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Preventive effect of the neurodynamic mobilization technique on delayed onset of muscle soreness: a randomized, single-blinded, placebo-controlled study

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Abstract

Background The neurodynamic mobilization (NM) technique is an intervention designed to restore homeostasis by mobilizing the nervous system and its surrounding structures. NM, through its physiological and biomechanical mechanisms, may play a role in modulating delayed Onset Muscle Soreness (DOMS) symptoms and regulating the emerging inflammatory response. The aim of this study was to determine the preventive effects of the NM technique on DOMS.

Methods Thirty-four untrained males were randomized into the NM ($n=17$) or placebo NM ($n=17$) group. Femoral nerve NM and placebo NM techniques were performed for three weeks in both groups. All the participants subsequently performed 300 maximal isokinetic eccentric contractions of the dominant knee extensors. Markers of muscle damage (creatine kinase, lactate dehydrogenase) and inflammation (IL-6, TNF-α), as well as muscle soreness, pressure pain threshold (PPT) and muscle function, were measured at baseline; immediately before (pre) and after (0 h) the completion of the exercise-induced muscle damage (EIMD) protocol; and at 24, 48, and 72 h.

Results Following the EIMD protocol, muscle soreness peaked at 24 h, while PPT reached its lowest level. The NM group exhibited significantly lower muscle soreness scores ($F_{3.160}=5.436$, $p=0.001$) and higher PPT values ($F_{3.160}=12.580$, $p<0.001$) compared to the placebo NM group at 0, 24, 48, and 72 h. Muscle function scores reached their lowest point at 0 h, with the NM group demonstrating significantly higher function scores than the placebo NM group both before the EIMD protocol and at 0 h ($F_{3.160}=8.532$, $p<0.001$). IL-6 levels peaked at 0 h, with the placebo NM group showing significantly higher IL-6 values compared to the NM group only at the 0 h time point ($F_{5.160}=5.377$, $p<0.001$). No significant group × time interaction effects were observed for the other variables ($p>0.05$).

Conclusions Three weeks of femoral nerve NM applied to healthy untrained participants had positive effects on the possible negative consequences of DOMS. NM may help alleviate inflammation and muscle damage symptoms and shorten the overall recovery time following DOMS.

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Trial registration (retrospectively registered): The trial was registered on [03/29/2022] with ClinicalTrials.gov (No: NCT05326893) and conducted according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Keywords Muscle soreness, Muscle damage, Inflammation, Nerve, Eccentric exercise

Introduction

Delayed Onset Muscle Soreness (DOMS), resulting from exercise-induced muscle damage (EIMD), is characterized by soreness, tenderness, edema, reduced range of motion, and impaired physical performance [1]. Despite the presence of unresolved questions regarding the mechanism of DOMS, the muscle damage and inflammation theories are the most commonly accepted explanatory models [1, 2]. According to these theories, strenuous eccentric exercises induce excessive stretching of muscle fibers, leading to microtrauma in sarcomere structures [3, 4]. The resulting damage increases protein breakdown at the cellular level and triggers the release of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [5, 6]. The released cytokines increase the sensitivity of peripheral nerve endings, contributing to heightened pain perception. Additionally, edema and increased tissue pressure, resulting from inflammation, stimulate intramuscular receptors, thereby exacerbating pain intensity [1, 7]. Although this condition is temporary, compensatory mechanisms negatively impact athletic performance, training efficiency, and daily activities [1, 8]. In this context, proper management of the inflammatory process may play a critical role in reducing both the severity and duration of DOMS.

Neurodynamic mobilization (NM) encompasses a comprehensive set of manual techniques designed to mobilize the neural system [9]. NM techniques are applied across individuals of varying ages and activity levels, both for the treatment of neuromusculoskeletal disorders and for enhancing functionality during or following strength, endurance, and aerobic exercises [10, 11].These techniques are categorized into tensioning and sliding methods, each exerting distinct mechanical and physiological effects on nerves [11–13]. In acute, irritable, and painful conditions, the nerve sliding technique is preferred, whereas in healthy individuals, chronic cases, and situations where nerve mobility is significantly reduced, the nerve tensioning technique is recommended [9]. From a mechanical perspective, NM enhances axoplasmic flow within the nerve and surrounding connective tissues, facilitating the distribution of local inflammatory mediators through the repetitive movement of nerve tissue [9, 14]. Moreover, NM increases the activity of glial cells, which play crucial roles in mediating communication between the immune system and the central nervous system, thereby contributing to the physiological regulation of inflammatory processes [15, 16]. The primary aim of NM techniques is to induce a mild and sterile inflammatory response (an inflammatory reaction occurring without the presence of microorganisms) during the healthy period, thereby supporting synaptic plasticity and maintaining the central nervous system in a state of preparedness against potential injuries [15, 17]. In this way, by enhancing the mobility of neural tissues, NM techniques contribute to reducing the risk of exercise-induced injuries, accelerating the recovery process, and regulating inflammatory responses that develop following nerve injuries through the reduction of intraneural edema [10, 12].

The literature suggests that NM techniques can be utilized to reduce peripheral neuroinflammation by enhancing the mechanical properties and mobility of neural tissues [11]. Additionally, these techniques are proposed to regulate circulation by improving nerve tissue mobility and modulating pain by activating mechanoreceptors [9]. Furthermore, NM require no additional costs, do not necessitate equipment for application, can be self-administered with minimal training, and have no known side effects [9, 10, 12]. Owing to these advantages, NM techniques are widely used both in the treatment of various conditions and in enhancing functionality and performance [10]. In this context, NM may have a potential impact on controlling inflammation levels and alleviating pain in conditions such as DOMS, where inflammation plays a significant role.

Numerous studies have been conducted to prevent and/or treat symptoms of DOMS [8, 18]. Furthermore, the literature has demonstrated the therapeutic role of NM techniques on the symptoms of DOMS [19–21]. However, research has yet to specifically investigate the preventive effectiveness of NM techniques. It was hypothesized that the application of NM techniques prior to EIMD could prevent or reduce the severity of DOMS symptoms by modulating the inflammatory response and minimizing muscle damage. Consequently, reducing the impact of DOMS-related symptoms may help preserve training continuity and prevent potential declines in athletic performance. Therefore, this study aimed to evaluate the preventive effects of NM on DOMS.

Methods

Trial design

This prospective, single-blind, randomized, placebo -controlled trial involved a 3-week preventive treatment protocol. The study was approved by the local Ethics Committee of GAZİ University (Approval Number:

02.10.2019/270). Written informed consent was obtained from all participants. This study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (See attachment in the additional file).

Participants

Forty-four young, untrained, sedentary men who did not perform regular physical activity participated in the study. The study had specific criteria for participant inclusion. These criteria included the following: (1) aged between 20 and 32 years; (2) male sex; and (3) a sedentary lifestyle, defined as engaging in less than 30 min of moderate physical activity for five days a week, according to the activity guidelines set by the American College of Sports Medicine [22]. Participants were excluded if they had a recent lower extremity injury or surgery, had vascular disease or neurological impairments, or were regularly using inflammation or analgesic medications. Ten out of the 44 individuals were excluded from the study due to various reasons, including COVID-19 infection, dental treatment, and insufficient blood sampling. As a result, the study was completed with 34 participants. Figure 1 shows the study flowchart.

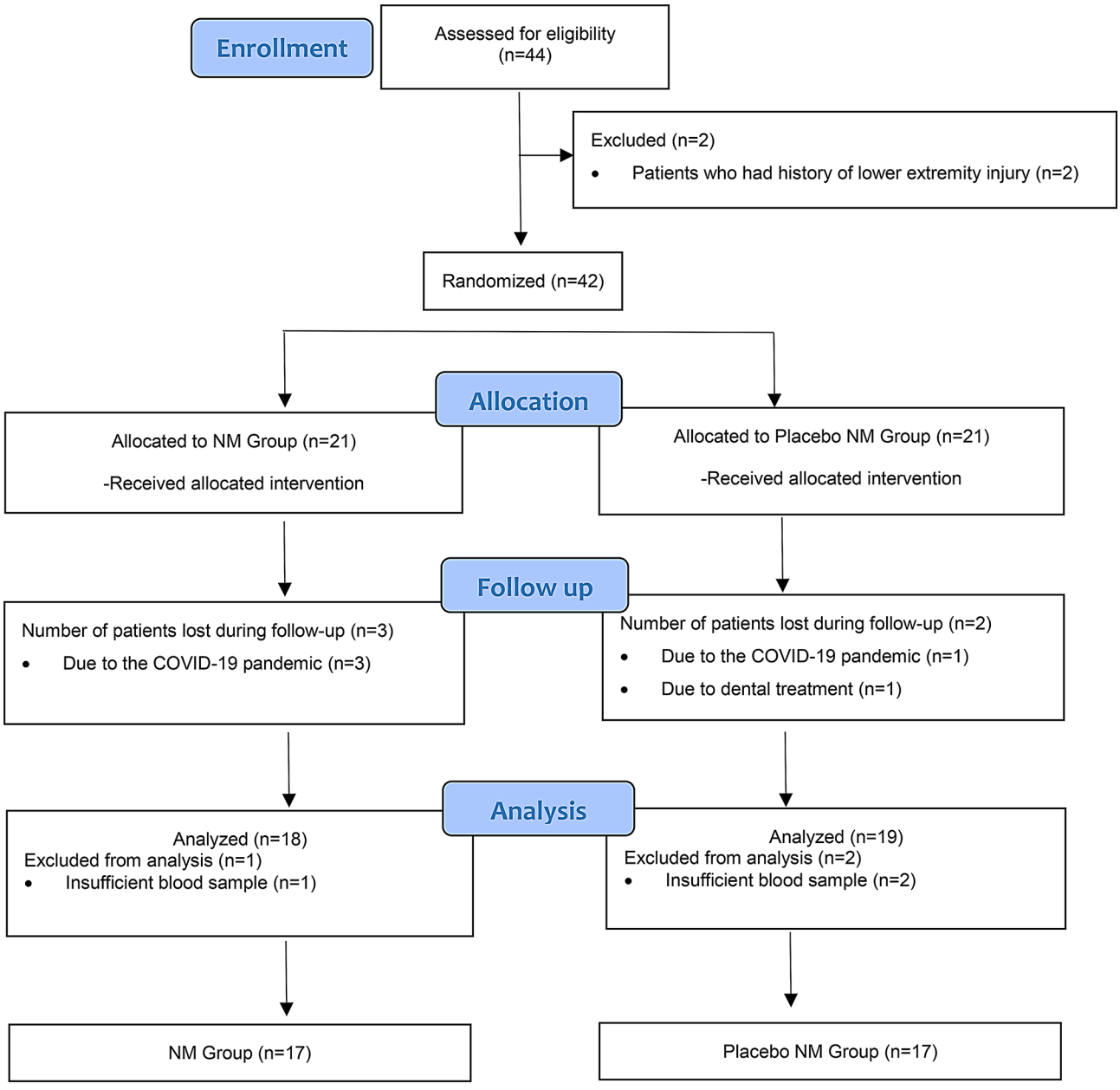

Fig. 1 CONSORT flowchart of the study

Experimental design

All interventions and the EIMD protocol were applied to the knee extensors of the dominant limb, which typically provides greater strength and motor control. This approach ensured standardization in the implementation of the EIMD protocol, which is considered one of the most demanding protocols in the literature [6], and minimized the risk of potential injury. All procedures and assessments were conducted by the same researcher at the Orthopedic Rehabilitation Unit of the Department of Physiotherapy and Rehabilitation, Gazi University (Ankara), under standardized environmental conditions and at consistent times of day. Prior to data collection, participants were informed about the purpose and procedures of the study to ensure standardization. They were also instructed to refrain from taking any medication or dietary supplements and from participating in sports or unaccustomed exercise during the data collection period. To remain blinded, participants were informed that they should not discuss the sampling procedures with each other. The participants were then randomly assigned to two groups.

The study consisted of 3 phases, as shown in Fig. 2. In phase I, the assessment included the collection of data on muscle soreness, the pressure pain threshold (PPT), and function (one-leg hop test). Additionally, blood samples were obtained for analysis. After the baseline measurements of all participants, femoral nerve tension and placebo femoral nerve tension techniques were applied for three weeks. As the literature does not report a standardized duration for NM application, a three-week intervention period was selected, based on evidence that neuromuscular adaptations typically develop within 2 to 4 weeks [23]. A 3-day break was then taken since the acute effects of NM are known to increase performance and functionality [19].

In phase II, baseline measurements were repeated, blood samples were taken, and the participants performed the EIMD protocol. The EIMD protocol employed in this study was chosen due to its recognition as one of the most intense and widely validated methods for inducing muscle damage in the literature [6]. Immediately after the EIMD protocol (0 h), baseline measurements were repeated, and blood samples were collected. All procedures were completed on the same day.

In Phase III, at 24, 48, and 72 h after the EIMD protocol, the baseline measurements were repeated, and blood samples were collected again.

Randomization and blinding

All the participants were selected and allocated into two groups via random allocation software (version 2.0). Only the participants were blinded, and the study was conducted as a randomized, single-blind study.

Interventions

A physiotherapist with ten years of clinical experience who attended a 14-hour neuroimmune system mobilization course (from Neuro Orthopedic Institute, Australia) provided femoral nerve tension and femoral nerve placebo tension to all participants. The EIMD protocol was administered by another physiotherapist with over 15 years of experience in the field, who was also blinded to the participants' group assignments.

Neurodynamic tension technique for the femoral nerve

The participants were positioned lying on their nondominant side. The therapist stood behind the participants and supported their upper legs to maintain their hips in a neutral position (no abduction/adduction). The upper leg's knee was flexed, and the hip was extended until the patient felt soreness or pain. This posture was

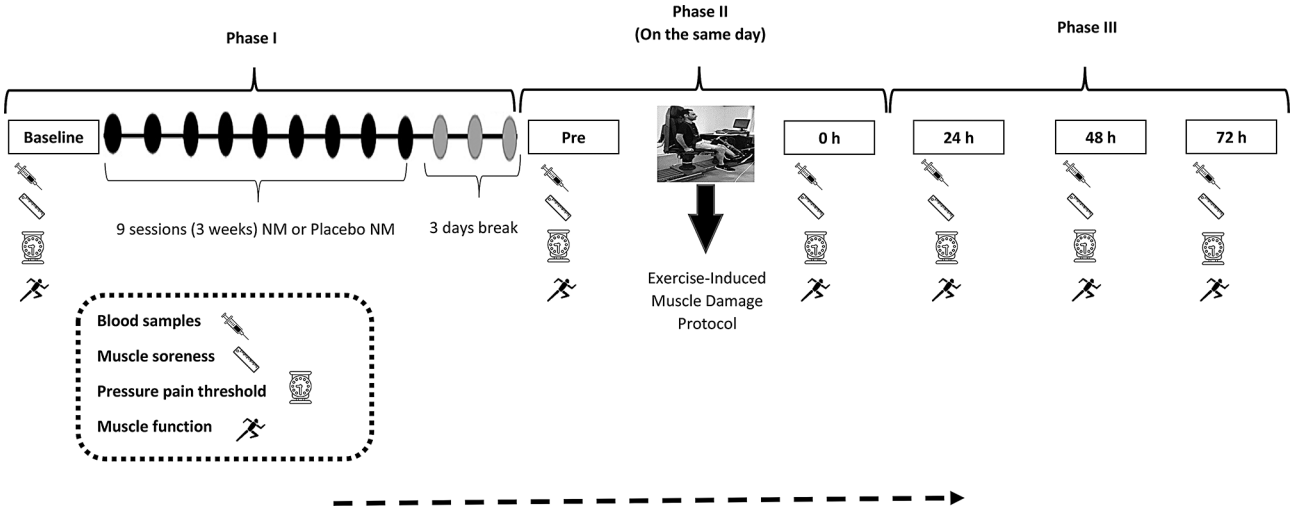

Fig. 2 Experimental design

held for three seconds before being released (Fig. 3A). Each session was performed in three sets of ten repetitions at each session, with a two-minute break between sets [12]. Nine sessions were conducted within three weeks.

Placebo neurodynamic tension technique for the femoral nerve

The participants were asked to lie on their non-dominant side with their heads on the midline. The upper leg was gripped in full knee extension, and the hip was abducted for 3 s while the pelvis was stabilized (Fig. 3B). This maneuver was performed in three sets of ten repetitions at each session, with a two-minute break between sets. Within three weeks, nine sessions were completed.

Exercise-induced muscle damage protocol

The participants were positioned on a dynamometer (Cybex Humac Norm Testing and Rehabilitation System, CSMI, USA), with the hip and knee flexed to 90°, secured with thigh and trunk stabilization straps. The rotational axis of the dominant knee joint (aligned with the lateral femoral epicondyle) was precisely aligned with that of the dynamometer's lever arm. The resistance pad was attached approximately 3 cm above the medial malleolus. After being seated, participants received a demonstration of the testing procedure, accompanied by standardized verbal instructions regarding movement execution. Instructions were consistent across participants: (a) for knee extensors: "Extend your leg as if kicking a ball, exerting maximum possible force"; (b) for knee flexors: "Allow the machine to straighten your knees during the lever arm's upward movement." Participants then performed 30 sets of 10 eccentric contractions targeting the dominant quadriceps femoris muscle (within a range of 35°-95° flexion) at a controlled velocity of 30°/s, with a 30-second interval between sets. Work and weight-normalized work were calculated [6].

(A) (B)

Fig. 3 Femoral nerve neurodynamic tension technique (**A**); Femoral nerve placebo neurodynamic tension technique (**B**)

Outcome measurements

Muscle soreness

Muscle soreness was assessed on a 100 mm visual analog scale (0 = no soreness, 10 = extremely painful). The participants were asked to mark their soreness while going downstairs (10-stair set) [6].

Pressure pain threshold

The pressure pain threshold (PPT) was measured at 5 cm above the superior of the patella (representing the musculotendinous junction) with a digital pressure algometer (JTECH Medical Industries, Salt Lake City, US). The average value of three trials was used in the analysis [24].

Muscle function

Muscle function was assessed by the one-leg hop test. The participants were instructed to stand on one leg, jump off and land on that leg without losing balance. Three hops were performed (with 60 s of rest between hops), and the distance hopped was measured via a standard tape measure. The average distance was recorded as a centimeter [25].

Blood sampling and analysis

Blood samples were drawn from the antecubital vein of the dominant arm and transferred into 5 mL plain vacutainer clot tubes. After collection, the tubes were gently inverted three times to mix the clot activator with the blood and then centrifuged at 3500 RPM for 10 min. The serum was subsequently transferred to storage tubes and immediately frozen at -80 °C until analysis. Biomarkers for muscle damage (creatine kinase [CK] and lactate dehydrogenase [LDH]) and inflammation (tumor necrosis factor-alpha [TNF-α] and human interleukin-6 [IL-6]) were analyzed according to the manufacturer's instructions at the University Hospital Biochemistry laboratories.

Statistical analysis

Data management and statistical analyses were conducted via two-way (group: 2; time: 6) split-plot repeated-measures ANOVA with SPSS version 20.0 (IBM Corporation, Chicago, IL, USA). Normality was assessed with the Kolmogorov–Smirnov test, and Levene's test was used to verify variance homogeneity across groups. Mauchly's test was used to assess sphericity; if it was violated, the Greenhouse–Geisser correction was applied to the ANOVA. Post hoc comparisons of variations in

Table 1 Subjects' characteristics

	NM (*n* = 17)	Placebo NM (*n* = 17)	*p*
Age (years)	25.2 ± 4.1	25.4 ± 4.6	0.383
Height (cm)	175.8 ± 6.2	176.8 ± 5.9	0.775
Weight (kg)	70.7 ± 10.3	73.3 ± 11.4	0.589
BMI (kg/m^2)	22.8 ± 2.5	23.6 ± 3.9	0.107
MET	1398.2 ± 139.7	1354.1 ± 117.8	0.327
Dominant side (Right/Left)	17/0	14/3	0.068

dependent variables within and between groups were conducted via Fisher's protected least significant difference test. Statistical significance was set at $p < 0.05$, with the data presented as the means ± SDs.

Sample size calculations

The sample size and power analysis were conducted via G*Power 3.1 software. For the preliminary sample size calculation, muscle soreness intensity was established as the primary outcome measure, and the effect size was calculated as 0.42 based on the basis of reference study data [20]. A minimum of 32 participants (16 per group) were required for the study, (85% power with f: 0.42 effect size, α = 0.05 type I error). Owing to the challenges inherent in the study, such as repeated blood sampling, the demanding EIMD protocol, and the possibility of DOMS not occurring, the drop-out rate was set at 25%, and 44 participants were invited to the study. The study included 34 participants, and subsequent power analysis demonstrated a statistical power of 90%, with an effect size of 0.46, an alpha level of 0.05, and a 95% confidence interval.

Results

Baseline characteristics

There were no significant differences between the two groups in terms of age, height, weight, body mass index (kg/m^2), or metabolic equivalent (MET), dominant side as determined by the IPAQ questionnaire (Table 1) or baseline responses to testing (Table 2) ($p > 0.05$).

Muscle soreness

For muscle soreness, a significant group × time interaction effect was observed ($F_{3,160}$ = 5.436, $p = 0.001$). Following the EIMD protocol, muscle soreness peaked at 24 h in both groups compared to baseline ($p < 0.001$). However, the placebo NM group exhibited a significantly greater increase in muscle soreness from baseline compared to the NM group (NM: +47%, Placebo NM: +60%; $p < 0.05$). Post hoc pairwise comparisons at each time point revealed that the NM group had significantly lower muscle soreness than the placebo NM group at 0, 24, 48, and 72 h post-EIMD protocol ($p < 0.05$ for all comparisons) (Table 2). Muscle soreness levels returned to baseline values in both groups at an unknown time point after 72 h following the EIMD protocol (Fig. 4A).

Table 2 Comparative analysis among groups of muscle soreness, PPT, muscle function, IL-6, TNF- A, CK, and LDH

	Groups	Baseline	Pre	0 h	24 h	48 h	72 h
Muscle soreness (VAS)	NM	0.0 ± 0.0	0.0 ± 0.0	33.2 ± 15.6	47.4 ± 13.7	36.9 ± 15.8	21.8 ± 12.7
	Placebo NM	0.0 ± 0.0	0.0 ± 0.0	46.1 ± 12.4	60.1 ± 12.9	52.4 ± 11.8	36.5 ± 9.1
	p $^{NM–Placebo\ NM}$	-	-	0.011	0.009	0.003	0.001
PPT (N/cm^2)	NM	112.2 ± 9.1	129.6 ± 16.6	111.4 ± 16.8	89.9 ± 19.6	92.3 ± 22.2	117.4 ± 18.5
	Placebo NM	119.9 ± 14.7	118.6 ± 15.0	84.2 ± 20.6	58.6 ± 23.3	72.5 ± 24.7	94.8 ± 23.9
	p $^{NM–Placebo\ NM}$	0.056	0.051	0.001	0.001	0.013	0.003
Muscle function (cm)	NM	95.4 ± 22.9	117.3 ± 22.51	78.5 ± 23.6	89.8 ± 25.9	91.8 ± 26.4	103.3 ± 25.8
	Placebo NM	106.8 ± 18.3	106.6 ± 18.1	61.6 ± 24.6	81.7 ± 26.1	90.5 ± 24.2	105.2 ± 27.1
	p $^{NM–Placebo\ NM}$	0.103	0.038	0.008	0.341	0.880	0.818
IL-6 (pg/ml)	NM	153.7 ± 24.5	153.6 ± 22.2	235.2 ± 25.5	176.8 ± 23.1	145.7 ± 21.2	152.2 ± 18.5
	Placebo NM	141.5 ± 20.3	140.1 ± 18.1	268.2 ± 38.0	179.1 ± 25.6	156.6 ± 20.4	157.8 ± 22.7
	p $^{NM–Placebo\ NM}$	0.128	0.060	0.006	0.786	0.134	0.431
TNF-α (pg/ml)	NM	150.3 ± 15.8	153.5 ± 16.1	204.8 ± 30.3	292.2 ± 32.8	261.3 ± 35.8	187.7 ± 30.6
	Placebo NM	156.3 ± 16.6	155.4 ± 18.2	213.1 ± 33.7	308.4 ± 37.7	273.5 ± 30.1	200.1 ± 24.5
	p $^{NM–Placebo\ NM}$	0.212	0.412	0.460	0.247	0.365	0.202
CK (U/L)	NM	112.3 ± 38.1	114.5 ± 34.1	199.3 ± 60.4	284.4 ± 73.6	213.2 ± 48.6	166.7 ± 59.7
	Placebo NM	115.1 ± 29.2	118.9 ± 27.5	259.5 ± 59.8	356.4 ± 96.6	225.1 ± 51.9	183.7 ± 79.6
	p $^{NM–Placebo\ NM}$	0.810	0.681	0.006	0.019	0.494	0.488
LDH (U/L)	NM	147.3 ± 14.1	144.2 ± 13.1	176.8 ± 52.9	166.1 ± 43.1	151.9 ± 16.1	150.5 ± 26.0
	Placebo NM	149.5 ± 14.5	140.8 ± 20.8	181.6 ± 46.6	172.4 ± 36.1	163.2 ± 23.2	160.1 ± 37.8
	p $^{NM–Placebo\ NM}$	0.674	0.571	0.755	0.651	0.111	0.393

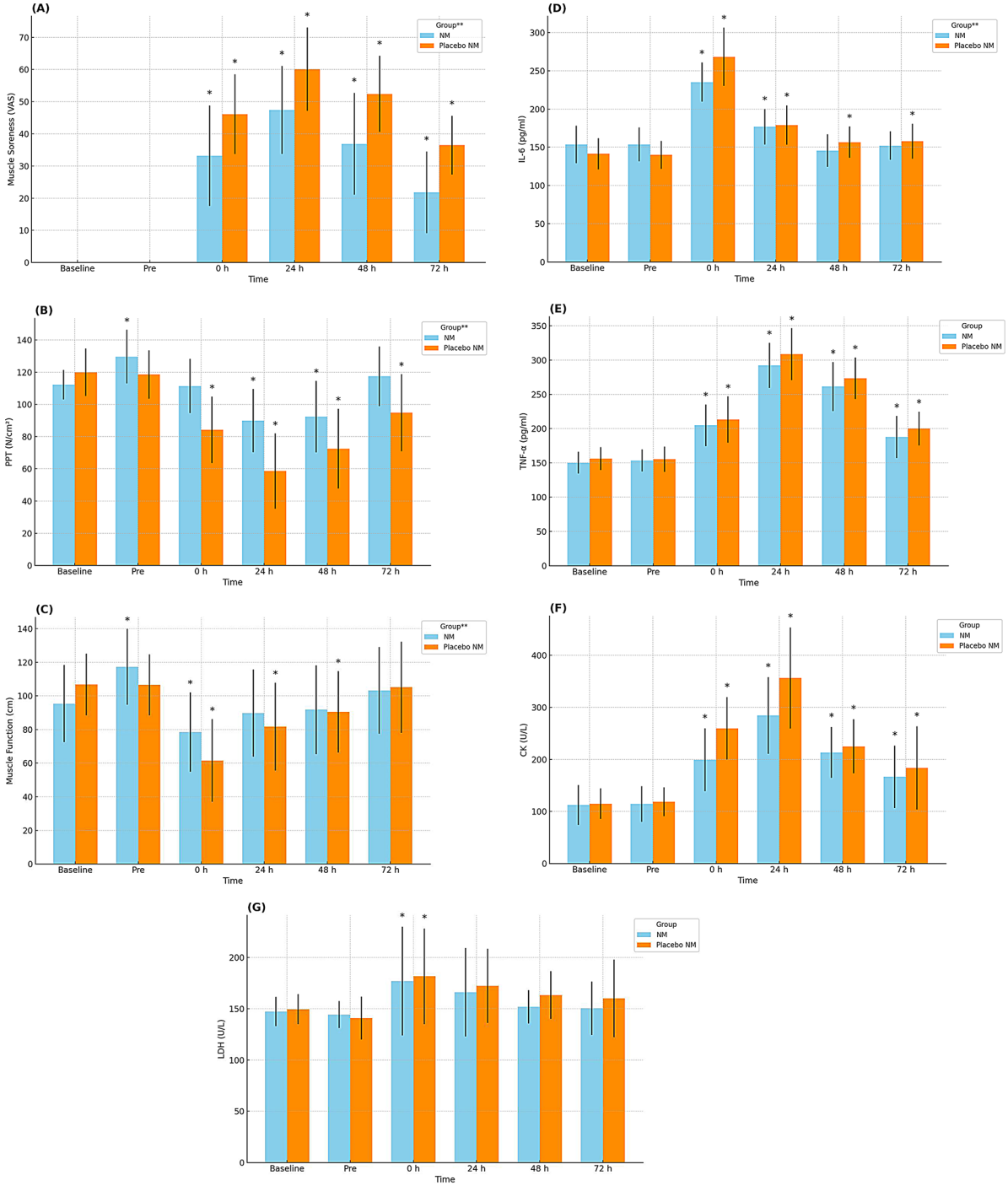

Fig. 4 Normalized changes in muscle soreness (**A**), PPT (**B**), muscle function (**C**), IL-6 (**D**), TNF- alpha (**E**), CK (**F**), LDH (**G**), from the baseline, at before EIMD protocol (pre), Immediately after EIMD protocol (0 h), 24 h, 48 h, and 72 h for the NM and placebo NM groups. * Significant differences with respect to Baseline. ** Indicates a significant interaction effect

Pressure pain threshold

A significant group × time interaction effect was observed for PPT ($F_{3.160}$ = 12.580, $p < 0.001$). Following the EIMD protocol, PPT reached its lowest point at 24 h in both groups compared to baseline ($p < 0.001$). However, the decrease in PPT was significantly greater in the placebo NM group compared to the NM group (NM: −20%, Placebo NM: −52%; $p < 0.05$). Post hoc pairwise comparisons at each time point demonstrated that the NM group had significantly higher PPT values than the placebo NM group at 0, 24, 48, and 72 h post-EIMD protocol ($p < 0.05$ for all comparisons) (Table 2). Additionally, the

return to baseline occurred 72 h after the EIMD protocol in the NM group, whereas in the placebo NM group, it occurred at an unknown time point after 72 h (Fig. 4B).

Muscle function

With respect to muscle function, a significant group × time interaction effect was observed ($F_{3.160}$ = 8.532, $p < 0.001$). Functional scores were lowest immediately after the EIMD protocol (0 h) in both groups compared to baseline ($p < 0.001$). However, the decrease in functionality was significantly greater in the placebo NM group compared to the NM group (NM: −18%, Placebo NM: −41%; $p < 0.05$). Post hoc pairwise comparisons revealed that the NM group demonstrated significantly better functional performance at the pre-EIMD protocol ($p = 0.038$) and immediately after EIMD protocol ($p = 0.008$) time points compared to the placebo NM group (Table 2). Additionally, the return to baseline values occurred 24 h after the EIMD protocol in the NM group, whereas it occurred 72 h after the protocol in the placebo NM group (Fig. 4C).

Inflammatory stress markers

A significant group × time interaction effect was observed only for IL-6 levels ($F_{5.160}$ = 5.377, $p < 0.001$), while for TNF-α, a significant main effect of time was detected without a group × time interaction ($F_{4.113}$ = 140.488, $p < 0.001$). IL-6 peaked immediately after the EIMD protocol (0 h), whereas TNF-α peaked 24 h after the EIMD protocol. Both groups exhibited significant increases in IL-6 (NM group: +53%; Placebo NM group: +90%) and TNF-α (NM group: +94%; Placebo NM group: +97%) compared to baseline ($p < 0.05$). IL-6 levels showed lower concentrations in the NM group compared to the placebo NM group only at 0 h ($p = 0.006$) (Table 2). Moreover, IL-6 levels returned to baseline at 48 h in the NM group, whereas in the placebo NM group, they returned to baseline at an unknown time point after 72 h (Fig. 4D). In contrast, TNF-α levels returned to baseline in both groups at 72 h (Fig. 4E).

Muscle damage markers

Significant main effects of time were observed for both CK ($F_{2.71}$ = 10.479, $p < 0.001$) and LDH ($F_{3.160}$ = 8.784, $p < 0.001$) concentrations, with no significant group × time interaction effects detected. Following the EIMD protocol, CK levels peaked at 24 h in both groups, while LDH levels peaked at 0 h. Significant increases in CK (NM group: +154%; placebo NM group: +210%) and LDH (NM group: +20%; placebo NM group: +21%) levels were observed compared to baseline in both groups ($p < 0.05$). However, significant between-group differences were found only for CK concentrations at 0 h ($p = 0.006$) and 24 h ($p = 0.019$) (Table 2). Furthermore, CK levels returned to baseline values at an unknown time point after 72 h in both groups (Fig. 3F), whereas LDH levels normalized by 24 h following the EIMD protocol (Fig. 3G).

Adverse events and dropouts

No adverse events or unintended effects were reported in either the NM or the placebo group during the intervention and follow-up periods.

Discussion

The aim of this study was to investigate the preventive effects of NM on DOMS. The main hypothesis was that NM applied before DOMS could prevent or regulate inflammation and muscle damage symptoms. As a result of the research, this hypothesis was partially supported. In the present study, we observed that the femoral nerve NM technique administered prior to the EIMD protocol has preventive effects on muscle soreness, the PPT, muscle function, and the IL-6 level. However, no protective effects were observed for the TNF-α, CK, or LDH levels.

To our knowledge, while no studies have specifically examined the preventive effects of NM on DOMS, three studies aimed to mitigate symptoms that occur after DOMS [19–21]. Kim et al. compared therapeutic ultrasound and the median nerve NM technique and reported that DOMS symptoms such as soreness, PPT, and lactate levels were less common in the NM group [21]. Romero et al. compared the femoral nerve NM and foam roller techniques and noted that both techniques had similar positive effects on soreness [20]. Vaidya et al. reported that the foam roller technique was more effective than the NM technique for improving DOMS symptoms, including pressure pain threshold (PPT), range of motion, and soreness [19].

Coppieters et al. suggest that NM techniques enhance nerve flexibility and circulation under mechanical stress, improve neural functions, and play an effective role in pain modulation [9]. Furthermore, another study emphasizes that NM improves the mechanical and physiological properties of nerves in clinical applications and alleviates pain symptoms [26].The current study revealed that soreness increased the most in the placebo group (NM: 47% and Placebo NM: 60%) 24 h after the EIMD protocol, and the NM technique had a preventive effect on muscle soreness. In the studies of Romero [20] and Vaidya [19], pain increased by ~40% and ~51%, respectively, and peaked at 48 h. In the study of Kim et al., pain increased by ~73% and peaked immediately after the protocol [21]. These differences between studies are likely due to the differences in the applied EIMD protocol and the timing of the final measurement. The NM technique is thought to increase the release of opioid receptors in the periventricular gray matter, stimulating the endogenous

opioid-related pain regulatory system and thereby reducing pain through this mechanism [27]. Furthermore, the role of NM in preventing or at least mitigating pain resulting from DOMS may be considered an important strategy for athletes and physically active individuals. In this context, alleviating DOMS symptoms may accelerate recovery between training sessions, reduce the rate of missed sessions, and contribute to consistent performance development.

The PPT is a key parameter that objectively assesses the pain sensitivity of muscle tissue and is recognized as an indicator of peripheral hyperalgesia [1, 28]. In this study, the PPT values of participants who received the NM technique showed less change following the EIMD protocol (NM: – 20% and Placebo NM: – 52%), and NM was protective against post-DOMS-related hyperalgesia. Although the positive effects of the NM technique on the PPT have been proven in previous studies [28, 29], to the best of our knowledge, only Kim et al. examined the effects of the NM technique on the PPT after DOMS, and no significant superiority was found [21]. Compared with that in the other groups, quadriceps femoris muscle tenderness was greater in the placebo NM group, suggesting that NM intervention may effectively reduce muscle tenderness. Several factors contribute to this finding. First, the NM technique has been shown to reduce the levels of nerve growth factor and glial fibrillary acidic protein, both of which contribute to hyperalgesia [15]. By modulating these biochemical markers, NM may help mitigate peripheral sensitization and pain perception [27]. Second, NM inhibits temporal summation by stimulating C fibers associated with continuous and delayed pain transmission [15]. This inhibitory effect on nociceptive processing ultimately leads to an increase in PPT levels, indicating a reduction in pain sensitivity [26]. In addition, NM techniques enhance the natural gliding movement of peripheral nerves [9]. This facilitates increased blood circulation and the removal of metabolic waste products, thereby supporting pain modulation and tissue healing [9, 10]. Although the findings indicate that NM has a protective effect on PPT, further studies are essential to investigate its long-term effects and its impact on other pain modulation parameters. In the future, studies with larger sample sizes and individuals from different sports disciplines may provide a more detailed understanding of the mechanical and neurophysiological effects of NM on DOMS symptoms.

The one-leg jump test is recognized as an objective measure that assesses not only functional capacity but also explosive power, coordination, and stability of the lower extremities [30]. Therefore, it serves as a sensitive parameter reflecting the adverse effects of DOMS on muscle function [31]. Studies have demonstrated that DOMS negatively affect physical performance and function [18, 32]. According to the results of the present study, the one-leg jump distance was less affected by the NM technique (NM: – 18%, Placebo NM: – 41%). In addition, the NM technique had a protective effect and increased the recovery rate. This result can be interpreted as a positive reflection of the preventive effects of the NM technique on muscle soreness and the PPT on lower extremity functionality. Nevertheless, the protective effect observed in one-leg jump performance suggests that NM possesses a mechanism for modulating muscle damage and inflammatory responses induced by DOMS, thereby contributing to the preservation of muscle function. This finding highlights the potential benefits of considering NM as a prehabilitation strategy for athletes and individuals with high levels of physical activity. Indeed, studies have demonstrated the positive effects of NM techniques on functionality, further supporting the efficacy of this approach [10, 33].

IL-6 and TNF-α are among the most critical proinflammatory cytokines used to determine inflammation in DOMS [34]. These cytokines are synthesized and released by peripheral immune cells and glial cells (microglia and astrocytes), which are the immune cells of the central nervous system [16, 35]. Santana et al. reported that the NM could increase the activation of glial cells, which are responsible for the production of cytokines [16]. In another study, Zhu et al. reported that the NM reduced TNF-α and IL-6 cytokine levels in rats with neuropathic pain [35]. In our study, cytokine levels increased more in the NM group (IL-6: 53%, TNF-α: 94%) than in the placebo group (IL-6: 90%, TNF-α: 97%). In addition, a preventive effect was observed only at the IL-6 level, and the speed of recovery was greater in the NM group. Although a preventive effect was not observed in terms of TNF-α levels, our findings demonstrate that NM application led to a significant reduction in DOMS symptoms such as soreness and tenderness. This suggests that the preventive effects of NM may be associated not only with inflammatory responses but also with nociceptive inputs, including mechanical stress, muscle damage, and central sensitization. The preventive effects observed on PPT and muscle function in our study further support this interpretation. Moreover, these findings are consistent with the existing literature emphasizing the role of nervous system modulation in the management of musculoskeletal pain [9, 10]. Future studies incorporating electrophysiological and imaging-based data may help to elucidate these mechanisms in greater detail. Additionally, limitations such as the sample size and the study being conducted on a sedentary population may restrict the generalizability of the findings. Future studies involving participants with diverse characteristics will allow for a more comprehensive evaluation of this topic.

It has been reported that neural adaptation reduces the stress per-fiber by positively regulating the workload distribution among muscle fibers so that muscle damage that may occur with DOMS is less severe [16]. In the present study, a peak in the typical recovery of muscle injury parameters was observed in the NM group (CK: 154%; LDH: 20%) compared with the placebo group (CK: 210%; LDH: 21%). These results indicate that the NM did not have a protective effect on any parameter; however, CK concentrations were lower in individuals who received NM than in those who did not. Considering these results, it was observed that with the NM technique we applied, the muscle damage and the enzymes released after damage caused less muscle damage. Nevertheless, the faster recovery of CK levels in individuals who received NM suggests that the muscle tissue healing process is accelerated and that post-injury repair mechanisms are activated more rapidly. These findings indicate that, although NM may not exert a direct protective effect on muscle damage biomarkers following DOMS, it has the potential to accelerate muscle recovery processes. Thus, it may be considered a clinically valuable strategy. However, to the best of our knowledge, the lack of studies examining the effects of the NM technique on muscle damage biomarkers has restricted the comparability of our results. Biopsy or animal studies examining the relationship between NM and muscle damage at the tissue level will clarify this issue.

Strengths and limitations of the study

This study has several notable strengths. Its prospective design, official registration, and the implementation of a rigorous randomization process ensured a homogeneous distribution of participants between the groups. Additionally, another major strength of the study is the use of an isokinetic dynamometer to induce muscle damage, which provided a high degree of control, standardization, and reproducibility.

This study has several limitations. Considering that DOMS symptoms disappear within 5–7 days, the fact that our measurements continue for 72 h is a limitation of our study. Another limitation of the study is that the DOMS was created experimentally. In this respect, there may be DOMS differences that occur under natural conditions. This study was limited to a sedentary healthy population. Whether these results can be generalized to athletic populations should be explored in future studies. Finally, NM is primarily applied to enhance neural mobility and reduce mechanical sensitivity; however, it may also elicit short-term physiological responses such as pain and inflammation. To prevent these acute effects from influencing the study outcomes, a 72-hour interval was maintained between the NM application and the EIMD protocol, aiming to evaluate only the preventive effects of NM. Nonetheless, this factor should be taken into account when interpreting the results.

Conclusions

This study indicated that the femoral nerve NM technique, applied for three weeks prior to the EIMD protocol, provides preventive effects on muscle soreness, the PPT, muscle function, and IL-6 levels. However, no preventive effects were observed on other muscle damage and inflammatory parameters, including TNF-α, CK, and LDH. To further validate the effectiveness of NM in attenuating DOMS, further clinical and laboratory research should be conducted with larger sample sizes and diverse participant groups.

Abbreviations

BMI	Body Mass Index
CK	Creatine kinase
CONSORT	Consolidated standards of reporting trials
DOMS	Delayed onset muscle soreness
EIMD	Exercise-induced muscle damage
IL-6	Interleukin-6
LDH	Lactate dehydrogenase
MET	Metabolic equivalent of task
NM	Neurodynamic mobilization
PPT	Pressure pain threshold
TNF-α	Tumor necrosis factor-alpha

Supplementary Information

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Supplementary Material 1

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Author contributions

US, SB and ASD were responsible for conceptualizing the project. US, RS and EA were responsible for curing the data. US and SB were responsible for the study's methodology. SB and ASD were responsible for the supervision. US and SB wrote the original draft. All authors reviewed & edited the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the local Ethics Committee of GAZİ University (Approval Number: 02.10.2019/270) and conducted in accordance with the Declaration of Helsinki. All the participants were informed about the purpose, content, and potential risks and benefits of the study and signed an informed consent form. The study is registered with ClinicalTrials.gov under the protocol number NCT05326893.

Consent for publication
All participants provided written informed consent for the publication of their anonymized personal and clinical data. No identifying images were used in this study.

Competing interests
The authors declare no competing interests.

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