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Revisiones

Effect of cryotherapy on the concentration of interleukin 6 induced by physical exercise: a systematic review

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ABSTRACT

Objective: The aim of this study was to carry out a literature review on the effect of cryotherapy on the concentration of interleukin 6 induced by physical exercise. **Methods:** The databases included were PubMed, Cochrane, the Physiotherapy Evidence Database (PEDro), Scopus, Web Of Science and LILACS. Also gray literature: Google Scholar, LIVIVO, Open Grey and Banco de Teses e Dissertações da CAPES. The risk of bias was assessed using the Cochrane tool, RoB 2. The outcome was the concentration of interleukin 6. **Results:** Two randomized controlled trials were selected from 8573 records. The overall risk of bias was of some concern in both studies. One suggests that cold water immersion (CWI) can reduce interleukin-6 (IL-6) levels during intense training. The other found that whole-body cryotherapy (WBC) and CWI versus passive recovery after a single run, with interventions at different times after exercise, had no significant interaction between group and time in significantly increasing IL-6 levels. **Conclusion:** CWI showed greater potential in intense training, while WBC showed more varied results. Future studies should standardize interventions and explore molecular mechanisms to optimize recovery.

Keywords: Cold therapy; exercise-induced muscle damage; muscle injury; interleukins.

Efecto de la crioterapia sobre la concentración de interleucina 6 inducida por el ejercicio físico: una revisión sistemática

RESUMEN

Objetivo: El objetivo de este estudio fue realizar una revisión de la literatura sobre el efecto de la crioterapia en la concentración de interleucina 6 inducida por el ejercicio físico. **Métodos:** Se incluyeron las bases de datos PubMed, Cochrane, Physiotherapy Evidence Database (PEDro), Scopus, Web of Science y LILACS. También se consultó literatura gris: Google Scholar, LIVIVO, OpenGrey y el Banco de Tesis y Disertaciones de la CAPES. El riesgo de sesgo se evaluó mediante la herramienta Cochrane RoB 2. El resultado analizado fue la concentración de interleucina 6. **Resultados:** De un total de 8573 registros, se seleccionaron dos ensayos clínicos aleatorizados. El riesgo global de sesgo fue considerado preocupante en ambos estudios. Uno de ellos sugiere que la inmersión en agua fría (CWI) puede reducir los niveles de interleucina-6 (IL-6) durante entrenamientos intensos. El otro estudio encontró que la crioterapia de cuerpo entero (WBC) y la CWI, comparadas con la recuperación pasiva tras una carrera única, aplicadas en diferentes momentos posteriores al ejercicio, no mostraron una interacción significativa entre grupo y tiempo para aumentar de forma significativa los niveles de IL-6. **Conclusión:** La inmersión en agua fría (CWI) mostró un mayor potencial durante entrenamientos intensos, mientras que la crioterapia de cuerpo entero (WBC) presentó resultados más variados. Los estudios futuros deberían estandarizar las intervenciones y explorar los mecanismos moleculares para optimizar la recuperación.

Palabras clave: Crioterapia; daño muscular inducido por el ejercicio; lesión muscular; interleucinas.

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Efeito da crioterapia na concentração de interleucina 6 induzida pelo exercício físico: uma revisão sistemática

RESUMO

Objetivo: O objetivo deste estudo foi realizar uma revisão da literatura sobre o efeito da crioterapia na concentração de interleucina 6 induzida pelo exercício físico. **Métodos:** As bases de dados incluídas foram PubMed, Cochrane, Physiotherapy Evidence Database (PEDro), Scopus, Web of Science e LILACS. Também foi consultada literatura cinzenta: Google Scholar, LIVIVO, OpenGrey e o Banco de Teses e Dissertações da CAPES. O risco de viés foi avaliado utilizando a ferramenta Cochrane RoB 2. O desfecho analisado foi a concentração de interleucina 6. **Resultados:** De um total de 8573 registos, dois ensaios clínicos randomizados foram selecionados. O risco global de viés foi considerado preocupante em ambos os estudos. Um deles sugere que a imersão em água fria (CWI) pode reduzir os níveis de interleucina-6 (IL-6) durante treinos intensos. O outro estudo verificou que a crioterapia de corpo inteiro (WBC) e a CWI, comparadas à recuperação passiva após uma corrida única, aplicadas em tempos diferentes após o exercício, não apresentaram interação significativa entre grupo e tempo no aumento dos níveis de IL-6. **Conclusão:** A imersão em água fria (CWI) demonstrou maior potencial durante treinos intensos, enquanto a crioterapia de corpo inteiro (WBC) apresentou resultados mais variados. Estudos futuros devem padronizar as intervenções e explorar os mecanismos moleculares para otimizar a recuperação.

Palavras-chave: Crioterapia; dano muscular induzido pelo exercício; lesão muscular; interleucinas.

INTRODUCTION

Over the centuries, cold temperatures have been used by humans for healing, health and sports recovery purposes. The application of cold for therapeutic purposes is regularly referred to as cryotherapy (1). From a physiological point of view, the benefits of cryotherapy are due to the reduction in metabolism and analgesic effects, resulting from the reduction in the speed of transmission of sensory nerve signals (2–6).

Traditionally, ice is used to treat musculoskeletal injuries (6,7), while cold water immersion or whole-body cryotherapy (WBC) are used for recovery from exercise. Among sports recovery methods, cold water immersion (CWI), contrast water therapy (CWT) and WBC have been widely applied to improve recovery after strenuous exercise (8,9).

Exercise-induced muscle damage usually results from performing unusual exercises or exercises of great intensity or duration. The most documented symptoms of muscle damage include prolonged impairment of muscle function; delayed onset muscle soreness (DOMS); the presence of muscle damage markers and inflammation (10–13). Following high-intensity stress or an inadequate level of exercise for around 24 hours, leukocytes secrete various inflammatory mediators (TNFα, IL-1, etc.), and even anti-inflammatory mediators such as interleukin 6 (IL-6) and IL-10, which alter the pain threshold (14–16). Specifically, IL-6, which is the main cytokine released by skeletal muscle and has an extremely high concentration during exercise, improves insulin sensitivity, mobilizes immune cells, reduces DNA damage and stimulates the production of other anti-inflammatory cytokines (16–18).

In a meta-analysis published by Leeder et al. (19) CWI has been shown to be an effective strategy for reducing the symptoms of DOMS after a series of strenuous exercises. One of the proposed mechanisms by which exposure to cold improves recovery is its vasoconstrictive and metabolism-reducing effect, which leads to a reduction in the inflammatory process (20). However, this effect can also influence a reduction in the levels of anti-inflammatory factors such as IL-6 (21), in other words, it could have a contradictory effect. This raised the question of the possible effects of cryotherapy in reducing the concentration of IL-6, hindering its activity in reducing insulin resistance, changes in lipid metabolism and inflammation. Although the widespread use of cryotherapy to reduce the symptoms of muscle damage after exercise is popular in the field of sports science, the evidence is still limited as to its effectiveness. Due to conflicting data, the aim of this research was to carry out a systematic review analyzing the effects of cryotherapy on IL-6 concentration in humans after physical exercise.

METHODS

Protocol

This review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, and registered with the Open Science Framework (OSF) https://doi.org/10.17605/OSF.IO/M97N8.

Eligibility criteria

The acronym PICOS was used to formulate the question focused on in this study. P (population) - physically active men and women; I (intervention) - cryotherapy; C (comparison) - exercise group or control group; O (outcome) - interleukin 6 concentration; S (study design) - randomized clinical trials.

Inclusion criteria: Physically active individuals, without the use of licit and/or illicit drugs, with no restrictions on the use of cryotherapy.

Exclusion criteria: Clinical trials that did not use cryotherapy as the main technique, studies that could not be read in full, even after contacting the author, were excluded from the study.

Search strategies

A comprehensive and sensitive search (table 1) was carried out, with no restrictions on period or language. The initial search was conducted using the keywords: Muscle damage, Cryotherapy and Muscular inflammatory responses, in the PubMed database, with the Medical Subject Headings (MeSH) medical metadata system and also free terms. The following databases were consulted: PubMed, Cochrane, the Physiotherapy Evidence Database (PEDro), Scopus, LILACS, Web Of Science. Grey literature was also consulted via Google Scholar, LIVIVO, Open Grey and the CAPES thesis and dissertation catalog.

Selection of studies

Two independent reviewers (1R and 2R) selected the included articles in two phases. In a first phase (Phase 1), the two reviewers assessed the titles and abstracts according to the eligibility criteria; in

Table 1. Database search

Database	06/11/24	References
PubMed NBIB	(("Sprains and Strains"[Title/Abstract]) OR ("Sprains and Strains") OR ("Sprains and Strains"[Mesh] OR "Strains and Sprains" OR "Sprains" OR "Sprain" OR "Strains" OR "Strain" OR "Trauma" OR "Traumas" OR "Wound" OR "Wounds" OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage") AND ((("Cryotherapy"[Mesh]) OR ("Cryotherapy")) OR ("Cryotherapy"[[Title/Abstract]) OR "Cryotherapies" OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature"[Mesh] OR "Cold Temperature" OR "Cold water immersion")	741
Web of Science RIS	("Strains and Sprains" OR Sprains OR Sprain OR Strains OR Strain OR Trauma OR Traumas OR Wound OR Wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage") (Topic) and (Cryotherapy OR cryotherapie OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature" OR "Cold water immersion") (Topic)	1.258
Scopus RIS	TITLE-ABS-KEY ("Strains and Sprains" OR sprains OR sprain OR strains OR strain OR trauma OR traumas OR wound OR wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage") AND TITLE-ABS-KEY (cryotherapy OR cryotherapies OR "Cold Therapy" OR "Cold Therapies" OR cryostimulation OR "Cold Temperature" OR "Cold water immersion")	4.298
Lilacs RIS	((Cryotherapy OR Cryotherapies OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature" OR Crioterapia OR "Cold water immersion")) AND (("Strains and Sprains" OR Sprains OR Sprain OR Strains OR Strain OR Trauma OR Traumas OR Wound OR Wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage" OR Lesiones OR Lesión OR Traumatismo OR Traumatismos OR "Heridas y Traumatismos" OR "Ferimentos e Lesões" OR Lesão OR Lesões))	296
Cochrane RIS	("Strains and Sprains" OR Sprains OR Sprain OR Strains OR Strain OR Trauma OR Traumas OR Wound OR Wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage") in Title Abstract Keyword AND (Cryotherapy OR Cryotherapies OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature" OR "Cold water immersion") in Title Abstract Keyword - (Word variations have been searched)Via Café	541
PEDro	Therapy: electrotherapies, heat, cold Subdiscipline: sports Method: clinical trial	488
Google scholar (cinzenta)	(Cryotherapy OR Cryotherapies OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature" OR Crioterapia OR "Cold water immersion") AND ("Strains and Sprains" OR Sprains OR Sprain OR Strains OR Strain OR Trauma OR Traumas OR Wound OR Wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage" OR Lesiones OR Lesión OR Traumatismo OR Traumatismos OR "Heridas y Traumatismos" OR "Ferimentos e Lesões" OR Lesão OR Lesões)	100
Open Grey (cinzenta)	(Cryotherapy OR Cold Therapy) AND (Muscle soreness)	39
LIVIVO RIS (cinzenta)	(Cryotherapy OR Cryotherapies OR "Cold Therapy" OR "Cold Therapies" OR Cryostimulation OR "Cold Temperature" OR Crioterapia OR "Cold water immersion") AND ("Strains and Sprains" OR Sprains OR Sprain OR Strains OR Strain OR Trauma OR Traumas OR Wound OR Wounds OR "Wounds and Injury" OR "Muscle damage" OR "Muscle soreness" OR "Muscular inflammatory responses" OR "Exercise-induced muscle demage" OR Lesiones OR Lesión OR Traumatismo OR Traumatismos OR "Heridas y Traumatismos" OR "Ferimentos e Lesões" OR Lesão OR Lesões)	808
Catálogo de Tese e dissertação da CAPES (cinzenta)	(Cryotherapy) AND (Muscle soreness) (Crioterapia) AND (Muscle soreness)	2 2
TOTAL		8573

a second phase (Phase 2), they examined the full texts. In the event of disagreements, a third reviewer (R3) was called in.

Data collected

Data was collected on the characteristics of the studies (authors, year of publication, country), the sample (age, gender), intervention modality, training/damage protocol, time points and conclusion.

Individual assessment of the risk of bias

The risk of bias assessment was carried out using the Cochrane tool, ROB 2, by two blinded reviewers; when there were disagreements, a third reviewer was called in to break the tie. The included studies were assessed in five domains: deviations from the planned interventions, lack of data in the results, measurement of the results, selection of the studies reported, overall result of the bias

analysis. Each domain with an overall result: low risk, some concern and high risk.

RESULTS

Study selection

During the search, 8573 records were found, 7722 in the main databases and 851 in the gray literature. The search was carried out in all databases on 02/Feb/24 and updated on 06/Nov/24. The EndNote Web and Rayyan reference managers were used for the exclusion of duplicates and the selection process (Figure 1).

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

Results of individual studies

The total number of subjects in this review was 63 men. Of the 2 randomized clinical trials, one was conducted in China (11) and the other in the UK (12). Included in the study by Guo et al. (11) elite runners, over a period of 15 consecutive days, at the start of the competitive season. The second study (12) included participants with an adequate level of physical fitness, participation in regular physical activities.

Intervention protocols

In the study by Guo et al. (11) the comparator was a group with simple stretching exercises. While in the study by Haq et al. (12) the control group underwent passive recovery.

In the research by Guo et al. (11) A 15-day training program was carried out, consisting of four light load sessions (distance 10 km, pace - 5 minutes and 20 seconds/km), one moderate load session (distance 20 km, pace 5 minutes/km) and two high load sessions (distance 30 km, pace - 4 minutes and 50 seconds/km). On the other hand, in the second study (12), the participants ran for 30 minutes on a treadmill inclined downwards at an incline of 15%, using the procedures described previously. The target heart rate was predetermined based on the relationship between VO_2 max and heart rate, so that a running intensity corresponding to 60% of VO_2 max was maintained.

In the study by Guo et al. (11) after each training day, the runners in the cold water immersion (CWI) and contrast water therapy (CWT) groups underwent a recovery intervention 6 times a week. The CWI group was immersed continuously in cold water at 10 °C, while the CWT group alternated immersions in water at 38 °C and 12 °C in 2.5-minute cycles. Each athlete remained immersed in a sitting position, until the water reached nipple level. In the study by Haq et al. (12) The WBC protocol was conducted in a cryogenic chamber in two phases. The first phase lasted 30 seconds (-60°C) and the second 150 seconds (-120°C). The WBC1 group received the intervention 60 minutes after a downhill run. The WBC4 group received the intervention 4 hours after the race. Finally, the CWI group was exposed to the recovery intervention immersed in a 200 L tank, with the water reaching the iliac crest, one hour after the race, with water at 15±0.5° C, for 10 minutes.

Outcome - interleukin 6 concentration

Guo et al. (11) suggest that cold water immersion (CWI) can reduce interleukin-6 (IL-6) levels more effectively than contrast water therapy (CWT) at specific times during training, such as the first adjustment and the second high-load period. This effect seems to coincide with DOMS and may help decrease inflammation, improving recovery and metabolism in athletes in later phases of training.

A different behavior occurred in the study by Haq et al. (12), in which the results showed no significant increases in IL-6 levels after exercise for any group ($p > 0.10$), and no significant interaction between group and time was observed ($p = 0.43$).

Analysis of the risk of bias

Regarding the randomization process and overall bias, the two studies were considered to have some concerns about the risk of bias (11,12). The other domains: deviations from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported outcome were scored with a low risk of votes.

More detailed information on the risk of bias of the studies is shown in Figures 2 and 3.

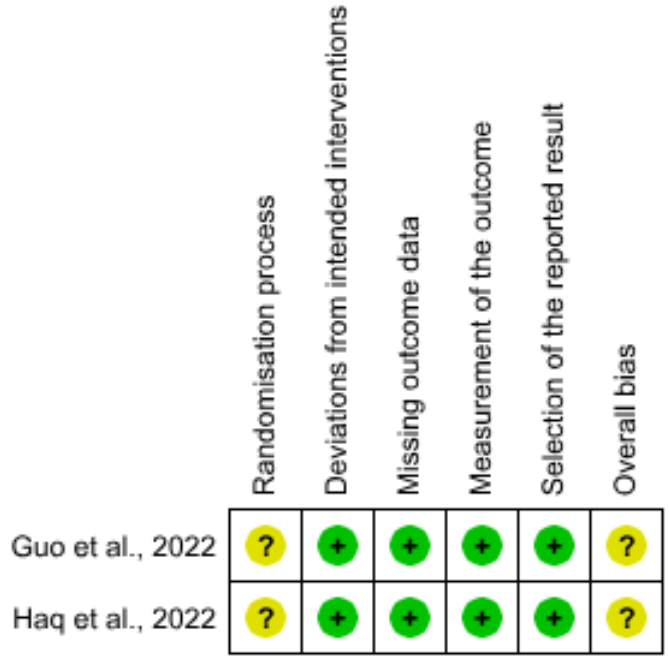

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented percentages across all included studies.

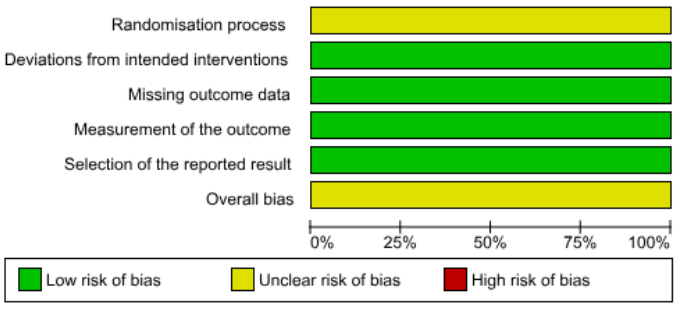

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

DISCUSSION

Only two randomized clinical trials were included in this review (11,12) who evaluated the effects of different cryotherapy protocols on

the concentration of Interleukin-6 (IL-6). Although both studies were conducted with physically active male populations, the differences in intervention protocols, sample collection methods and analysis strategies offer important insights, but limit direct comparability, thus limiting the performance of a metanalysis.

The studies included in this review adopted different approaches to muscle exercise protocols. Guo et al. (11) implemented a 15-day progressive program for elite runners, with sessions designed to simulate real training demands during the start of the competitive season. The sessions ranged from light loads (10 km to 5'20''/km) to moderate loads (20 km to 5'00''/km) and high loads (30 km to 4'50''/km). This continuous and progressive training model made it possible to assess the cumulative effects of intense exercise on inflammation and muscle recovery. On the other hand, Haq et al. (12) used a single, controlled approach, with participants running on a treadmill at a negative incline for 30 minutes at 60% of VO_2max. This strategy aimed to induce an eccentric load, known to cause muscle damage and an inflammatory response, allowing analysis of the acute impact of recovery.

The cryotherapy recovery protocols also differed greatly between the studies. Guo et al. (11) used cold water immersion (CWI) at 10 °C and contrast therapy (CWT) alternating between hot (38 °C) and cold (12 °C) water, six times a week after training. Haq et al. (12) investigated whole body cryotherapy (WBC) in two phases (-60 °C for 30" and -120 °C for 150") at different times after exercise, as well as CWI at 15 ± 0.5 °C for 10'. Such differences in the protocols, such as the form, temperature, timing and duration of the interventions may have an impact on the effectiveness of recovery and inflammatory modulation. Guo et al. (11) used water at 10 °C, with immersion up to the level of the nipples, carried out six times a week after each training session. In a different way, Haq et al. (12) used water at 15 ± 0.5 °C, with immersion up to the iliac crest, performed only once, one hour after exercise. Both studies maintained the 10-minute duration, but the greater frequency and body area submerged in the protocol by Guo et al. (11) suggest a more intense impact on the reduction of a possible inflammatory process and late muscle pain, while the protocol by Haq et al. (12) had a localized and punctual focus.

There were variations in the centrifugation protocol between the studies, which could affect the quality and volume of the fraction obtained (serum or plasma). The revolutions per minute (rpm) in the study by Guo et al. (11) were not converted to relative force of gravity (g), which also makes a direct comparison difficult. Haq et al. (12), specified a highly reliable quantitative method for IL-6, while Guo et al. (11) did not detail the method. Thus, these factors may influence the levels of IL-6 and other biomarkers detected, making direct comparisons between the results of the studies difficult.

The study by Guo et al. (11) investigated the effects of different water immersion protocols on levels of IL-6, a key cytokine that connects immune and endocrine responses in cases of muscle damage caused by exercise. IL-6 is one of the first and most striking indicators of muscle damage and is usually elevated after high-intensity exercise, which results in muscle pain and lower sports performance. The findings indicated that there was no significant difference in IL-6 levels between contrast water therapy (CWT) and cold water immersion (CWI) immediately after low-intensity training. However, during the first adjustment period (L1) and the second period of high-intensity training (H2), IL-6 levels in the CWI group were significantly lower than in the CWT group, coinciding with the onset of delayed-onset muscle soreness (DOMS), i.e. there was less protection by IL-6 in the inflammatory phenomenon, which is one of the important implications of this interleukin in skeletal muscle, understanding it as an endocrine organ and not just functional in physical aspects (21). But these authors (11) also observed a significant reduction in the concentration of prostaglandin-2, i.e. cryotherapy in itself may have had a direct influence on reducing the inflammatory process, not depending on IL-6 levels for this. On the other hand, Haq et al. (12) observed that IL-6 levels did not show significant increases after exercise in any of the groups, and the group-time interaction analysis showed no significant differences. These findings can be attributed to the lower impact of the exercise protocol used, characterized by a single moderate eccentric session, compared to the progressive and intensive program adopted by Guo et al. (11).

Regarding the risk of bias, both studies were assessed as having some concerns in the area of randomization, but with low risk in important aspects such as deviations from the planned intervention, missing data, measurement of the outcome and selection of reported results. This methodological consistency reinforces the reliability of the findings, although differences in populations, intervention protocols and exercise intensities limit direct comparisons. Thus, while Guo et al. (11) show the potential of CWI to reduce IL-6 under high load conditions, the results of Haq et al. (12) suggest that cryotherapy can prevent acute inflammatory responses to lower intensity exercise.

A major limitation of this study was the inclusion of only two primary studies, with different exercise and cryotherapy protocols. It is therefore suggested that future studies should consider standardizing exercise and intervention protocols in order to clarify the role of cryotherapy in modulating cytokines such as IL-6.

CONCLUSION

CWI showed greater potential in intense training, while WBC showed more varied results. Future studies should standardize interventions and explore molecular mechanisms to optimize recovery.

CONFLICT OF INTERESTS

None.

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