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Nonsteroidal Anti-Inflammatory Drug Use and Endurance During Running in Male Long-Distance Runners

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Context: The effect of ibuprofen on pain tolerance during exercise is controversial, and its effects on endurance performance have been poorly investigated.

Objective: To investigate the effect of prophylactic administration of the nonsteroidal anti-inflammatory drug ibuprofen on the time until the self-report of fatigue (t_{lim}) in runners with exercise-induced muscle damage.

Design: Randomized controlled clinical trial.

Setting: Laboratory.

Patients or Other Participants: Twenty healthy male long-distance runners (age = 18.8 ± 0.4 years, maximal oxygen consumption = 55.5 ± 5.9 $mL \cdot kg^{-1} \cdot min^{-1}$).

Intervention(s): Participants were assigned to 2 groups (ibuprofen group = 10, placebo group = 10) to perform t_{lim} trials (speed corresponded to their previously determined second-ventilatory thresholds) 48 hours before and 48 hours after the induction of a lower limb muscle-damage protocol (isokinetic dynamometry). One hour before the second t_{lim} trial, the ibuprofen group received 1.2 g ibuprofen, and the placebo group received lactose orally.

Main Outcome Measure(s): Time until self-reported fatigue, heart rate, respiratory quotient, oxygen consumption, and perceived exertion were recorded during each t_{lim} test.

Results: Both groups reported increases in muscle pain in the knee extensors and flexors 48 hours after the muscle-damage protocol. We observed a reduction in the endurance performance of both groups ($P < .01$) but no difference between groups ($P = .55$).

Conclusions: Ibuprofen did not reduce the effect of muscle damage and pain on performance. Prophylactic use of nonsteroidal anti-inflammatory drugs did not have an ergogenic effect on running performance after exercise-induced muscle damage in male long-distance runners.

Key Words: NSAIDs, ibuprofen, muscle pain, fatigue, exercise

Key Points

- Muscle-damage induction negatively affected endurance performance in both the ibuprofen and placebo groups, which suggests that ibuprofen probably did not preserve muscle-endurance performance in athletes with muscle damage before exercise.
- Nonsteroidal anti-inflammatory drugs should be used with caution when the goal is improving muscle-endurance performance because side effects may be greater than expected benefits.

Anti-doping–control testing of athletes during the 2007 Pan-American Games demonstrated that many athletes regularly use nonsteroidal anti-inflammatory drugs (NSAIDs) immediately before or during competition.[1] The number of NSAID users in this group was higher than the number of NSAID users outside the competition.[1] The use of NSAIDs by high-performance athletes has also been reported in several other studies.[2–5] These medications inhibit cyclooxygenase activation, and the consequent reduction in the excitability of nociceptors in the damaged tissue produces an analgesic effect.[6,7]

Muscle damage during continuous and extenuating effort, such as long-distance running, results from the eccentric activity during exercise, which impairs muscular contraction via the disruption of cellular ultrastructure (eg, cytoskeleton, Z-disk, sarcomere, T-tubules, and sarcolemma), the loss of calcium homeostasis, and impaired excitation-contraction coupling.[8–11] This loss of strength is also related to localized muscle pain, which is caused by an increase in levels of inorganic phosphates and hydrogen; ischemia; exacerbated mechanical strain; decreased systemic oxygen and carbon dioxide pressure; and the production of free radicals during intense, severe exercise[12] or the increased sensitivity of nociceptors (ie, allodynia) generated by endogenous substances, including bradykinin, serotonin, histamine, and prostaglandin E_2, that are produced when muscles are damaged.[13] The excitation of local metaboceptors and nociceptors relays information to the supramedullary motor centers that modulate motor efferent signaling.[14]

Peripheral and central mechanisms attenuate pain perception,[11–15] but endurance is vulnerable to acute

Table 1. Participant Demographics

Characteristic	Group (Mean ± SD)			*P* Value
	Entire (n = 20)	Ibuprofen (n = 10)	Placebo (n = 10)	
Age, y	18.8 ± 0.4	18.8 ± 0.4	18.8 ± 0.5	.86
Height, cm	173.5 ± 5.9	174.8 ± 5.7	172.2 ± 6.1	.39
Mass, kg	69.7 ± 6.6	71.9 ± 4.0	66.2 ± 5.6	.004[a]
Body mass index[b]	23.0 ± 1.5	23.1 ± 1.1	22.3 ± 1.5	.006[a]
Body fat, %	7.1 ± 3.2	8.0 ± 2.7	6.2 ± 3.5	.004[a]
Maximal oxygen uptake[c]	55.5 ± 5.9	51.3 ± 4.7	59.8 ± 3.7	<.001[a]
Oxygen uptake at second ventilatory threshold, % maximal oxygen uptake	78.9 ± 8.2	78.8 ± 6.5	79.4 ± 7.5	.28
Velocity at second ventilatory threshold[d]	15.1 ± 1.4	14.1 ± 1.0	16.1 ± 1.1	.001[a]

[a] Indicates difference between treatment groups ($P \leq .05$).
[b] Calculated as $kg \cdot m^{-2}$.
[c] Calculated as $mL \cdot kg^{-1} \cdot min^{-1}$.
[d] Calculated as $km \cdot h^{-1}$.

algogenic stimuli that negatively affect the ability to maintain high-power output levels.[16] Sgherza et al[15] administered a bolus injection of the opioid antagonist naloxone to 18 participants who were conditioned to endurance exercise and demonstrated a decrease in workload capacity and an increase in perceived exertion. However, Mauger et al[13] administered the analgesic acetaminophen prophylactically to 13 conditioned cyclists and demonstrated improvements in time-trial performance during 10 miles (16 km) of stationary cycling. Only Vanheest et al[7] have investigated the effect of NSAIDs alone and in combination with analgesic opioids on aerobic performance (eg, running economy and efficiency) under conditions of induced muscle damage; no positive effects were demonstrated. However, NSAID administration (800 mg distributed in 4 doses beginning 24 hours after induction of muscle damage and 24 hours before the aerobic performance test) did not mimic NSAID use in endurance athletes who ingested a single maximal dose of analgesics before exercise, as observed by Da Silva et al[1] and Gorski et al.[4] Therefore, the effect of NSAID use on aerobic performance in endurance athletes is unknown.

The analgesic effects achieved using pharmacologic substances, such as opioids and other analgesics (ie, acetaminophen, acetylsalicylic acid), should not be extrapolated to NSAID use during exercise because of the different pharmacodynamic and pharmacokinetic characteristics of analgesic substances. In addition, the effect of ibuprofen on pain tolerance during exercise is controversial, and the effects on endurance performance are unknown. Thus, the purpose of our study was to investigate the effect of prophylactic ibuprofen administration on the time until runners with exercise-induced muscle pain reported fatigue. We hypothesized that the prophylactic use of a maximal, single dose of an NSAID before exercise would reduce the deleterious effect of local pain in damaged muscles and thereby maintain or improve running performance.

METHODS

Participants

Twenty male members of the military who were well-conditioned endurance runners participated in this study (Table 1). They were selected randomly from a local military unit among soldiers with excellent physical fitness, as assessed by the Cooper test and according to measures of the Brazilian army (3200 m in 12 minutes); all selected participants completed the experimental protocol. Volunteers were included if they were not taking painkillers or other medications that would influence hormonal and neuromuscular metabolism. They were excluded if they reported histories of neuromuscular, metabolic, or hormonal diseases.

To ensure good health, a medical history and physical examination were completed for each participant. No participants reported anti-inflammatory or analgesic drug use in the 48 hours before testing. No participant had ever been diagnosed with asthma or gastrointestinal problems or had a known hypersensitivity to NSAIDs. No participant began any type of treatment that involved analgesics during the study, and no gastric distress from ibuprofen administration was reported. The procedures were conducted according to the ethical standards of the *International Journal of Sports Medicine*.[17] All participants provided written informed consent, and the Ethics Committee of the Federal University of Rio Grande do Sul approved the study.

Experimental Design

We designed a randomized, double-blind clinical investigation to test the hypothesis that ibuprofen would affect endurance performance by reducing pain. Participants visited the laboratory on 5 occasions. They received detailed information regarding the survey, provided informed consent, and underwent familiarization during the first visit. We determined the individual running speed used in the time until the self-report of fatigue (t_{lim}) test, which corresponded to the second ventilatory threshold, during a progressive treadmill running test after 72 hours of familiarization. During the third visit, all participants performed a continuous run to exhaustion at the speed that corresponded to their second ventilatory threshold, and we recorded the total time of exercise until t_{lim}, heart rate, respiratory quotient, oxygen consumption, and perceived exertion. On the fourth visit, which occurred 48 hours later, they underwent a lower limb muscle-damage induction (MDI) protocol with an isokinetic dynamometer, using eccentric and concentric combined exercise to induce

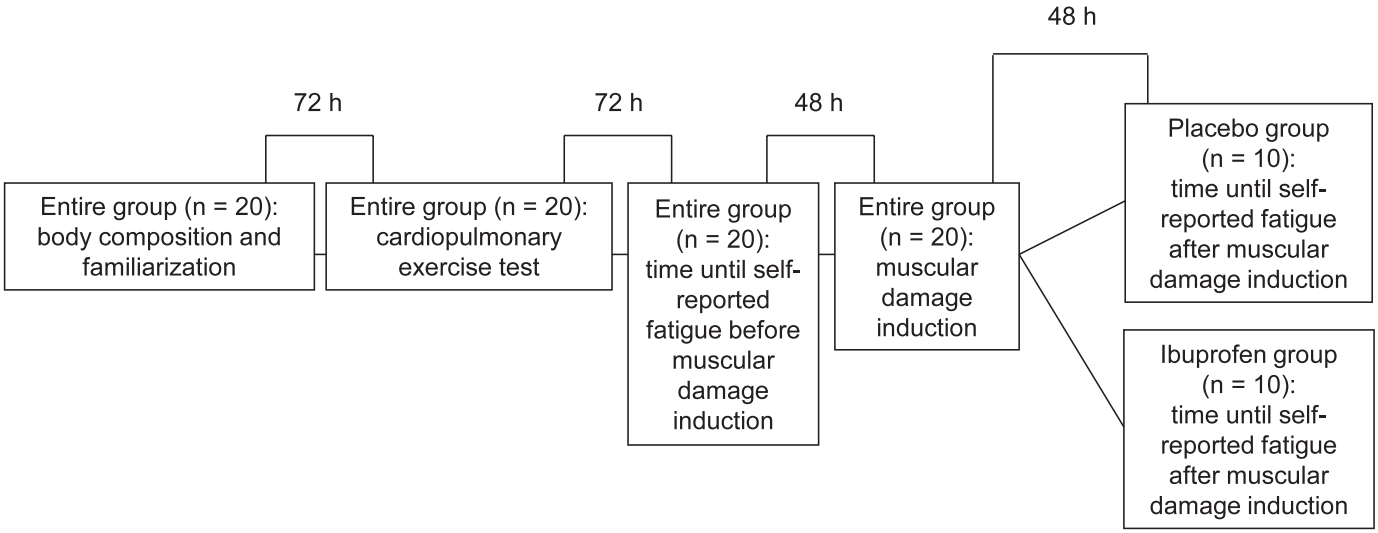

Figure 1. Flow chart represents the experimental protocol.

muscle pain. We randomly divided the participants into 2 groups that received either a prophylactic administration of 1.2 g ibuprofen (ibuprofen group [IG] = 10) or placebo (placebo group [PG] = 10) in the last visit (48 hours after the MDI) and performed a second t_{lim} test. A staff member was assigned to randomize the participants into treatment groups after MDI for blinding. All samples were collected at the same time (in the morning) in a controlled environment (laboratory temperature range, 18°C to 21°C). The experimental design is summarized in Figure 1.

Body Composition Assessment

Body mass and height were measured during the first visit using an analog scale (model PL-200; Filizola, São Paulo, Brazil) and stadiometer (Filizola) with resolutions of 0.1 kg and 1 mm, respectively. Body composition was assessed using skinfold measurement, and a 7-site skinfold equation was used to estimate body density.[18] The same technician (not an author) obtained all anthropometric measurements on the right side of the participant's body, and body fat was calculated using the Siri equation.[19]

Cardiopulmonary Variables

Participants performed a progressive running protocol using a treadmill (model C9641; Precor, Inc, Woodinville, WA) and a metabolic cart (model VO_{2000}; Inbrasport, Rio Grande do Sul, Brazil) at least 72 hours after the first visit to determine the maximal oxygen uptake ($\dot{V}O_2max$) and the second ventilatory threshold. The metabolic cart was calibrated using environmental conditions after each sampling. The exercise protocol began at a speed of 6 $km \cdot h^{-1}$ with no grade (0%). The speed was increased to 9 $km \cdot h^{-1}$ with a 1% grade, and progressively increased 1 $km \cdot h^{-1}$ every minute. Participants were encouraged orally to overcome as many stages as possible before self-reporting fatigue. Data acquisition was performed in real time using Aerograph software (version 2.3; Micromed, Brasília/DF, Brazil), and measurements were recorded every 10 seconds. The average of the 2 highest consecutive oxygen uptake ($\dot{V}O_2$) values was taken as the $\dot{V}O_2max$.[20] Two blinded experienced physiologists (not authors) determined the ventilatory threshold by simultaneously analyzing the following graphs: (1) ventilatory equivalent of O_2 and CO_2, (2) excess output of carbon dioxide ($[\dot{V}CO_2^2 \cdot \dot{V}O_2^{-1}] - \dot{V}CO_2$), and (3) carbon dioxide output plotted with $\dot{V}O_2$.[21] A third physiologist (not an author) analyzed the data with up to 3% variability if the 2 evaluators disagreed. A participant's data were discarded if the third opinion was also discordant. Heart rate was monitored using a Polar monitor (model 610i; Oulu, Finland).

Muscle-Damage Protocol

Participants performed an exercise session in an isokinetic dynamometer (Cybex NORM; Cybex International, Inc, Medway, MA) with each leg separately to induce muscular damage using eccentric and concentric exercise in the knee-flexor and -extensor muscles as described in Table 2. The angular velocity for both types of contractions ($60° \cdot s^{-1}$) has been used in studies of

Table 2. Muscle-Damage Induction Protocol

Repetitions	Muscle Action	Knee Muscle Group	Velocity, $° \cdot s^{-1}$	Interval, s
3	Concentric	Flexors and extensors	60	15
20	Concentric	Flexors and extensors	60	60
3	Concentric and eccentric	Flexors	60	15
20	Concentric and eccentric	Flexors	60	60
3	Concentric and eccentric	Flexors and extensors	60	15
50	Concentric and eccentric	Extensors, flexors, extensors, flexors, and extensors	60	30

muscle-damage induction,[22,23] primarily because it provides high levels of force output and a longer duration of constant speed.[24,25] The countermovement (jump and squat jump) was performed on a contact mat (Ergo Jump; Minas Gerais, Brazil) immediately before and 48 hours after the isokinetic exercise to confirm functional muscle damage. A category-ratio scale was used to assess perceived pain 48 hours after MDI. This scale uses scores from 0 (*no pain at all*) to 10 (*extremely intense pain*); a number greater than 10 (*unbearable pain*) was available when necessary. Participants received an explanation of the pain scale before testing.[26] Plasma levels of creatine kinase were measured in 5-mL blood samples taken from the antecubital vein before exercise and 48 hours after exercise. Blood samples were stored on ice in heparinized tubes for analysis. The plasma samples were extracted after centrifugation and stored at –70°C before analysis. Duplicate samples were analyzed for total creatine kinase using a standard commercial kit (Labtest Enzymatic – UV; Minas Gerais, Brazil).[27] The intra-assay and interassay variances were less than 5% and 10%, respectively. We instructed the participants to report any prolonged muscle pain up to 168 hours after MDI, and medical care and physical therapy were provided.

Endurance-Performance Test

The participants performed a trial to measure t_{lim} 48 hours before and after the MDI. The trial consisted of treadmill running after a 5-minute warm-up at 6 $km \cdot h^{-1}$ (1% grade). The speed was increased immediately to the participant's second ventilatory threshold speed. The athletes were evaluated according to their exercise t_{lim}. The electronic display was hidden during exercise to conceal the test information from the athletes. The time of exercise, heart rate, peak $\dot{V}O_2$ ($\dot{V}O_2$peak), respiratory exchange ratio, and rating of perceived exertion (RPE) were recorded at the moment of t_{lim}. Blood lactate accumulation was determined after exercise completion using the enzymatic-reaction technique and a portable lactometer (Accutrend Lactate; Basel, Switzerland). We instructed participants to refrain from ingesting alcohol for 48 hours, ingesting caffeine for 8 hours, and taking part in any exhaustive exercise in the 48 hours before the t_{lim} test. The test-retest intraclass correlation coefficients were 0.88 for $\dot{V}O_2$peak, 0.89 for t_{lim}, 0.87 for RPE, and 0.92 for heart rate and blood lactate accumulation.

Administration of NSAIDs

The pharmacologic treatment consisted of oral administration of a single pill that contained 1.2 g racemic ibuprofen, which is the total daily dose recommended for analgesic effect,[28] or placebo (lactose) 1 hour before the second t_{lim} test. The pills in both treatments had the same color, flavor, weight, size, smell, and excipient material (gelatin). Thus, participants were blinded to each treatment during the study. One researcher (E.L.C.) randomized and administered the treatment for each dependent variable, whereas the researchers (E.D.S., R.S.P.) who assessed the dependent variables were blinded to each treatment. Ibuprofen is absorbed from the gastrointestinal tract and achieves peak plasma concentrations 1 hour after administration.[28] Participants were fed the same type of food in similar quantities 2 hours before the second t_{lim} trial because variables such as the volume, pH, and composition of food in the digestive system may interfere with the gastric absorption of ibuprofen. A nutritionist (not an author) prepared the diets based on individual body mass. The meal comprised approximately 60% carbohydrates, 30% fatty acids (saturated, unsaturated, and monounsaturated), and 10% protein.

Data Analysis

We used the Shapiro-Wilk test to assess the normality of the data. A 2-way analysis of variance was calculated to compare the intragroup (time) and intergroup (treatment) variables. A 3-way analysis of variance was conducted to compare t_{lim} and lactate values between treatment groups before and after MDI. Bonferroni post hoc procedures were used to identify pairwise differences when we found an F value that was different. The Wilcoxon test was used to compare nonparametric data. We calculated the sample size using G*Power software (version 3.0.1; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), which determined that a sample of 12 participants in each group would provide a statistical power of more than 90% in all variables. Given that the available sample size was 10 in each group, we recalculated the statistical power for this sample size and found it was greater than 80% for all analyses. In addition, the parametric assumptions were not violated because of the sample size. The effect size (ES) of the main effects was calculated using the following formula: pretest–posttest ES = (posttest mean – pretest mean) / pretest standard deviation. The α level was set at $\leq .05$. We used SPSS statistical software (version 15.0; SPSS Inc, Chicago, IL) to analyze all data. The results are reported as the mean ± standard deviation.

RESULTS

We observed an increase in muscle pain values 48 hours after MDI ($P < .05$). No participants reported muscle pain before the MDI protocol. However, participants in the IG and PG reported pain in the quadriceps (IG: 1.9 ± 1.6, 95% confidence interval [CI] = 0.6, 3.2; PG: 3.1 ± 2.9, 95% CI = 0.9, 5.2) and hamstrings (IG: 5.7 ± 3, 95% CI = 4.1, 7.3; PG: 5.1 ± 3.1, 95% CI = 3.7, 6.5) muscles 48 hours after MDI and before the second t_{lim} trial. These results support the efficacy of the MDI for producing delayed-onset muscle soreness (Figure 2).

Reductions in the height of the squat jump and countermovement jump and an increase in plasma creatine kinase activity after MDI, which indicated tissue damage and the functional impairment of skeletal muscle, are illustrated in Table 3. The exhaustion times before and after MDI in the IG and PG are presented in Figure 3. We observed reductions in t_{lim} ($P < .01$) in the IG from 806.2 ± 287.7 seconds (95% CI = 600.4, 1011.9) before MDI to 653.3 ± 245.8 seconds (95% CI = 477.4, 829.1) after MDI and in the PG from 698.3 ± 340.1 seconds (95% CI = 455.0, 941.5) before MDI to 596.4 ± 267.1 seconds (95% CI = 405.3, 787.4) after

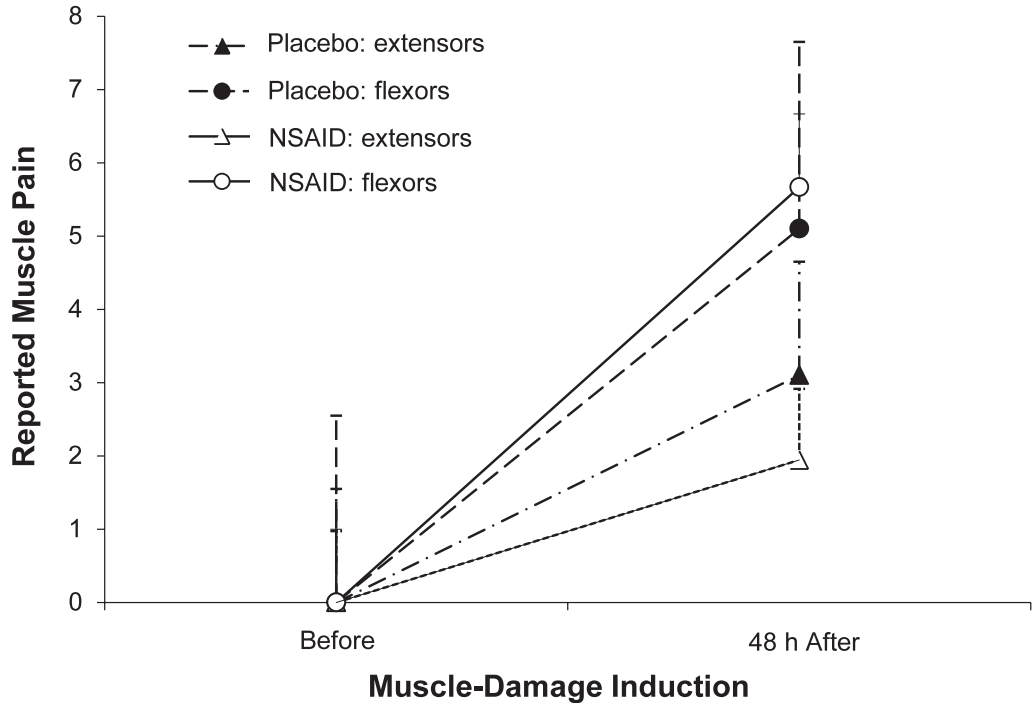

Figure 2. Reported pain values (mean ± SD) before and 48 hours after muscle-damage induction in the ibuprofen and placebo groups. Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

MDI. No interaction with the t_{lim} over time was seen between groups ($P = .55$), which suggests that the NSAID was ineffective as an ergogenic resource in this condition.

The physiologic variables at the end of each t_{lim} before and after MDI are shown in Table 4. Only the $\dot{V}O_2$peak was different between groups ($P = .005$). No other differences were noted in any variables between or within groups or in the interaction of time variations ($P > .05$).

The values of peak RPE exertion and lactate levels before and after MDI are provided in Table 5. We observed no difference in RPE at the end of the t_{lim} test between the IG and PG before ($P = .98$) or after ($P = .45$) MDI (ie, no analgesic effect). Blood lactate levels increased in both groups from baseline ($P < .01$), but no differences or interactions were present between groups before ($P = .99$) or after ($P = .42$) MDI.

DISCUSSION

Our primary finding was that the prophylactic administration of ibuprofen did not beneficially affect t_{lim} of runners experiencing lower limb muscle pain. Our initial hypothesis was that the NSAID would reduce muscle pain and attenuate the negative effect of muscle damage on athletic performance. However, this hypothesis was not supported because, although exercise time decreased in both groups from pretest to posttest, the posttest results did not differ between the groups.

Our results are similar to those of Vanheest et al,[7] who examined participants conditioned to run economy tests at different speeds before and after (on 5 subsequent days) a damage-induction protocol to the dominant lower limb only. The 3 groups received a daily treatment of placebo, ibuprofen (4 doses of 200 mg), or Vicoprofen (4 doses of 200 mg of ibuprofen with 7.5 mg of hydrocodone bitartrate) in the 24 hours preceding the test. No positive effects of treatment on running economy or efficiency were observed. Marvin et al[29] attempted to pharmacologically alter the time to exhaustion in young, healthy, conditioned participants using the serotonin agonist buspirone. The participants demonstrated a reduced time to fatigue and an increased RPE. The researchers, therefore, suggested that central mechanisms exist for decision making regarding exercise interruption that depend on musculoskeletal and cardiopulmonary signals.

The increase in blood lactate levels that we observed may have been accompanied by increases in the intramuscular concentrations of other substances we did

Table 3. Jump Performance and Creatine Kinase Activity Before and 48 Hours After the Muscle-Damage Induction Protocol

Variable	Mean ± SD (95% Confidence Interval)		*P* Value
	Before Protocol	48 h After Protocol	
Squat jump, cm	33.0 ± 4.1 (30.0, 35.9)	29.4 ± 3.7 (26.7, 32.1)	.03[a]
Countermovement jump, cm	35.3 ± 4.5 (32.2, 38.3)	31.8 ± 4.0 (28.9, 34.7)	.03[a]
Serum creatine kinase activity, U/l	180.6 ± 112.4 (100.1, 261)	12388.0 ± 65.9 (7667.4, 17108.5)	.003[a]

[a] Indicates difference ($P \leq .05$).

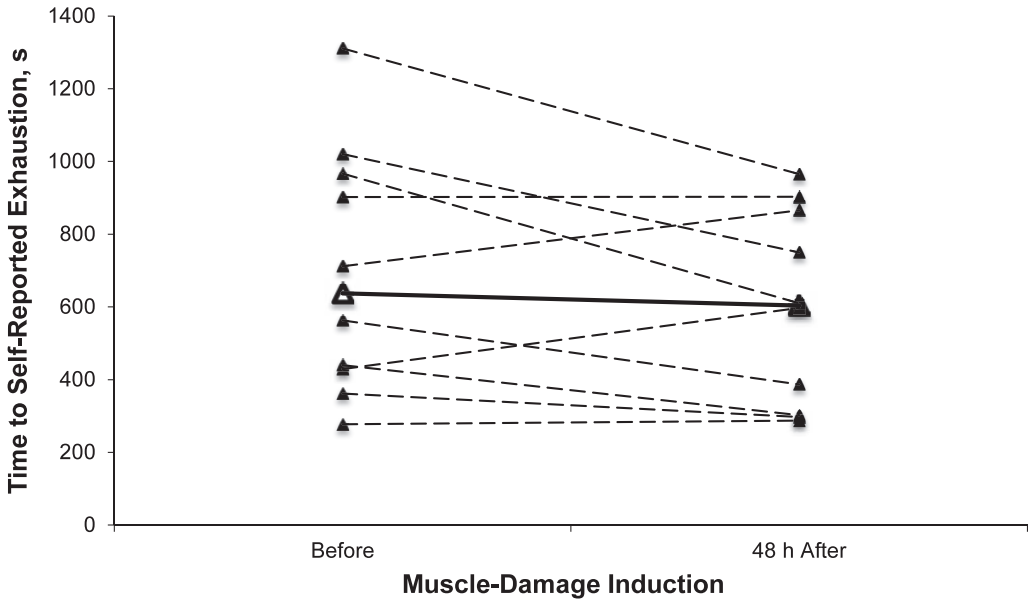

Figure 3. Time to exhaustion in the ibuprofen and placebo groups before and 48 hours after muscle-damage induction (dashed line). Inset (solid line) presents the groups' means ± SDs for exhaustion time. We observed no effect of ibuprofen to reduce impaired performance in the race after muscle-damage induction.

not measure, such as adenosine diphosphate, inorganic phosphate, and hydrogen ions, or an elevation in body temperature, and these factors may have limited exercise time.[30,31] Pain perception is also a crucial factor for performance during exercise. Amann et al[12] examined 8 cyclists in a double-blind, crossover, controlled clinical trial using 5-km time trials on a stationary cycloergometer. The afferent activity of type III Aδ fibers and type IV C fibers was reduced after a bolus injection of the μ-opioid receptor agonist fentanyl. Improved performance was observed in several biomechanical and physiologic variables.

One explanation for the lack of efficacy of ibuprofen is the magnitude of mechanical compromise in the isokinetic protocol. The morphologic alterations in the muscle tissue arising from the negative contraction, such as the failure of the contractile process of myofilaments, adversely affect maximal and submaximal neuromuscular function, especially in type II fibers.[9,32–34] Therefore, activities that require the participation of the stretch-shortening cycle are compromised by these alterations. Two findings suggest that these alterations of the muscle tissue result from damage: the compromised jump height (Table 3) and the decline in t_{lim} in the IG and PG (Figure 3).

Another explanation for the absence of an ergogenic effect of ibuprofen in our study is that inhibiting cyclooxygenase may induce secondary effects in the cardiovascular system that limit the expected tachycardia during exercise[35] or reduce muscular hyperemia.[36,37] These changes would negatively affect oxygen uptake and neutralize the expected ergogenic effect. Analgesic interventions that exhibit greater potency[12] or different pharmacodynamics[13] attenuate the deleterious effect of muscle damage on running performance.

Our study had limitations. The MDI protocol did not exactly reproduce running during exercise. Thus, the effect of ibuprofen on running performance when lower limb muscle pain is present must be investigated further. Another limitation is the anthropometric and muscle composition variations present in young military personnel, which prevents the extrapolation of our results to other populations of runners or athletes in other sports. In addition, we noted differences among the physical characteristics of the IG and PG, such as body mass, body mass index, body fat, $\dot{V}O_2max$, and velocity at the second ventilatory threshold. However, we do not believe these variations explain the lack of differences between groups in the running performance after exercise-induced muscle damage. Moreover, the effect of ibuprofen on the exercise performed after muscle soreness, which did not result in performance improvement, should not be compared with the possible effects of other analgesics due to different pharmacodynamic and pharmacokinetic characteristics among analgesics. The sample size may also have contributed to the lack of effect of ibuprofen on the t_{lim}.

CONCLUSIONS

Our purpose was to examine the effect of the NSAID ibuprofen on t_{lim} in runners with exercise-induced muscle damage. The MDI negatively affected endurance performance in both groups, which suggests that the NSAID ibuprofen probably did not preserve muscular-endurance performance in athletes experiencing muscle damage before exercise, which is consistent with previous reports. These observations indicate that long-distance runners should take caution when using NSAIDs to improve muscle-endurance performance because the side effects previously described[28,35,36] may outweigh the expected benefits. Our participants were young military personnel, so our results should be interpreted with caution because they cannot be easily generalized to high-level endurance athletes.

Table 4. Physiologic Variables at the End of the Time-Until-Self-Report-of-Fatigue Test Before and After Muscle-Damage Induction (Mean ± SD [95% Confidence Interval])

Variable	Placebo Group			Ibuprofen Group		
	Before Protocol	After Protocol	*P* Value	Before Protocol	After Protocol	*P* Value
Peak heart rate, beats·min^{-1}	192.2 ± 10.3 (182.8, 197.5)	187.5 ± 6.2 (182.7, 192.3)	.96	188.3 ± 9 (181.4, 195.2)	186.4 ± 10.1 (179.1, 193.6)	.53
Peak respiratory exchange ratio	1.06 ± 0.1 (0.99, 1.13)	1.10 ± 0.1 (1.05, 1.15)	.29	1.13 ± 0.1 (1.07, 1.17)	1.11 ± 0.1 (1.04, 1.16)	.61
Peak oxygen uptake[a]	54.2 ± 5.1 (50.7, 57.8)	52.9 ± 4.6 (49.5, 56.1)	.005[b]	46.9 ± 4.1 (43.9, 49.8)	46.1 ± 2.9 (44.0, 48.2)	.23
Maximal oxygen uptake, %	90.5 ± 6.7 (85.7, 95.3)	88.7 ± 10.1 (81.4, 95.8)	.67	91.5 ± 5.6 (86.6, 96.4)	90.3 ± 7.2 (96.5, 84.1)	.32

[a] Calculated as mL·kg^{-1}·min^{-1}.
[b] Indicates difference ($P < .05$).

Table 5. Perceived Exertion and Lactate Plasma Levels Before and After Muscle-Damage Induction (Mean ± SD [95% Confidence Interval])

Variable	Placebo Group		Ibuprofen Group		*P* Value[a]	
	Before Protocol	After Protocol	Before Protocol	After Protocol	Before Muscle-Damage Induction	After Muscle-Damage Induction
Peak rating of perceived exertion	19.3 ± 1.5 (18.2, 20.0)	19.3 ± 1.3 (18.4, 20.1)	19.8 ± 0.4 (19.4, 20.0)	19.4 ± 1.3 (18.4, 20.0)	.98	.45
Peak lactate plasma level	10.3 ± 3.9 (7.3, 13.1)	9.3 ± 2.3 (7.6, 10.9)	8.6 ± 3.5 (6.1, 11.1)	9.2 ± 3.5 (6.7, 11.7)	.99	.42

[a] *P* values correspond to the comparisons between groups before and after muscle-damage induction.

REFERENCES

1. Da Silva ER, De Rose EH, Ribeiro JP, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med*. 2011;45(2):91–94.
2. Alaranta A, Alaranta H, Helenius I. Use of prescription drugs in athletes. *Sports Med*. 2008;38(6):449–463.
3. Corrigan B, Kazlauskas R. Medication use in athletes selected for doping control at the Sydney Olympics (2000). *Clin J Sport Med*. 2003;13(1):33–40.
4. Gorski T, Cadore EL, Pinto SS, et al. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) in triathletes: prevalence, level of awareness, and reasons for use. *Br J Sports Med*. 2011;45(2):85–90.
5. Huang SH, Johnson K, Pipe AL. The use of dietary supplements and medications by Canadian athletes at the Atlanta and Sydney Olympic Games. *Clin J Sport Med*. 2006;16(1):27–33.
6. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res*. 2003;110(5–6):255–258.
7. Vanheest JL, Stoppani J, Scheett TP, et al. Effects of Vicoprofen and ibuprofen on physical performance after exercise-induced muscle damage. *J Sport Rehabil*. 2002;11(2):210–224.
8. Braun WA, Dutto DJ. The effects of a single bout of downhill running and ensuing delayed onset of muscle soreness on running economy performed 48 h later. *Eur J Appl Physiol*. 2003;90(1–2):29–34.
9. Friden J, Lieber RL. Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fibre components. *Acta Physiol Scand*. 2001;171(3):321–326.
10. Place N, Lepers R, Deley G, Millet GY. Time course of neuromuscular alterations during a prolonged running exercise. *Med Sci Sports Exerc*. 2004;36(8):1347–1356.
11. Proske U, Morgan DL. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. *J Physiol*. 2001;537(pt 2):333–345.
12. Amann M, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA. Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. *J Physiol*. 2009;587(pt 1):271–283.
13. Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. *J Appl Physiol (1985)*. 2010;108(1):98–104.
14. Katz WA, Rothenberg R. Section 3: the nature of pain. Pathophysiology. *J Clin Rheumatol*. 2005;11(suppl 2):S11–S15.
15. Sgherza AL, Axen K, Fain R, Hoffman RS, Dumbar CC, Haas F. Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry. *J Appl Physiol (1985)*. 2002;93(6):2023–2028.
16. Noakes TD, St Clair Gibson A. Logical limitations to the "catastrophe" models of fatigue during exercise in humans. *Br J Sports Med*. 2004;38(5):648–649.
17. Harriss DJ, Atkinson G. *International Journal of Sports Medicine*: ethical standards in sports and exercise science research. *Int J Sports Med*. 2009;30(10):701–702.
18. Jackson AS, Pollock ML. Generalized equations for predicting body density of men. *Br J Nutr*. 1978;40(3):497–504.
19. Heyward VH, Wagner DR. *Applied Body Composition Assessment*. 2nd ed. Leeds, UK: Human Kinetics; 2004.
20. Martin NA, Zoeller RF, Robertson RJ, Lephart SM. The comparative effects of sports massage, active recovery, and rest in promoting blood lactate clearance after supramaximal leg exercise. *J Athl Train*. 1998;33(1):30–35.
21. Gaskill SE, Ruby BC, Walker AJ, Sanchez OA, Serfass RC, Leon AS. Validity and reliability of combining three methods to determine ventilatory threshold. *Med Sci Sports Exerc*. 2001;33(11):1841–1848.
22. Baroni BM, Leal EC Jr, De Marchi T, Lopes AL, Salvador M, Vaz MA. Low level laser therapy before eccentric exercise reduces muscle damage markers in humans. *Eur J Appl Physiol*. 2010;110(4):789–796.
23. Chapman D, Newton M, Sacco P, Nosaka K. Greater muscle damage induced by fast versus slow velocity eccentric exercise. *Int J Sports Med*. 2006;27(8):591–598.
24. Dvir Z. *Isokinetics: Muscle Testing, Interpretation and Clinical Applications*. 2nd ed. Philadelphia, PA: Elsevier Group; 2004.
25. Ellenbacker TS, Davies GJ. The application of isokinetics in testing and rehabilitation of shoulder complex. *J Athl Train*. 2000;35(3):338–350.
26. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics; 1998.
27. Pantoja PD, Alberton CL, Pilla C, Vendrusculo AP, Kruel LF. Effect of resistive exercise on muscle damage in water and on land. *J Strength Cond Res*. 2009;23(3):1051–1054.
28. Hardman JG, Limbird LE, Gilman AG. *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001.
29. Marvin G, Sharma A, Aston W, Field C, Kendall MJ, Jones DA. The effects of buspirone on perceived exertion and time to fatigue in man. *Exp Physiol*. 1997;82(6):1057–1060.
30. Ansley L, Marvin G, Sharma A, Kendal MJ, Jones DA, Bridge MW. The effects of head cooling on endurance and neuroendocrine responses to exercise in warm conditions. *Physiol Res*. 2008;57(6):863–872.
31. Robergs RA, Ghiasvan F, Parker D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol*. 2004;287(3):R502–R516.
32. Byrne C, Twist C, Eston R. Neuromuscular function after exercise induced muscle damage: theoretical and applied implications. *Sports Med*. 2004;34(1):49–69.
33. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. *Am J Phys Med Rehabil*. 2002;81(suppl 11):S52–S69.
34. Paschalis V, Koutedakis Y, Baltzopoulos V, Mougios V, Jamurtas AZ, Theoharis V. The effects of muscle damage on running economy in healthy males. *Int J Sports Med*. 2005;26(10):827–831.
35. Takayama K, Yuhki K, Ono K, et al. Thromboxane A2 and prostaglandin F2[alpha] mediate inflammatory tachycardia. *Nat Med*. 2005;11(5):562–566.
36. Bradford CD, Cotter JD, Thorburn MS, Walker RJ, Gerrard DF. Exercise can be pyrogenic in humans. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(1):143–149.
37. Scharage WG, Joyner MJ, Dinenno FA. Local inhibition of nitric oxide and prostaglandins independently reduces forearm exercise hyperaemia in humans. *J Physiol*. 2004;557(pt 2):599–611.

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