ANTI-INFLAMMATORIES FOR DELAYED ONSET MUSCLE SORENESS: SYSTEMATIC REVIEW AND META-ANALYSIS

ANTI-INFLAMATÓRIOS PARA DOR MUSCULAR DE INÍCIO TARDIO: REVISÃO SISTEMÁTICA E METANÁLISE

ANTIINFLAMATORIOS PARA EL DOLOR MUSCULAR DE INICIO TARDÍO: REVISIÓN SISTEMÁTICA Y METANÁLISIS

SYSTEMATIC REVIEW
REVISÃO SISTEMÁTICA
REVISIÓN SISTEMÁTICA

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ABSTRACT

Objective: To investigate the effectiveness of pharmacological interventions in the treatment of delayed onset muscle soreness (DOMS). Design: A systematic review and meta-analysis of randomized controlled clinical trials (RCTs). Data sources: The PubMed/MEDLINE, EMBASE, SPORTDiscus, Scielo and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for RCTs published prior to August 3, 2020. Eligibility criteria for selecting studies: Studies that 1) used an RCT design; 2) evaluated the effectiveness of steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs) in treating DOMS; and 3) therapeutically used drugs after exercise were included. Results: In total, 26 studies (patients = 934) were eligible for inclusion in the qualitative analysis on the treatment of DOMS. The results of the meta-analysis showed no superiority between the use and non-use of NSAIDs in the improvement of late muscle pain, as no statistically significant differences were verified (21 studies, n= 955; standard mean difference (SMD)= 0.02; 95% confidence interval (CI) -0.58, 0.63; p=0.94; I2=93%). The quality of the synthesized evidence was very low according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, and there was significant heterogeneity among the included studies. Conclusion: The results demonstrate that NSAIDs are not superior to controls/placebos in treating DOMS. The inclusion of both studies with dose-response protocols and those with exercise protocols may have influenced the results. In addition, the high risk of bias identified reveals that limitations need to be considered when interpreting the results. ***Level of evidence I; ystematic review of RCT (Randomized and Controlled Clinical Trials).***

Keywords: Pharmacology; Medical overuse; Sports medicine; Nonsteroidal anti-inflammatory drugs (NSAID); Recovery of function.

RESUMO

Objetivo: Investigar a eficácia das intervenções farmacológicas no tratamento da dor muscular de início tardio (DOMS). Desenho: Revisão sistemática e metanálise de estudos clínicos randomizados e controlados (RCTs). Fontes de dados: Os bancos de dados PubMed/MEDLINE, EMBASE, SPORTDiscus, Scielo e Cochrane Central Register of Controlled Trials (CENTRAL) foram pesquisados em busca de RCTs publicados antes de 3 de agosto de 2020. Critérios de elegibilidade para selecionar estudos: Estudos que 1) usaram um desenho de RCT; 2) avaliaram a eficácia de anti-inflamatórios esteroides ou não esteroides (AINEs) no tratamento de DOMS e 3) incluíram tratamento medicamentoso depois de exercício. Resultados: No total, 26 estudos (pacientes = 934) foram elegíveis para inclusão na análise qualitativa do tratamento de DOMS. Os resultados da metanálise não mostraram superioridade entre o uso e não uso de AINEs na melhora da dor muscular tardia, pois não foram verificadas diferenças estatisticamente significativas (21 estudos, n = 955; diferença média padronizada (SMD) = 0,02; Intervalo de confiança (IC) de 95% -0,58, 0,63; p = 0,94; I^2 = 93%). A qualidade da evidência encontrada foi muito baixa de acordo com os critérios da Grading of Recommendations Assessment, Development and Evaluation (GRADE), e verificou-se heterogeneidade significante entre os estudos incluídos. Conclusão: Os resultados demonstram que os AINEs não são superiores aos controles ou placebos no tratamento de DOMS. A inclusão de estudos com protocolos de dose-resposta e com protocolos de exercícios podem ter influenciado os resultados. Além disso, o alto risco de viés identificado revela que as limitações devem ser consideradas na interpretação dos resultados. ***Nível de evidência I; Revisão sistemática de ECRC (Estudos clínicos randomizados e controlados).***

Descritores: *Farmacologia; Uso excessivo de medicamentos; Medicina do esporte; Fármacos anti-inflamatórios não esteroides; Recuperação de função.*

RESUMEN

Objetivo: Investigar la efectividad de las intervenciones farmacológicas en el tratamiento del dolor muscular de aparición tardía (DOMS). Metodología: Revisión sistemática y metanálisis de ensayos clínicos controlados aleatorios (RCT). Fuentes de datos: Se realizaron búsquedas en las bases de datos de PubMed/MEDLINE, EMBASE, SPORTDiscus, Scielo y Cochrane Central Register of Controlled Trials (CENTRAL) para ECA publicados antes del 3 de agosto de 2020.

Criterios de elegibilidad para la selección de estudios: Estudios en los que 1) se utilizó un diseño de RCT; 2) se evaluó la eficacia de los fármacos antiinflamatorios no esteroideos (AINE) y esteroideos en el tratamiento de DOMS; y 3) se incluyó el uso terapéutico de medicamentos para dolor después del ejercicio. Resultados: En total, 26 estudios (pacientes = 934) fueron elegibles para su inclusión en el análisis cualitativo sobre el tratamiento de DOMS. Los resultados encontrados en el metanálisis no demostraron superioridad entre el uso y no uso de AINE para mejorar el dolor muscular tardío cuando se comparó con una condición de control, ya que no hubo diferencias estadísticamente significativas (21 estudios, n = 955; media estándar diferencia = 0,02; intervalo de confianza (IC) del 95% -0,58, 0,63; p = 0,94; I2 = 93%). La calidad de la evidencia encontrada se clasificó como muy baja según los criterios del "Grading of Recommendations Assessment, Development and Evaluation" (GRADE), principalmente porque existe una heterogeneidad significativa entre los estudios incluidos. Conclusión: Los resultados demuestran que los AINE no son superiores a los controles o placebos en el tratamiento de DOMS. La inclusión de ambos modelos de estudio con protocolos de dosis-respuesta y protocolos de ejercicio puede haber influido en los resultados. Además, el alto riesgo de sesgo identificado revela que la interpretación de los resultados debe verse con limitaciones. ***Nivel de evidencia: I; Revisión sistemática de ECRC (Ensayos clínicos aleatorizados y controlados)***

Descriptores: *Farmacología; Uso excesivo médico; Medicina deportiva; Medicamentos antiinflamatorios no esteroideos (AINE); Recuperación de la función.*

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INTRODUCTION

Excessive exercise in individuals with any physical conditions can cause inflammation. Strenuous and unusual exercises can cause tissue damage, which is associated with symptoms such as stiffness, limited range of motion and discomfort. These events normally result in late--onset muscle pain. When the exercise is overload, vigorous or, more commonly, the loads cause eccentric contraction this resultis more significant. This clinical situation is known as delayed onset muscle soreness (DOMS), and are responsible for impairing sports performance.[1] Pain is not perceived either during or immediately after exercise but generally occurs 24 - 48 hours after exercise.[2, 3] The inflammatory response that develops after exercise involves tissue recovery and is related to muscle recovery and adaptations essential for functional gain.[3] Pain is an unpleasant experience that limits individuals' ability to perform in daily activities. Pain relief is the treatment goal for both clinicians and patients. Thus, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is commonly suggested to limit the severity of pain and improve the recovery process.

NSAIDs act by inhibiting cyclooxygenase family (EC 1.14.99.1) enzymes. This process leads to a decrease in prostaglandins, prostacyclins and thromboxane synthesis. The decrease in prostaglandin concentration reduces acute inflammation, reduces the activity pain neural pathways and inhibits the development of oedema.[4] It is well known that NSAIDs block mTOR signalling.[5] Consequently, the use of NSAIDs may suppress myofibril regeneration as well as cell proliferation or differentiation and hypertrophy.[4, 6]

Previous studies have shown inconsistent results on the use of NSAIDs in treating DOMS. Ibuprofen decreases macrophage infiltration in the damaged tissue within 24 hours after exercise.[7] On the other hand, the use of naproxen does not affect the infiltration of inflammatory cells in tissue, according to an experimental muscle damage study.[8]

Vella et al.[9] suggested that NSAIDs decrease the intensity of the inflammatory response and leukocyte infiltration in skeletal muscle. The authors hypothesized that the intensity of exercise and tissue responses influence the clinical and side effects of anti-inflammatory drugs used to treat DOMS.[9]

Regarding pain, a classic sign of inflammation, clinical trials using NSAIDs showed that diclofenac[10] and ibuprofen[11] can relieve pain related to exercise. There are conflicting data about the use of NSAIDs for the treatment of DOMS. Some reports show a decrease in pain, while other reports show impairment in the process of adaptation or function and a lack of an effect on pain.[12, 13] Thus, more studies need to be performed to resolve this apparent inconsistency in results. The dose-response relationship, study population characteristics and type of exercise must be considered when studying therapies. Furthermore, personalized medicine can used to elucidate the differences in the effects of NSAIDs across exercise protocols.[14]

The clinical management of DOMS involves attenuating the inflammatory process, which inhibits both function and performance. Although various NSAIDs have been used for the treatment of DOMS, little is known about the magnitude of their clinical effects, mostly due to the use of different protocols across studies. An additional concern is the high frequency of adverse reactions resulting from the use of these drugs. These collateral effects are worsened by indiscriminate use without a medical recommendation.[15]

Because there are many pharmacological options and the management of DOMS is complex, a review may be useful for understanding the clinical management of DOMS. Therefore, the objective of the present review and meta-analysis was to investigate the effects of NSAID-type pharmacological interventions in the treatment of DOMS.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.[16, 17] This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO). We analyzed a total of 13,497 studies retrieved from different databases and one study retrieved from the reference list of another study.[18]

Study search and selection strategy

We performed a broad search of articles published in large databases using keywords and terms related to DOMS, late muscle pain and anti-inflammatory drugs. We searched PubMed/MEDLINE, EMBASE, SPORTDiscus, Scielo and Cochrane Central Register of Controlled Trials (CENTRAL) for manuscripts published prior to August 03, 2020. In addition, a manual search of the reference lists of all the included studies was performed in addition to the electronic searches. A summary of this process is shown in Figure 1.

Inclusion and exclusion criteria

Next, the articles were reviewed in stages (title, abstract, and full text). We included studies that 1) used a randomized controlled clinical

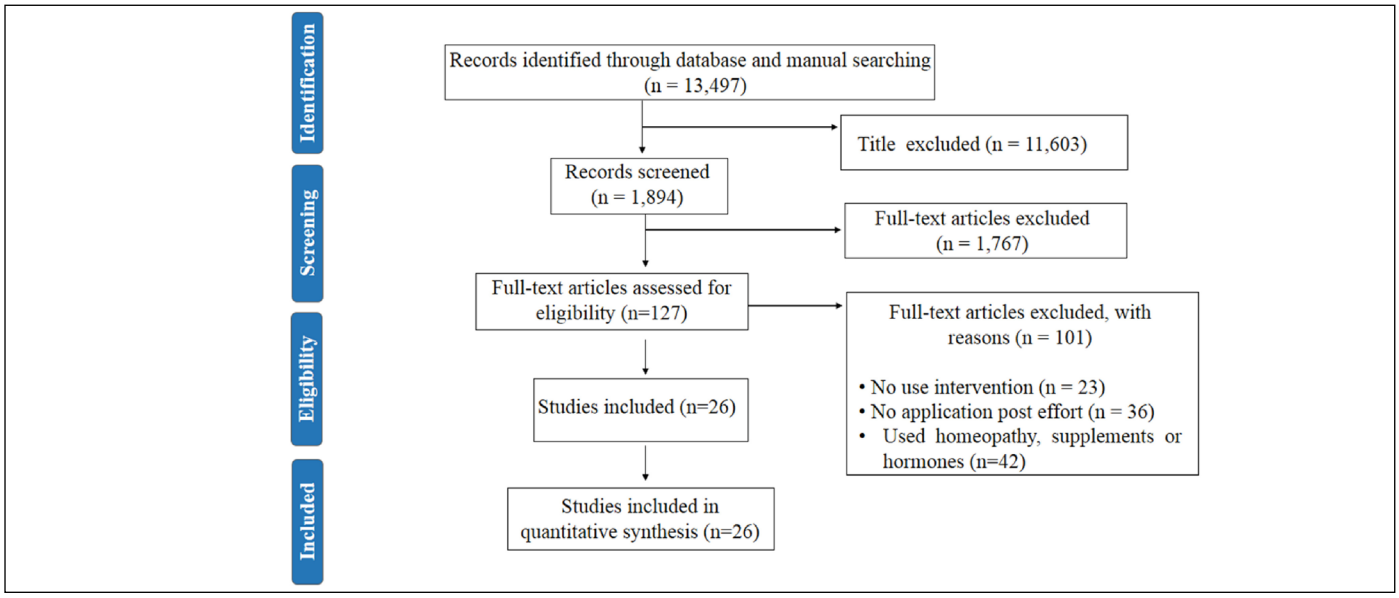

Figure 1. Description of the studies excluded on the basis of the established criteria.

trial (RCT) design, 2) evaluated the effectiveness of NSAIDs for DOMS treatment, and 3) analyzed the effectiveness of therapeutic drugs after exercise. Case reports, case series, comments, editorials, letters to the editor and literature reviews were excluded. There were no restrictions regarding the participants' age, sex, clinical condition, or level of activity; the date of publication; or the language in which the article was written. Both studies including individuals with pathological and healthy clinical conditions were considered for inclusion. We included only studies with healthy participants who were free of acute or chronic diseases. The detailed search strategies used can be found in the supplemental material. To this review and meta-analysis, we did not seek studies related to steroidal anti-inflammatory drugs.

Data extraction

We collected the following information from the eligible studies: (1) general characteristics of the study (authors, year of publication and design), (2) data on the study population (sample size, sex distribution and age), (3) information related to late muscle pain (the protocol used for inducing muscle damage, type of intervention, dose-response, the method for assessing pain intensity, evaluation timeframe) and (4) outcomes related to clinical pain improvement. When there was missing information, the corresponding author of the study was contacted for additional information.

Risk of bias assessment

The risk of bias of each included study was assessed. The following types of bias were assessed and reported: selection bias (regarding sequence generation and allocation concealment), performance bias (the blinding of the subjects and assessors), detection bias (blinding of the evaluation results), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. Thus, for each item described, the studies received on the following ratings: low, high or unclear risk (when the information presented in the study was not sufficient to determine the level of bias).[19]

The inclusion and exclusion criteria extracted data and risk of bias assessment results were simultaneously analyzed by two independent authors using the Cochrane Collaboration Risk of Bias Tool.[17,20] The data were analyzed using Review Manager (RevMan, 5.3.5).

Systematic Review Registration

Registration number PROSPERO - CRD42020179798

Statistical analysis

The data were grouped in the meta-analysis and reported as standardized mean differences (SMDs) with 95% confidence intervals (CIs). A random-effectiveness model was adopted due to there being heterogeneity across the studies (I^2=93%), as assessed by the I^2 value. We included 19 studies in the meta-analysis. Seven studies were excluded because of the use of a visual analogue scale, and three presented incomplete data (the authors did not provide the requested information).

RESULTS

Because different types of DOMS were included in this review, we considered late-onset muscle pain and DOMS the same condition in both the analyses and discussion. A total of 13,497 studies were retrieved in the broad search. A total of 127 studies were considered eligible according to the inclusion criteria (Figure 1). Of these, 23 studies were excluded for not using NSAID-type pharmacological interventions, 36 were excluded for not using the intervention after exercise, and 42 studies were excluded because of the use of supplements, hormones, or homoeopathy. We did not seek studies related to steroidal anti-inflammatory drugs. Finally, we included 26 studies that met the proposed criteria (Table 1).

We analyzed the characteristics of the subjects and studies and summarized them in Table 1. We retrieved studies conducted over three decades, starting in 1988. Most of the studies had a parallel-group design (65.4%), some had a crossover design (30.8%), and a minority of them had a counterbalanced design (3.8%). A total of 934 subjects were included in the studies (18-70 y, mean and SD = 35.9± 34.2 y), of whom 55.0% were male. The subjects were described as trained (15.4%) or physically active or healthy (84.6%).

The majority of the studies were carried out in North America (57.7%), including the United States[7,10,21-30] and Canada[8,31,32]; Europe (34.6%), including the United Kingdom,[33-35] Germany,[36,37] Greece,[11] Denmark,[18,38] and Belgium[39]; Africa (3.8%), including South Africa[40]; and Oceania (3.8%), including Australia.[9]

Concerning sample size, 13 articles (51.8%) included sample sizes of as many as 20 participants, 12 studies (44.4%) included between 21 and 100 participants, and one study included more than 100 participants (3.8%). Most of the studies (57.7%) included only men, while other studies included both sexes.

The protocols used in the studies for inducing muscle damage varied both in terms of the anatomical region and the type of equipment used for

Table 1. Summary of data analysis

Year	Subjects	Exercise Protocol*	Drugs and route of administration	Dose	Assessment	Assessment protocol	Results & Conclusion*
Arendt-Nielsen et al., 2007[18]	n=60 60 men 24.3 ± 3.1 y	eccentric	Oral Ibuprofen, glucosamine sulphate or placebo	1,200 mg/d 22d	VAS (0-9 cm)	BEx; AEx (15, 16 and 22 days)	Not significant
Bourgeois et al., 1999[8]	n=8 8 men 21.8 ± 2.2 y	concentric/ eccentric	Oral naproxen or placebo	1,000 mg/d 2d	VAS (0-10 cm)	BEx; AEx (0, 24 and 48 h)	Not significant
Cannavino et al., 2003[27]	n=32 32 men t18-35 y	Maximal Extension and flexion	Topic ketoprofen or placebo	cream 10% 8/8 h	VAS (0-10 cm)	BEx; AEx (24 and 48 h)	Significant
Croisier et al., 1996[39]	n=10 10 men 22.4 ± 0.4 y	Maximal extension and flexion	Oral piroxicam or placebo	20 mg/d 6d	VAS (0-10 cm)	BEx; AEx (0, 24 and 48 h)	Not significant
Donnelly et al., 1988[33]	n= 20 20 men 20 ± 1 y	Running at 75% maximum .heart rate	Oral diclofenac or placebo	150 md/d (50 mg 8/8 h;72 h)	VAS (1-10 cm) and pain tolerance threshold	BEx and AEx (6,24,48 and 72 h)	Not significant
Donnelly et al., 1990[34]	n=32 32 men 18 - 30 y	Running at 75% maximum .heart rate	Oral ibuprofen or placebo	2,400 mg/d (600 mg 6/6 h;72 h)	VAS (1-10 cm) and pain tolerance threshold	BEx and AEx (6, 24, 48 and 72 h)	Not significant
Dudley et al., 1997[26]	n=8 8 men age: DNR	eccentric	Oral Naproxen or placebo	600 mg/d (200 mg 8/8 h;4d)	VAS (1-100 mm)	BEx and AEx (24, 96 and 240 h)	Significant
Grossman et al., 1995[22]	n=30 20 men 22.1 ± 6.9 y	Resistive up to exhaustion	Oral ibuprofen or placebo	2,400 mg/d (600 mg 6/6 h) 5d	VAS (0-10 cm)	BEx and AEx (0; 48; 72; 96; 120 h)	Not significant
Hasson et al., 1993[23]	n=20 10 men 23.8±4.3 y	Cycling	Oral ibuprofen, placebo or control (no intervention)	1,200 mg/d (400 mg 8/8 h) (1d started 24 h after the baseline)	Pressure pain threshold (level of soreness after the application of 50N)	Baseline, 24, and 48 h	Significant
Hyldahl et al., 2010[25]	n= 106 41 men 18 - 65 y	Extension and flexion	Topical ibuprofen or placebo	gel 125 mg/d; 36 h	VAS (0-100 mm)	BEx and AEx (0,36,60,84 and 108 h)	Not significant
Krentz, et al., 2008[32]	n=18 12 men 24.1 ± 0.6 y	Extension and flexion	Oral ibuprofen or placebo	400 mg/d (200 mg; 12/12 h) 6 weeks	VAS (0-9 cm)	Subjects rated their muscle soreness daily per 6 weeks	Not significant
Lecomte et al., 1998[31]	n=20 20 men 24.0 ± 3.5 y	Eccentric	Oral naproxen or placebo	1 g/d (500 mg; 12/12 h) 8d	VAS (0-10 cm)	Perception of muscle soreness was evaluated daily throughout each phase	Significant
Loram et al., 2005[40]	n=15 10 men 24.0 ± 4.5 y	Running Downhill	Oral rofecoxib; tramadol or placebo	rofecoxib 50 mg/d Once a day 4d tramadol 150 mg/d (50 mg/d; 8/8 h) 4d	VAS (0-100 mm) and pressure pain threshold	BEx and AEx (24 and 72 h)	Not significant
McAnulty et al., 2007[24]	n=60 45 men 45.3 ± 1.1 y	Running 160 km	Oral or topical route not clear in methodology "Categorized as NSAID users if reported use during running and non-users reported to avoid NSAIDs"	The ingested doses were performed individually, as performed routinely by the participants.	VAS (0-10 cm)	BEx and AEx (24,48,72,96,120,148 and 172 h)	Not significant
Nieman et al., 2006[29]	n=29 29 men 47.9 ± 1.4 y	Running 160-km	Oral ibuprofen or control (no intervention)	600 mg/d And 1,200 mg/d the day before and on race day, respectively	VAS (1-10 cm)	BEx and after AEx (24,48,72,96,120,148 and 172 h)	Not significant
Rahnama et al., 2005[35]	n=44 44 men 24.3 ± 2.4 y	eccentric and concentric	Oral ibuprofen or control (no intervention)	2,800 mg 1 h before the eccentric actions up to 48 h after it	VAS (1-30 cm)	BEx and after AEx (1, 24 and 48 h)	Significant
Rother et al., 2014[37]	n=48 25 men Group 1 young (18-40 y) Group 2 elderly (50-70 y)	Eccentric	Oral etoricoxib or placebo	90 mg/d 7d	VAS (0-10 cm)	BEx and AEx (24,48,72,96,120,148 and 172 h)	Not significant

Seidel et al., 2016[36]	n=168 86 men 18-55 y	Descended stairs	Topical ketoprofen + oral placebo (two groups); Oral ketoprofen or oral placebo (two groups)	Topical Group1: 100 mg ketoprofen + oral placebo. Group2: 200 mg ketoprofen+ oral placebo Oral Group 1: 100 mg oral ketoprofen + topical placebo Group 2: placebo capsule + topical ketoprofen 12/12 h 7d	VAS (0-9 cm)	BEx and AEx (24, 48, 96, 192 and 288 h)	Not significant
Simmons et al., 2018[28]	n= 37 age: DNR	Exercise regimen and a customized, non-invasive armband (Band-O™),	Oral ibuprofen or placebo	1600 mg/d (400 mg 4doses) 1d	VAS (0-10 cm); sum of pain intensity differences (SPID); and sum of stiffness movement differences (SSMD)	BEx and AEx (0,24 and 48 h)	Significant
Singla et al., 2015[10]	n=24 15 men 28+3.5 y	Extension and flexion	Topical Diclofenac or placebo	Diclofenac gel 1% (DSG 1%; 48 h)	VAS (0-10 cm)	BEx and AEx (24,48,72,96,120,148 and 172 h)	Significant
Smith et al., 1995[21]	n=36 36 men 24.4 ± 1.5 y	Eccentric	Oral aspirin, acetaminophen or placebo	Aspirin 3.0 g/d (750 mg 6/6 h) 5d Acetoaminophe (3.0 g/d 750 mg; 6/6 h) 5d	VAS (1-10 cm)	BEx and AEx (24,48,72,96 and 120 h)	Not significant
Stone et al., 2002[30]	n=40 20 men 23 ± 3.2 y	Extension and flexion	Oral ibuprofen, bromelain, placebo or control (no intervention)	Bromelain 900 mg/d (300 mg; 8/8 hours) 3 days; Ibuprofen 1,200 mg/d (400 mg; 8/8 h) 3d	VAS (1-10 cm)	BEx and AEx (24,48,72 and 96 h)	Not significant
Svensson et al., 1997[38]	n=10 10 men age: DNR	Eccentric	Topical ibuprofen, Oral ibuprofen or placebo	Oral 1,200 mg/d (400 mg; 8/8 h) 3d Topical 2 g (5%) 8/8 h 3d	Pain tolerance threshold	BEx and AEx (24,48 and 72 h)	Significant
Tokmakidis et al., 2003[11]	n=19 14 men 24.6 ± 3 y	Eccentric and concentric	Oral ibuprofen or placebo	1,200 mg/d (400 mg; 8/8 h) 2d	VAS (1-10 cm)	BEx and AEx (4,6,24 and 48 h)	Significant
Trappe et al., 2002[7]	n=24 24 men 25 ± 3 y	Eccentric and concentric	Oral ibuprofen; acetaminophen or placebo	Ibuprofen 1,200 mg/d (400 mg three doses) 1d Acetaminophen 4000 mg/d 8/8 h 1st. dose one 1,500 2nd. dose 1,500 mg, 3rd. dose 1,000 mg 1d	VAS (1-9 cm) and level of soreness after the application of 40N	BEx and AEx (0, 24 and 48 h)	Not significant
Vella et al., 2016[9]	n=16 16 men 23.9 ± 1.3 y	Extension and flexion	Oral ibuprofen or placebo	1,200 mg/d (400 mg three doses) First dose immediately prior to the first muscle biopsy two doses at 6 and 12 h following the exercise protocols.	VAS (1-10 cm)	BEx and AEx (0 and 24 h)	Not significant

Legend: y=years; n= number of participants; DOMS= delayed onset muscle soreness; RM= maximum repetition; VAS= visual analogue scale; DNR: unreported data; d=days; h=hours; mg=milligrams; BEx = before exercise; AEx = after exercise; N = Newtons; The characteristics of the studies, subjects and protocols are reported exactly as they were in the paper.* written exactly as stated in the article.

evaluation. Thus, based on the anatomical site, the studies included either a systemic protocol (23.1%)[24,29,33,34,37,40] or localized protocol; among the studies with localized protocols, 8 (30.8%) addressed upper limb damage,[18,21,22,25,28,30,32,35] 11 (42.2%) addressed lower limb damage[7-11,23,26,27,31,37] and one study (3.8%) addressed exercises involving the temporomandibular joint.[33] Regarding the equipment used to compare the results, two studies (7.7%) used an isokinetic dynamometer,[37,39] and 17 studies (65,4%) used conventional weight machines[7-11,18,21-23,25-28,31,32,35]; 6 studies (23.1%) involved aerobic exercises lasting more than 30 min.[24,29,33,34,37,40]

NSAIDs are classified according to their selectivity for cyclooxygenase (COX) 2 inhibition. We found 23 studies that used non-selective inhibitors (88.4%), while two studies investigated selective models (7.6%). One study[24] did not investigate the type of NSAID used since the participants were free to choose which NSAID they took.

The studies differed by the type of non-selective NSAID used, with more than half of the studies investigating ibuprofen (56.0%).[7,9,11,18,22,23,25,28-30,32,34,35,38] The other types that were used included naproxen (12.0%),[8,26,31] diclofenac (8.0%),[10,33] ketoprofen (8.0%),[27,36] acetaminophen (8%),[7,21] aspirin (4.0%)[21] and piroxicam (4%).[39]

The major route of administration was oral (77.0%).[6-8,10,17,20-23,25,27-34,36-39] Some studies used topical (11.5%) [9,24,26] or both topical and oral methods (11.5%).[23,35,37] Treatment began after exercise and continued for different periods of time, with a maximum duration of seven days.

Thirteen studies (50.0%) did not show significant effectiveness of the oral use of non-selective NSAIDs in the treatment of DOMS, while ten (38.5%) showed positive outcomes. All studies that used topical routes had good outcomes of DOMS.

Regarding the two studies investigating selective NSAIDs, one used etoricoxib[37] (90 mg/day for 7 days), and the other used rofecoxib [40] (50 mg/day for 3 days). No significant effectiveness was found in either study.

Pain was assessed by either a visual analogue scale (82.2%) or mechanical method (17.8%). Pain was evaluated at different time points in the studies. Most commonly, the follow-up period started before exercise (baseline). Additionally, different follow-up periods were used, ranging from 24 hours to 7 days.

Risk of bias assessment

The bias risk results for each study are presented in Figure 2. Different proportions of the studies had low risk of bias for random sequence generation (80.9%), allocation concealment (4.7%), blinding of the participants and personnel (71.4%), blinding of the outcome assessment (14.2%), incomplete outcome data (33.3%), selective reporting (0%) and other bias (42.8%).

Effect of NSAIDs to treat DOMS

To assess the significance of the described use of NSAIDs on DOMS, we evaluated the studies using a random-effectiveness model (I^2=93%). Our analyses showed no difference regarding the attributed use of NSAIDs (21 studies, n= 955; SMD= 0.02; 95% CI -0.58, 0.63; p=0.94; I2=93%) (Figure 3).

DISCUSSION

Both inflammation and pain can be limiting factors for training and exercise, and NSAIDs are widely used to treat both symptoms. These drugs are either prescribed by a clinician or purchased over the counter.[41] In this study, we conducted a meta-analysis of the studies on the effectiveness of selective and non-selective NSAIDs in the management of DOMS related to exercise.

We did not exclude studies on the basis of specific characteristics. This method allowed us to take a holistic perspective in performing analyses on the different dose responses, NSAIDs and study population profiles. The mechanisms of and the relationship between DOMS and

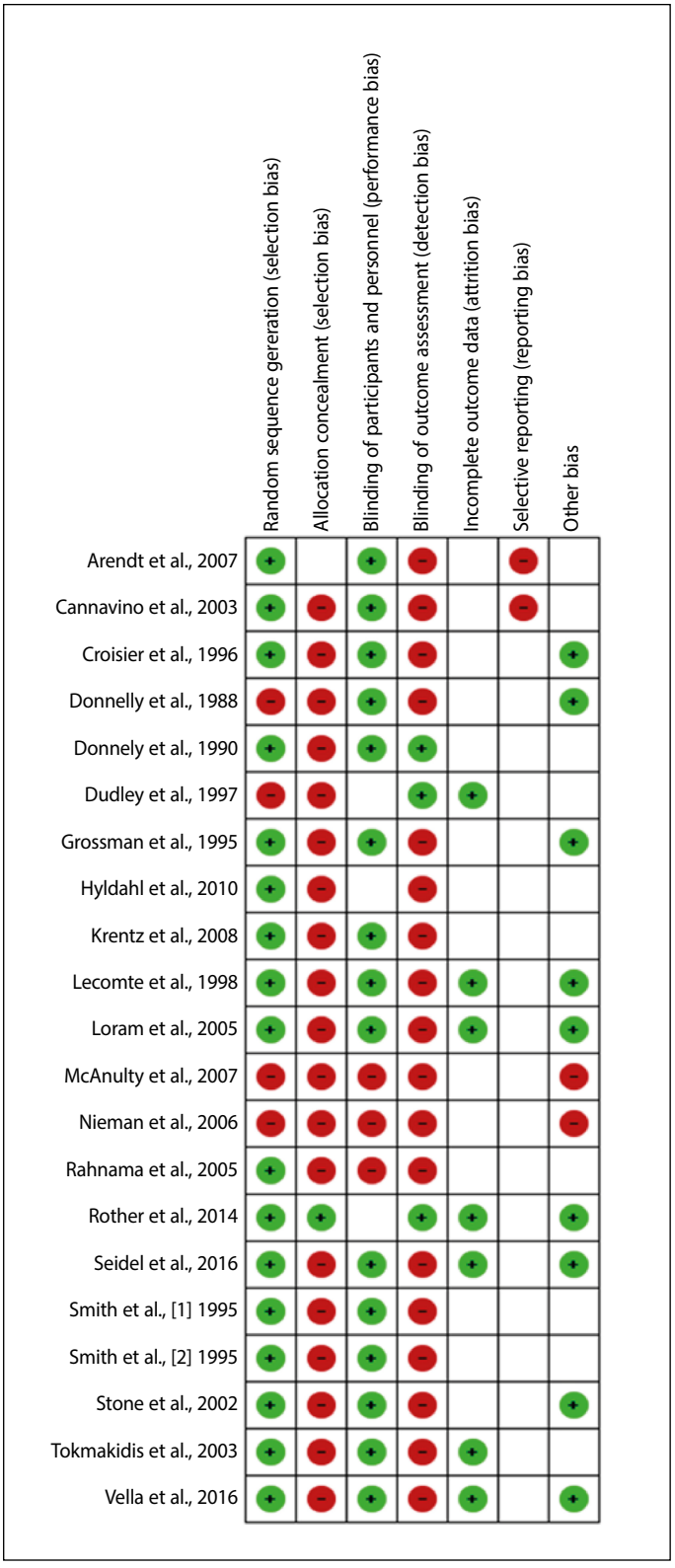

Figure 2. The risk of bias results for the selected studies examining the efficacy of NSAIDs for muscle soreness. The studies were considered to have low risk (+), unclear risk (blank) or high risk (-) of bias for different aspects of the Cochrane risk of bias tool.

inflammation have been described previously.[9] There is current evidence showing improvement in pain and inflammatory processes in response to the use of these drugs.[28,35,38,39] However, other studies have shown that the use of NSAIDs is related to the inhibition of satellite cells, negatively influencing the development of healing, the adaptation to stress and subsequent muscle regeneration.[42,43]

There is controversy in the literature about the functional effects of NSAIDs in signaling and muscle regeneration. Mackey et al.[44] evaluated

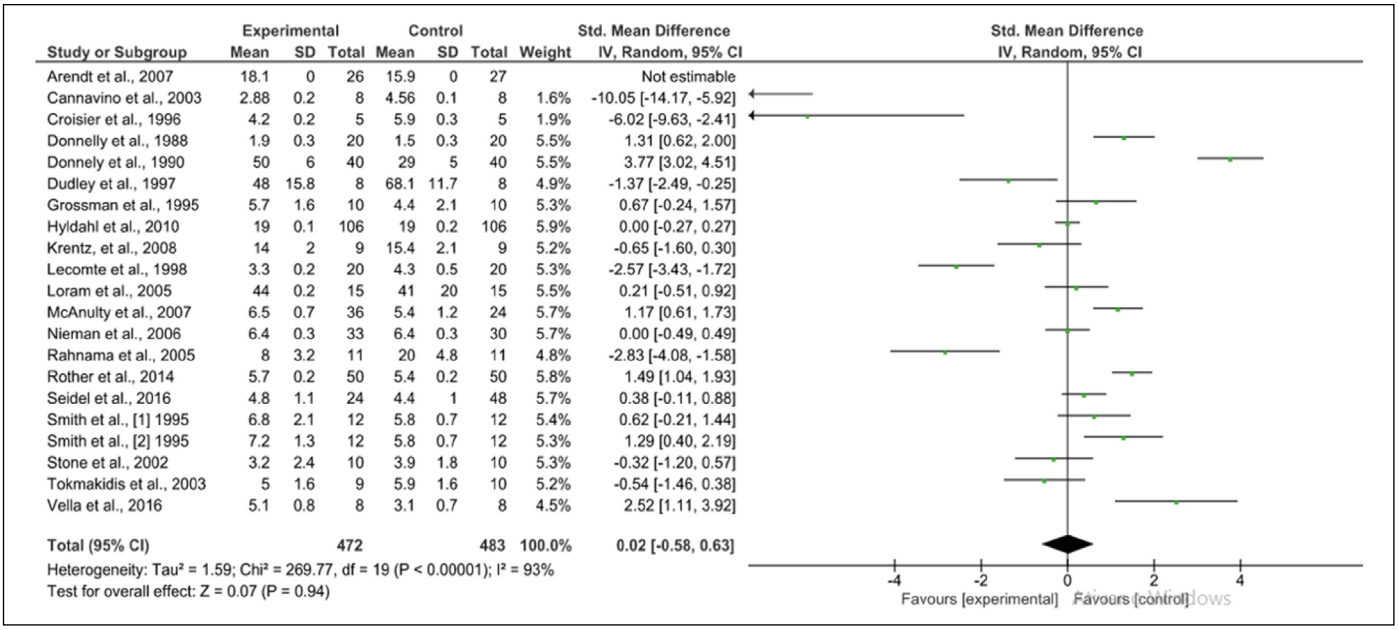

Figure 3. Forest plot showing the effectiveness of NSAIDs (experimental) versus control condition on the management of DOMS. SD: standard deviation; Std: standardized; CI: confidence interval. Program: RevMan, version 5.3.5; heterogeneity: $Tau^2 = 1.59$; $Ch^2 = 2269,77$, df = 19 (P 0.000001); I2 = 93%.

the effect of ibuprofen on satellite cell activity after eccentric contractions induced by electrical stimuli.[44] Their study showed that ibuprofen-treated subjects exhibited increased levels of cell proliferation and faster myofibril repair. It is important to highlight that the use of electrical stimulation to induce muscle damage is a limiting factor of the study. Electrically induced muscle contractions do not fully reflect the physiological conditions of exercise.[45] Thus, it is important to emphasize this limitation. Other studies showed a lack of correlations in the effectiveness of NSAIDs on the outcomes, pain and functional limitations associated with DOMS.[7,9,32,40] A possible explanation is the occurrence of a reduced muscle regeneration capacity due to a decrease in monocyte differentiation followed by the inhibition of the inflammatory process and a change in cytokine signaling. These effects together could be responsible for the systemic responses of neuromuscular adaptation and muscle regeneration.[4,12] In a practical context, the weakening of the described functions tends to limit an individual's subsequent performance in either training or competitions.[46]

NSAIDs are widely used in clinical practice for the treatment of various conditions, including DOMS.[41] The studies by Paulsen et al.[12] and Schoenfeld et al.[4] suggest that mild clinical manifestations of DOMS do not require treatment with NSAIDs. Clinical trials using rofecoxib showed an exponential increase in acute myocardial infarction, supported by high levels of toxicity in selective cyclooxygenase inhibitors.[15] Additionally, NSAIDs inhibit prostanoid synthesis, resulting in adverse effects on systems including the gastrointestinal tract and renal and cardiovascular systems.[15,47-50] Such information is of concern and should be taken into consideration to evaluate the actual need for NSAID use for the specific clinical condition of each patient.[51] Due to the risk of adverse effects and functional impairment, the indiscriminate use of NSAIDs is alarming. This problem is aggravated by its prolonged use, mostly without a medical prescription.[15]

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the effectiveness of the use of NSAIDs in the treatment of DOMS. Our meta-analysis showed that the use of NSAIDs is neither superior nor responsible for significant levels of improvement compared to a control/placebo. The importance of our findings for clinical practice lies in highlighting important evidence about the ineffectiveness of NSAIDs in treating DOMS and the possible hazards of their indiscriminate use. The current literature provides a variety of therapeutic options for the treatment of muscle pain[52] with a lower risk of adverse effects, and these options should be considered whenever possible.

Our meta-analysis did not support the use of oral NSAIDs for the treatment of DOMS. Two articles using topical NSAIDs were included in our meta-analysis, both of which reported "good outcomes". It is difficult to conduct a blinded topical NSAID study since some subjects can feel the presence of the active compound. Another possible explanation is that the local drug concentration in the topical treatments may yield better results than that in the oral treatments.[53]

Diclofenac and aspirin are the world's most used NSAIDs, while ibuprofen or naproxen are used less commonly.[54] In conducting our review, we found that ibuprofen was the most studied oral NSAID (52.2%), followed by naproxen (13.0%). The less commonly investigated drugs included aspirin and diclofenac (4.3% each). Most of the studies (96.2%) were conducted in countries with a very high human development index (HDI) according to the United Nations Development Program.[55] We think that researchers and volunteers either propose or engage in studies according to their experiences and resources. The lack of original studies may present a bias in the previously published papers, leading to a limitation in the results analyzed. Our analyses can be biased by the heterogeneity among the original investigations. It is always important to emphasize that correlation does not necessarily imply causation. A more comprehensive experimental study of the most used NSAIDs (in both oral and topical administration) should be conducted to investigate the mechanisms of action in treating DOMS.

The majority of the 26 studies included in this study (~92%) used a visual analogue scale (VAS) to assess pain severity in the subjects. The VAS is a reliable and efficient tool for clinical research on pain.[56] However, the VAS is an ordinal scale presented in numbers and should not be confused with a linear numeric scale. This misunderstanding of the scale leads to an essential misconception in data analysis. While the VAS has been used in several scientific papers, it is not wise to convert subjective perceptions to numbers for further statistical analyses. Pain is a subjective symptom, and its perception includes both psychological inputs and subjective behaviour.[57] Performing a meta-analysis with subjective data is always a challenge and a limitation of the methodology.

Some limitations inherent to the presented outcomes need to be reported. First, most of the protocols used in the included trials were

unsatisfactory, which leads to inadequate evidence. The lack of consistency among the methodologies of the studies prevented a homogeneous comparison from being conducted and conclusive evidence from being reported. Therefore, our results and discussion should be interpreted by taking into consideration such circumstances. It needs to be emphasized that our findings are based on those reported in studies that used different drugs with different dose-response relationships, as well as different protocols for inducing muscle damage. Such facts should be considered, and the results cannot be extrapolated to conditions different from those reported in this study. Analyzing the results of different small clinical studies with varied methodology is always a challenge, and our goal was to accumulate relevant evidence to enlighten the field.

CONCLUSIONS

This study provides evidence that the use of NSAIDs in the management of DOMS does not appear to be superior to a control condition and/or placebo. However, these interpretations should be analyzed with caution since the type of NSAID, dose/response relationship and volume/intensity of the effort made to induce different kinds of muscle damage varied across studies. As the continuous use of NSAIDs can trigger several adverse effects in body systems, additional studies should be conducted to determine the actual benefits of NSAIDs in treating DOMS.

And, since the use of NSAIDS did not show improvement when used for the treatment of DOMS and following the logic that treatment should only be implemented if it demonstrates clinical improvement. The authors do not recommend the use of NSAIDs for the treatment of DOMS.

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