10% difference in full recovery rate between the experimental group and a control group, a total number of 396 participants would have been required (power=0.80; α=0.05).[20] In summary, while the literature on pain perception supports a reduction in immediate pain perception during cryotherapy application, there is currently no evidence of any other therapeutic benefit on muscle healing in humans.[21 22] Noteworthy, it has been hypothesised that the reduction in pain after cryotherapy could allow an earlier and more aggressive exercise rehabilitation, but no evidence currently supports this theory.[17] Thus, while waiting for more human studies, it is necessary to rely on animal studies for now. The current literature search identified 25 animal trials investigating muscle injuries (figure 1), performed on rodents or rabbits and using ice, cold water immersion or muscular perfusion as a cryotherapeutic intervention. A large variability between protocols (eg, mode of cooling, cooling time and frequency, animal characteristics, injury methods and muscles injured) and conflicting results were observed (table 1).

The modification of the postinjury vascular response to restrict hematoma and swelling often represents one of the main reasons to justify the use of cryotherapy postinjury. Indeed, in rats, postinjury cryotherapy decreased blood flow rate, venule diameter and erythrocyte velocity[23] and limited the postinjury increase in paw volume up to 4 hours and 6 hours[24 25] suggesting a limitation of early swelling and haematoma formation. Furthermore, local perfusion of cold saline in injured skeletal muscle was reported to attenuate postinjury microcirculatory dysfunctions at 1 hour, 5 hours and 24 hours postinjury.[26–28] Contrastingly for longer-term recovery, decreases in blood vessel volume and in the expression of angiogenic markers were found in rats during the first 7 days postinjury after a single 20 min ice application suggesting an impairment of angiogenic mecanisms.[29]

Regarding muscle architecture, applying ice postinjury (from 1×20 min immediately post to repeated application up to 48 hours postinjury) in mice and rats delayed the recovery of muscle fibre cross-sectional area.[30–32] Furthermore, a single 20 min postinjury ice application was also reported to induce a higher increase in collagen fibre area than a control condition up to 28 days after the injury.[30 33] The effect of cryotherapy on postinjury inflammatory mechanisms remains unexplored in humans but has been widely studied in animals. Along with the modification in the vascular response, a decreased number of rolling and adhering leucocytes was illustrated immediately after a local perfusion of cold saline, 90 min and 24 hours after a contusion injury.[23 27 28] Importantly, cryotherapy decreased the number of neutrophils and macrophages present around the injury 3 hours to 5 days after the injury and potentially perturbed their infiltration into necrotic fibres.[29 32 34] This resulted in a slowed disappearance of the necrotic tissue, suggesting an impairment of efferocytosis; the clearance process of the apoptotic tissue from the muscle.[32] A delay in the macrophages phenotype shift from proinflammatory to anti-inflammatory was also observed after icing, which may be responsible for the observed decrease in satellite cell accumulation in the regenerative area[31 32] and the excessive collagen deposition.[33] Indeed, the importance of the postinjury inflammatory response has been extensively debated.[35–37] Inflammation was usually considered to have harmful effects mainly due to the cytotoxic nature of the proinflammatory cells, so treatment tried to reduce the inflammatory response using cryotherapy or non-steroidal anti-inflammatories.[36 37] However, despite potential adverse effects, the acute inflammatory response has been shown to be necessary to achieve complete muscle regeneration. Preventing inflammatory processes may actually hinder and delay muscle regeneration.[38–40] In summary, animal studies suggest that cryotherapy postinjury impairs and delays muscle regeneration and recovery. However, in some studies, though cryotherapy attenuated and/or delayed some aspects of angiogenesis/revascularisation, it did not induce substantial differences in capillary density or muscle growth.[29]

Although the majority of animal studies indicate the potential negative effect of cryotherapy on the recovery from large necrotised injury, the transfer to lower-grade human injury has to be done with caution. Indeed, it has been argued that the negative results observed with cryotherapy on injured animals could be due to excessive cooling.[6 41] Similarly, the magnitude of the injury may represent a key factor modulating the effects of cryotherapy on muscle regeneration (figure 2). As presented above, cryotherapy decreases macrophage activity and slows regeneration of large muscle injuries but, in contrast, icing a minor injury may accelerate the accumulation of activated satellite cells and facilitate the cross-sectional area recovery of the regenerative cells. Indeed, in a model of limited myofibre necrosis (necrotising approximately 10% of the muscle) on rats, Nagata *et al*[42] found a facilitated muscle recovery after multiple sessions of icing (three sets of 30 min icing each with 90 min interval immediately after the injury and at 24 and 48 hours postinjury). The authors concluded that the decrease in proinflammatory inducible nitric oxide synthase macrophages following cryotherapy, limited the injury expansion and facilitated the resolution of inflammation leading to an acceleration of the regenerative process. They proposed that, cryotherapy could be an appropriate intervention on limited muscle damage but should be avoided on large-scale muscle injury.[42] Another limitation in transferring animal studies to humans is within the nature of experimentally induced lesions as injection[33] or eccentric lesions[32] would not be accompanied by intramuscular haematoma. Thus, as illustrated previously, cryotherapy (especially when associated with compression) may have a clinical effect by limiting this haematoma, an effect that would not be accounted in some animal model.

In this context, cryotherapy could facilitate a decrease in secondary injury proliferation,[1 9 43] as injury expansion has also

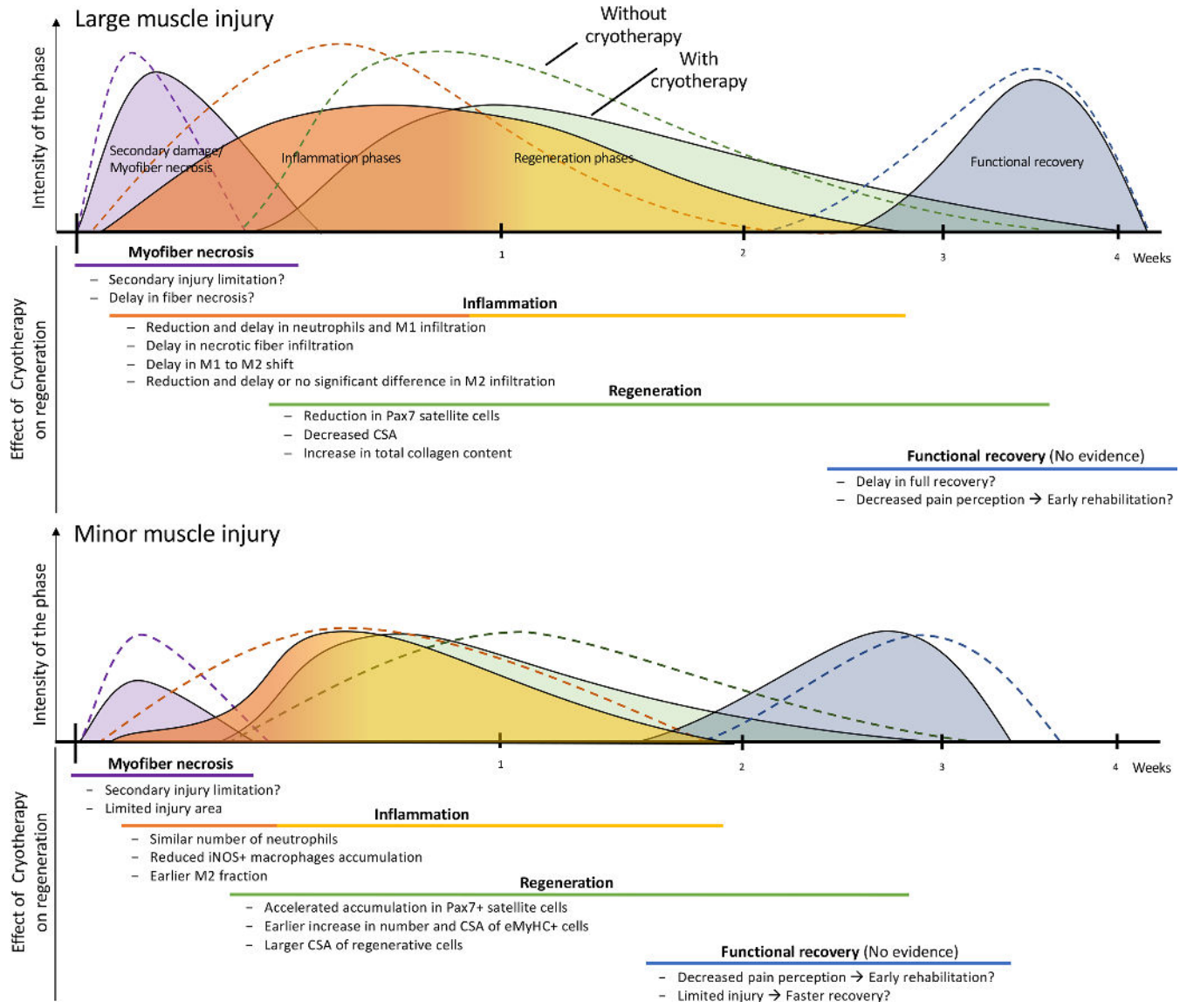

Figure 2 Model of muscle regeneration kinetic from animal studies. Cryotherapy reduces the inflammatory response but delays the muscle regeneration for large muscle injury in animals. Representation based on animal literature results. CSA, cross-sectional area; eMYHC, embryonic myosin heavy chain; iNOS+, inducible nitric oxide synthase positive; M1, proinflammatory macrophage phenotype, M2, anti-inflammatory macrophage phenotype.

been shown to be reduced following the use of non-steroidal anti-inflammatories in animals.[44] The concept of secondary injury was introduced in 1995 without scientific evidence[43] and can be defined as the proliferation of the initial tissue injury due to the acute inflammatory and oxidative stress response; it is also referred to the literature as injury expansion.[1 42] However, the involved mechanisms remain obscure, and no evidence exists in humans to confirm such an effect. In animals, only a few studies provided evidence involving possible benefits of cryotherapy on secondary injury. In rats, a 5-hour ice application following a crush injury was shown to limit the decrease in triphenyltetrazolium chloride (TTC) immediately post-icing, with a decrease of TTC being indicative of possible mitochondrial disruption.[45] A subsequent study observed a smaller injured area 270 min after 3×30 min of ice application compared with an injury control group.[46] Furthermore, a decrease in oxidative stress was observed during the 14 days following a freezing injury in rats treated with cryotherapy (3 times 30 min icing every 2 hours immediately postinjury and at 24 and 48 hours post).[47] A similar limitation in oxidative stress was observed during the 15 days following a strain injury in rats treated twice daily with 5 min icing.[48]

In summary, even if a limited necrotised injury model in some animal studies may more closely resemble the conditions of most human injuries, a direct translation of these findings (either negative or positive) to clinical practices remains speculative considering the large differences between human and animal models.[6] While some cryotherapy effects such as a decrease in inflammatory and oxidative stress responses may be present in human as well, all responses to cryotherapy will also be modulated by the large differences in muscle (and fat) mass between species. As such, to date, it is, therefore, not possible to list the effects of cryotherapy and even less to generate evidence-based guidelines on timing, duration and temperature for cryotherapy application in humans.

Current knowledge of cryotherapy for tendon/ligament injury treatment

The systematic literature search revealed that there was no study in humans on the effect of cryotherapy on either tendon or

ligament healing (figure 1). It should, however, be acknowledged that there are several studies focusing on patient responses, with some reporting that cryotherapy can reduce postoperative pain, thereby minimising the use of pain medications,[49–53] whereas others found no significant benefits in terms of pain relief, limb swelling reduction or increased range of motion.[53–57] A meta-analysis based on seven studies nevertheless estimated that cryotherapy has a role in postoperative pain control, though without improvements in range of motion or drainage.[58] However, Miranda *et al*[59] highlighted the major methodological limitations of existing systematic reviews,[17 60 61] such as the inclusion of non-RCTs, high risk of bias, lack of appropriate control and included only two RCTs, which did not provide convincing evidence of cryotherapy's effectiveness. In summary, the evidence that cryotherapy benefits patient response is limited and the evidence that cryotherapy benefits tissue healing is nil. Waiting for much-needed human studies, it is, therefore, necessary to extrapolate from animal studies in the meantime.

Only one animal study investigated the effect of cryotherapy on tendon healing (figure 1, table 1). This study reported that 30 min of cryotherapy postinjury reduced renal prostaglandin E2 (PGE2) levels by 46% in patellar tendons and 51% in Achilles tendons within the first 3.5 hours.[62] Indeed, cryotherapy has the potential to inhibit the production of PGE2 and cyclooxygenase-2 (COX-2) protein, hence reducing the inflammatory phase.[62 63] As such, our understanding to date of the effects of cryotherapy on tendon and ligament healing is largely based on animal studies investigating the inhibition of PGE2 and COX-2 following tendon or ligament injuries.[64] In this context, studies on rats and mice demonstrated that early treatment with parecoxib or ibuprofen delayed the restoration of the extracellular matrix and reduced various mechanical properties of healing tendons (eg, stiffness and modulus).[65–67] However, the early inflammatory phase following an injury is responsible for breaking down damaged tissue and promoting tissue repair.[68] Therefore, even if blocking the early inflammatory phase provides short-term pain relief, animal studies suggest that it may compromise long-term tissue healing and mechanical integrity. In view of this, the widespread use of cryotherapy is not evidence-based and more research is needed, particularly in humans. In the meantime, based on animal studies, it would be appropriate to use cryotherapy with caution for anything else than pain relief.

Which practice to adopt when there are no evidence-based protocols?

As presented above, the literature is equivocal regarding cryotherapy for soft tissue injuries. Despite no evidence of a beneficial effect of continuous application of cryotherapy except for pain relief[1] and the emerging evidence of its drawback, a recent survey reported that athletes use chronic cryotherapy with an average of 2–3 applications (of 15–20 min) per day for 4 days.[8] Moreover, due to the absence of human clinical trials, recommendations for cryotherapy on muscle injury are mainly based on animal studies. For example, it has been advised to use prolonged icing early after an injury to achieve a 5°C–15°C muscle temperature,[1 6 69] but this value may not even be attainable in humans, especially when considering deep muscle tissue or area covered by adipose tissue.[70] In fact, both the cooling effect and the effect of cooling of different cooling interventions on various injured human tissues remains largely unknown. Thus, both the positive and negative results observed in animal studies using aggressive cooling and injury models may be irrelevant in human. Therefore, given the extent to which both medical and sports practitioners use and recommend cold applications for athletes, more research is warranted. Indeed, '*if cryotherapy was a pharmacological therapy, would it be an evidence base to support its use?*'.[19] Moreover, future human studies will also need to clarify the posology of such treatment in terms of timing, duration and temperature; acknowledging that those parameters likely depend on injury type and severity, but also on the parameter affecting the thermal responses of the targeted tissue such as fat and muscle mass and injury location. For example, some surgeons have anecdotally mentioned that they recommend to their patients to apply ice postknee surgery but a hot pack postshoulder surgery.

In the meantime, waiting for human studies, we should consider that (1) cryotherapy has been advised as an acute intervention immediately postinjury,[1] with the aim to limit secondary injury,[1] but without human evidence and through mechanisms that remain obscure; (2) some animal studies failed to demonstrate a reduction in secondary injury with icing[29 30 32] and instead suggest that using cryotherapy postinjury may have negative effects by delaying the inflammatory processes and the regeneration cascade,[32 71] but not necessarily substantially impacting muscle regeneration[29 71] and (3) a few studies reported a decrease in injury expansion with an early and chronic icing treatment[42 46] when using a limited necrotic area which may be closer to human injuries than more extreme animal models.

CONCLUSION

Contrary to popular belief, there is currently no evidence of any positive (or negative) effect of cryotherapy on human tissue regeneration. Conversely, animal literature raises some concerns about its use, but those concerns may not be applicable to human. As such, acknowledging clinical experience along the limited literature, we conclude that cryotherapy may still be recommended in the first hours following an injury to reduce pain and possibly haematoma. Afterwards, cryotherapy should be used with caution while awaiting the results of human studies as animal studies suggest that it may delay the regeneration processes. Most importantly, more research is needed in humans to adapt this empirical practice for the good of our patients.

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