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Effects of neural mobilization in disorders associated with chronic secondary musculoskeletal pain: A systematic review and meta-analysis

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ABSTRACT

Purpose: To evaluate the effect of neural mobilization (NM) in people with disorders associated with chronic secondary musculoskeletal pain due to persistent inflammation or diseases of the nervous system.
Methods: A database search was conducted to select randomized controlled trials where NM, alone or within a multimodal protocol, was the main intervention for patients with neurological, autoimmune, or auto-inflammatory disorders. The risk of bias and the certainty of evidence were assessed using the Cochrane Risk of Bias Tool for Randomized Trials and the GRADE approach. The primary outcome was pain intensity. Secondary measures were inflammatory biomarkers, range of motion and the level of spasticity.
Results: Eleven studies were included (360 participants; 57% females). The most reported condition was arthritis, and the overall risk of bias was high in more than half of the studies. Pooled data showed a significant effect of NM, based on very low quality of evidence, on reducing pain intensity in people with systemic disorders (three studies: SMD = −0.58; 95% CI = −0.98, −0.18; p = 0.005), and the level of spasticity in individuals with brain or spinal cord injury (two studies: SMD = −0.85; 95% CI = −1.70, 0.00; p = 0.05).
Conclusions: There is scant and very low certainty of evidence to support that NM, compared to control interventions, may improve pain intensity and spasticity in patients with disorders associated with chronic secondary musculoskeletal pain. Further research with high methodological quality is needed to recommend for or against the use of NM in this population.

1. Introduction

Inflammation is a major mechanism in many chronic musculoskeletal pain conditions [1]. Pain from persistent inflammation is common in systemic autoimmune and autoinflammatory disorders [1,2]. These include a broad range of conditions caused by dysregulation of the immune system, i.e., rheumatoid arthritis [3]. Pain can also be derived from diseases of the nervous system, where the presence of pain has been related to impaired sensorimotor function and different musculoskeletal problems, i.e., spasticity [4,5]. Chronic secondary musculoskeletal pain is defined as pain that arises from an underlying disease [5]. Persistent local or systemic inflammation and nervous system disorders are two of the main causes of such pain [5]. Autoimmune and autoinflammatory diseases can affect the peripheral nervous system [6], leading occasionally to painful neuropathies [7], as a form of autoimmune reactivity [8]. Similarly, neuroinflammation is a recognized feature in most neurological diseases, with detrimental, but also beneficial, consequences for the nervous system [9]. For example, neuroinflammation

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promotes axonal regeneration, neurogenesis, and remyelination, which fosters recovery in patients after stroke or with multiple sclerosis or spinal cord injury [10].

Conservative non-pharmacological interventions, together with medical treatments [11,12], are recommended to manage pain and associated symptoms in this population [13,14]. Recent reviews concluded that neural mobilization (NM) can be used to improve pain and disability in adults with chronic primary musculoskeletal problems [15] or painful peripheral neuropathies [16]. NM aims to restore the balance between the neural tissue and the surrounding structures [17], and helps to modulate the immune response after nerve injury [18]. It has been suggested that NM could also be beneficial for chronic secondary musculoskeletal pain, with a potential positive impact on function, activity, and participation domains [19,20]. To date, the role of NM techniques has not been systematically investigated in individuals with systemic or nervous system diseases. The aim of the present systematic review was to determine the effect of NM on pain intensity and pain-related outcomes in individuals with disorders associated with chronic secondary musculoskeletal pain.

2. Methods

The review protocol was registered at PROSPERO prior to article selection and data extraction processes (CRDXXXXXXXXXXX).

2.1. Data sources and search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) literature search guidelines were followed to conduct the present review [21]. Two independent researchers (RGM and VAP) consulted PubMed (Medline), Physiotherapy Evidence Database (PEDro), Cochrane Database of Systematic Reviews, SCOPUS and CINHAL (via EBSCOhost), from their inception until May 2021 (search updated in January 2022). Possible disagreements were resolved by consensus, and additional searches were carried out using the reference lists of the included studies. The initial strategy was built for PubMed and then translated into other databases. It included all available records retrieved with the combination of relevant terms: pain, as "chronic pain" or "widespread pain" or "musculoskeletal pain"; neurodynamic, "nerve treatment" or "neural treatment"; and outcomes of interest, e.g., "range of motion", flexibility, strength, disability, and "quality of life". Simple and advanced searches using MeSH (Medical Subjects Heading) terms were conducted whenever possible (Appendix I).

2.2. Research question and eligibility criteria

Based on the PICO model (Population, Intervention, Comparison and Outcome measures) [22], the research question was: Is the use of neural mobilization effective at improving pain intensity and pain-related outcomes in individuals with autoimmune or autoinflammatory disorders or with diseases of the nervous system? The PICO framework was used to establish the eligibility criteria. The inclusion criteria were as follows:

[I] Patient: Participants aged over 18 and diagnosed with a systemic autoimmune or autoinflammatory disorder or with a neurological condition, reflecting two of the main causes of chronic secondary musculoskeletal pain [5].
[II] Intervention: NM, alone or combined with other forms of manual therapy. Included techniques could be active or passive, applied to the upper or lower extremities, and directed towards the nervous system or surrounding structures [15].
[III] Comparison: No treatment control; waitlist control; active control; or placebo.
[IV] Outcomes: Pain intensity was the primary measure. Secondary outcomes included pain and functional-related measures, e.g., range of motion, spasticity, disability, quality of life, and inflammatory biomarkers.
[V] Studies: Randomized controlled trials written in English or Spanish.

As for the exclusion criteria, we did not include studies investigating the impact of NM on people with: chronic primary musculoskeletal pain [15,23]; chronic secondary musculoskeletal pain caused by infection, crystal deposition, or trauma [5]; or painful peripheral neuropathies indicative of neural tissue dysfunction [16], e.g., trigeminal or postherpetic neuralgia [24]. Studies where participants received treatment immediately after surgery were excluded.

2.3. Data extraction and quality assessment

Two independent researchers (RGM and VAP) selected all studies by screening the title and abstract. Duplicate references were removed by hand checking. Then, the full texts of eligible trials were checked to determine whether they met the eligibility criteria. A third researcher (AMHR) was consulted to resolve potential disagreements. After that, two reviewers (RGM and AMHR) independently extracted relevant data using a standardized data extraction form: first author's name and year of publication; number of participants per study group, diagnosis, age range, and sex distribution; NM technique/s and treatment protocol (number of sessions, duration, and periodicity); control group (or intervention 2); outcome measures; and main results.

The methodological quality of studies was independently evaluated by two researchers (RGM and AMHR) using version 2 of the Cochrane Risk of Bias Tool for Randomized Trials (RoB2) [25]. Any disagreements were resolved by consensus, and a third reviewer (MJCH) was consulted if necessary. The RoB2 tool covers all types of bias in five different domains: randomization process; deviations from intended interventions; missing outcome data, measurement tools; and reported findings. Within each domain, several "signalling questions" need to be answered to elicit relevant information. Based on the results, the risk of bias can be judged as 'high' or 'low' or may indicate 'some concerns' [25].

2.4. Certainty of the evidence

The certainty of evidence for each outcome of interest was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [26]. The GRADE framework considers five domains: risk of bias; imprecision; indirectness; inconsistency; and publication bias. Two independent reviewers categorized the overall evidence as: high, it is very likely that the true effect is similar to the estimated effect; moderate, the true effect is probably close to the estimated effect; low, denoting that the true effect may be considerably different from the estimated effect; and very low, when any estimate of effect is very uncertain [27]. Randomized trials start with high quality of evidence that can be downgraded one (serious) or two levels (very serious) based on the assessed domains [28]. As regards the risk of bias, we downgraded by two levels when more than 50% of the included studies reported a high overall risk of bias. For inconsistency, we downgraded by one level when the I^2 was greater than 60%. For indirectness, we downgraded by one level in the case of high heterogeneity amongst NM interventions (for example active vs. passive techniques). As for the imprecision domain, we downgraded by one level for small sample sizes (less than 400 participants for continuous data).

2.5. Data synthesis

For data quantitative synthesis, findings from comparable trials based on disease, control group, and study measures were pooled in a meta-analysis. The estimated effect and standard error for each comparison was calculated using a generic inverse variance method [29]. Fixed or random effects models were used according to the degree of

heterogeneity (I^2 coefficient), assuming a 95% confidence interval (CI) for all analyses. The Review Manager software (RevMan v.5.4.1, The Cochrane Collaboration, 2020) was used to summarize the effects and construct the forest plots.

3. Results

The initial search retrieved 1423 citations. Upon removing duplicates and screening all records, 11 randomized controlled trials were included [30–40] of which six were analysed in the quantitative synthesis [30,36–40]. The detailed selection process is illustrated in Fig. 1. Appendix II lists all potentially relevant records that were excluded from the review, including the reasons for exclusion [41].

3.1. Study characteristics

The overall sample size ranged from 9 to 72 participants, with a total of 360 individuals (206 females, 57%). Six of the trials investigated people with autoinflammatory disorders, e.g., osteoarthritis [33–35,39], or rheumatoid arthritis [37,38], whereas four included patients with diseases of the nervous system: traumatic brain injury [30]; stroke [36]; spinal cord injury [40], or multiple sclerosis [32]. The remaining study analysed adults with leprosy [31]. Overall, the most reported condition was arthritis. NM mainly consisted of passive sliding mobilization techniques for the upper or lower limbs [30–36,39,40]. Interventions ranged from 4 to 8 weeks, with a minimum of five [32] to six sessions [33,35], and a maximum of two daily sessions during a 1- to 2-month period [36–38]. As for the control intervention, three studies compared NM with a placebo (inactive ultrasound) [33–35], and the rest used active controls, mostly mobilizations [37,38], or stretching and strengthening programs [31,32,36,39,40]. Table 1 provides a detailed description of the included studies.

3.2. Risk of bias

Fig. 2 shows the summary and the graph for the risk of bias. Most studies had a low risk of selective reporting bias and did not show deviations from the intended initial interventions. The overall risk of bias was high in 65% of studies (7 out of 11) [30,31,33,34,36–38] and low in only three of them [32,35,39]. The domain with the highest percentage of studies with a high risk of bias was the allocation sequence concealment (selection bias).

3.3. Main results and certainty of the evidence

Due to heterogeneity among studies, we could only synthesize the evidence regarding the effects of NM, compared with active controls, for pain intensity and inflammatory biomarkers in people with autoimmune or autoinflammatory disorders (Fig. 3), and for the range of motion and the level of spasticity in adults with diseases of the nervous system

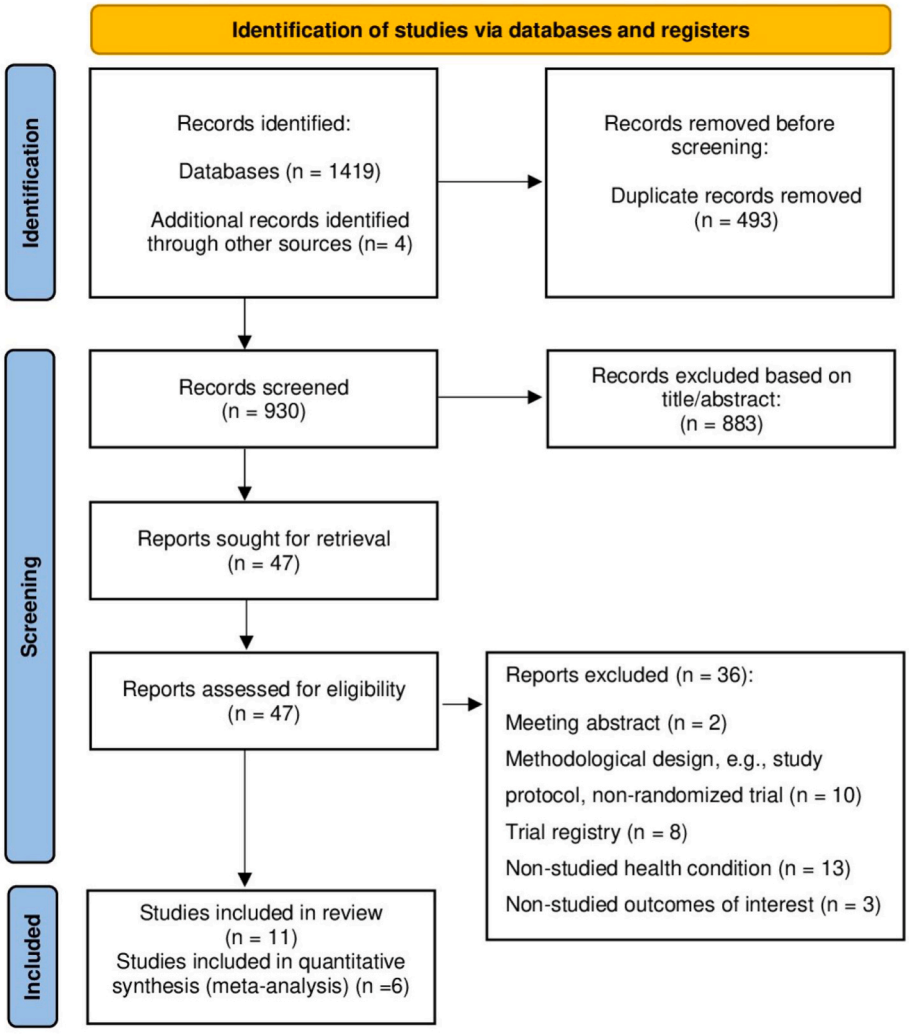

Fig. 1. PRISMA flow diagram.

Table 1
Main study characteristics.

Author/s	Participants. Age; Sex. Diagnosis	Intervention Group (Neural mobilization)	Control Group (or intervention 2)	Outcome measures Assessment points	Main Results (NM vs. CG, favors NM group)
Lorentzen et al. [30]	N = 10 (Cross-over design). 31.5 ± 12.1 yrs; 40% (4) female. TBI	Passive movements of the hip, knee, and ankle during SLR (4 sets, 30 movements). Duration: 20 min; weeks, N/S	Passive hip, knee, and ankle movements with no tension applied. Duration: 20 min; weeks, N/S	Spasticity (MAS); muscle tone change (VAS); stiffness (dynamometer); ROM (catch angle - R1, compensatory angle - R2). Assessment: T0, T1	For non-blinded rater: ↑ R1 and R2 ($p < 0.01$) No effect for blinded rater
Véras et al. [31]	N = 56 (NM = 29, CG = 27). Age: N/S; Sex: N/S. Leprosy	NM of the lumbosacral roots and passive sciatic nerve slider mobilization. 3 sets, 30 movements/minute. Duration: 18 sessions; 6 weeks; 3 times/week	Ankle flexibility and strengthening exercises or electrotherapy. Duration: 6 weeks; 3 times/week plus exercises at home	Pain (VAS); disability (simplified evaluation of neural function and complications); tibialis anterior muscle function and strength (EMG). Assessment: T0, T1	↓ Disability ($p < 0.05$) ↑ Function ($p < 0.05$) ↑ Strength ($p < 0.05$) ↓ Pain ($p < 0.05$)
Villafañe et al. [33]	N = 60 (NM = 30, CG = 30). 81.3 ± 7 yrs; 90% (54) female. First CMC joint OA	Passive radial nerve slider mobilization (3 repetitions, 4 min; 1 min break). Duration: 6 sessions; 4 weeks	Placebo: Inactive pulsed US + gel over hypothenar area (10 min). Duration: 6 sessions; 4 weeks	PPT (affected side) at scaphoid, hamate bones, and trapeziometacarpal joint (algometer); tip and tripod pinch strength (pinch gauge). Assessment: T0, T1, 1 and 2 mo.	↑ PPT trapeziometacarpal joint at T1, 1 mo, and 2 mo ($p < 0.001$) ↑ Tip pinch at T1 ($p = 0.047$)
Villafañe et al. [34]	N = 60 (NM = 30, CG = 30). 82 ± 6 yrs; 85% (51) female. First CMC joint OA	First CMC joint passive mobilization (3 min); passive median and radial nerves slider mobilization (2 sets, 5 min, 1 min break); active flexibility and strengthening hand exercises. Duration: 3 sessions/week; 4 weeks	Placebo: Inactive pulsed US + gel over hypothenar area (10 min). Duration: 3 sessions/week; 4 weeks	Pain intensity (VAS); bilateral PPT at first CMC joint, hamate bone, lateral epicondyle (algometer); tip pinch (pinch gauge) + grip strength (dynamometer). Assessment: T0, T1, 1 and 2 mo.	↓ VAS at T1, 1 mo, and 2 mo ($p < 0.001$) ↑ PPT hamate bone at T1 ($p = 0.025$)
Villafañe et al. [35]	Same sample than Villafañe et al. [33]	Passive radial nerve slider technique (3 reps, 3 min, 1 min break). Duration: 6 sessions; 4 weeks	Placebo: Inactive pulsed US + gel over hypothenar area (10 min). Duration: 6 sessions; 4 weeks	PPT (contralateral side) at first CMC joint, lateral epicondyle, scaphoid, and hamate bones (algometer). Assessment: T0, T1, 1 and 2 mo.	↑ PPT at first CMC joint, lateral epicondyle, hamate, and scaphoid bones at T1, 1 mo, and 2 mo.
Cha et al. [36]	N = 20 (NM = 10, CG = 10). 61.75 ± 10.7 yrs; 40% (8) female. Stroke	Bilateral passive sciatic nerve mobilization (10 min) + usual physical therapy. Duration: 2 daily sessions, 40 min; 4 weeks	Usual physical therapy (stairs, sitting to standing) Duration: Two daily sessions, 30 min; 4 weeks	Feet pressure distribution and postural sway (foot pressure test); knee joint angle (imaging system); balance (FRT). Assessment: T0, 2 weeks, T1	↑ Pressure distribution, ↓ sway ($p < 0.05$) ↑ Knee angle ($p < 0.05$) ↑ Balance ($p < 0.05$)
Lo et al. [37]	N = 9 (NM = 5, CG = 4). 57.5 ± 8.8 yrs; 89% (8) female. RA	Active sliding and tensioning mobilization of musculocutaneous, saphenous, median nerves, and slump test (10 reps daily, 2 times/day). Duration: 4 weeks	Active hand, wrist, elbow, shoulder, spine, and lower limbs mobilization (10 reps, 5 min). Duration: 4 weeks	Pain (RA Pain Scale and VAS); Inflammatory biomarkers (C-reactive protein + erythrocyte sedimentation rate). Assessment: T0, T1	↓ Pain (p value, N/S)
Lau et al. [38]	N = 21 (NM = 11, CG = 10). 57.5 ± 7.1 yrs; 100% (21) female. RA	Active tensioning mobilization of spinal cord, median, saphenous, musculocutaneous, and femoral nerves (10 reps daily, 2 times/day). Duration: 4–8 weeks	Active hand, shoulder, elbow, spine, and lower limbs mobilization (10 reps daily, 2 times/day). Duration: 4–8 weeks	Pain, function, fatigue, sleep, coping (RA Impact Disease Questionnaire); Inflammatory biomarkers (erythrocyte sedimentation rate). Assessment: T0, T1	↓ Pain ($p = 0.013$) ↑ Coping ($p = 0.03$)
Pedersini et al. [39]	N = 72 (NM = 36, CG = 36). 70 ± 11.5 yrs; 57% (40) female. Hand OA	Passive sliding mobilization of median, radial, and ulnar nerves (3 reps for 3 min, 1 min break); active flexibility and strengthening hand exercises. Duration: 12 sessions; 4 weeks	Robotic passive flexion + extension movements; active strengthening and flexibility hand exercises. Duration: 12 sessions; 4 weeks	Pain last 24 h, last week, and during tip pinch (VAS); PPT at first CMC joint, hamate bone, median, radial, and ulnar nerves (algometer); grip + pinch strength (dynamometer, pinch gauge) Assessment: T0, T1, 3 mo.	↓ VAS last 24 h at T1 ($p < 0.01$) ↑ PPT at first CMC joint, median, and radial nerves at T1 ($p < 0.05$)
Saxena et al. [40]	N = 20 (NM = 11; CG = 9). 31.93 ± 9.23 yrs; 5% (1) female. Spinal cord injury	Passive mobilization of median nerve with slow wrist oscillations (3 sets, 20 reps/min, 3 min, 1 min break., 5 times/week) Duration: 20 sessions; 4 weeks	Passive stretching of upper limb muscles (9 sets, 1 min, 5 times/week) Duration: 20 sessions; 4 weeks	Spasticity of wrist and finger flexors (MAS); upper limb function (CUE); F-wave amplitude, latency, and F-wave/M-wave amplitude ratio. Assessment: T0, T1	↓ MAS wrist ($p = 0.003$) and fingers flexors ($p = 0.004$) ↓ F amplitude ($p = 0.010$) ↑ CUE ($p = 0.007$)
Pérez-Bruzón et al. [32]	N = 32 (NM = 16; CG = 16). 49.5 ± 9.5 yrs; 59% (19) female. Multiple sclerosis	Bilateral passive sliding mobilization of median, radial, and ulnar nerves (15–20 min/nerve, 1 min break., 2 times/week); + strength, stretching exercises, soft tissue mobilization. Duration: 5 sessions; 3 weeks	Strength, stretch exercises, soft tissue mobilization (30 min, 2 times/week) Duration: 5 sessions; 3 weeks	PPT (bilateral) at median, radial, ulnar nerves, 2nd metacarpal, tibialis anterior (algometer); upper limb pain at rest and worst (NRS); light touch sensitivity (von Frey); manual dexterity (NHPT). Assessment: T0, T1	↑ PPT at median, radial, ulnar nerves, tibialis anterior 2nd metacarpal, ($p < 0.05$) ↓ NRS at rest, light touch sensitivity ($p < 0.05$) ↑ Dexterity ($p < 0.05$)

Abbreviations: CG, control group; CMC, carpometacarpal; CUE, Capabilities of Upper Extremity Questionnaire; EMG, Electromyography; FRT, Functional Reaching Test; HAQDI, Health Assessment Questionnaire Disability Index; MAS, Modified Ashworth Scale; mo., month/s; NHPT, nine-hole peg test; NM, neural mobilization; NRS, numeric rating scale; N/S, non/specified; OA, osteoarthritis; PCS, Pain Catastrophizing Scale; PPT, Pressure pain threshold; RA, rheumatoid arthritis; ROM, range of movement; SLR, Straight-leg raise; TBI, Traumatic brain injury; T0, Baseline; T1, Immediately after intervention; ULNT, Upper limb neurodynamic test; VAS, Visual Analogue Scale.

(Fig. 4).

3.4. Pain intensity and inflammatory biomarkers

The pooled analysis showed a significant overall effect in favour of using NM to reduce pain intensity in people with arthritic conditions (three studies: SMD = −0.58; 95% CI = −0.98, −0.18; p = 0.005; I^2 = 0%) [37–39] (Fig. 3A), but no positive impact was observed on inflammatory biomarkers in rheumatoid arthritis [37,38] (two studies: SMD = −0.20; 95% CI = −0.92, 0.52; p = 0.58; I^2 = 0%) (Fig. 3B). For both outcomes, the certainty of evidence was judged as very low and downgraded due to risk of bias, indirectness, and imprecision (Table 2). Hence, it is uncertain whether NM evokes positive changes in pain intensity and inflammatory biomarkers in this population.

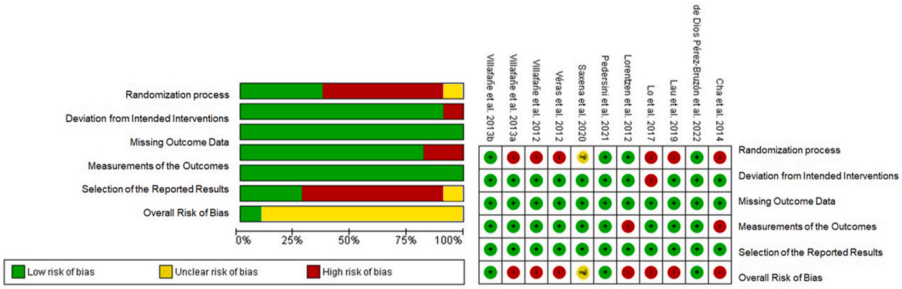

Fig. 2. Cochrane risk of bias summary.

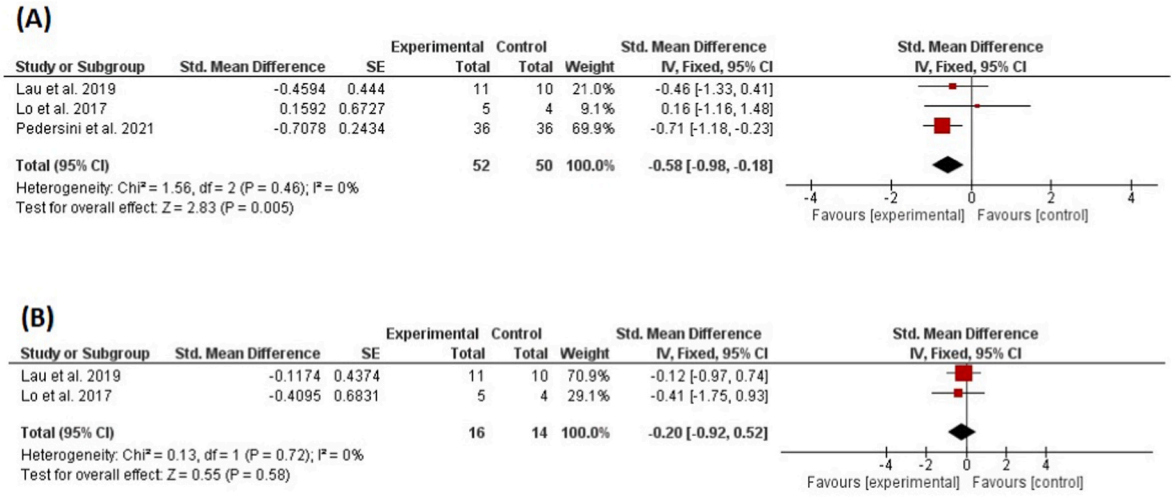

Fig. 3. Forest plots of the meta-analysis in adults with autoinflammatory diseases. A: Pain intensity in arthritic conditions. B: inflammatory biomarkers in rheumatoid arthritis.

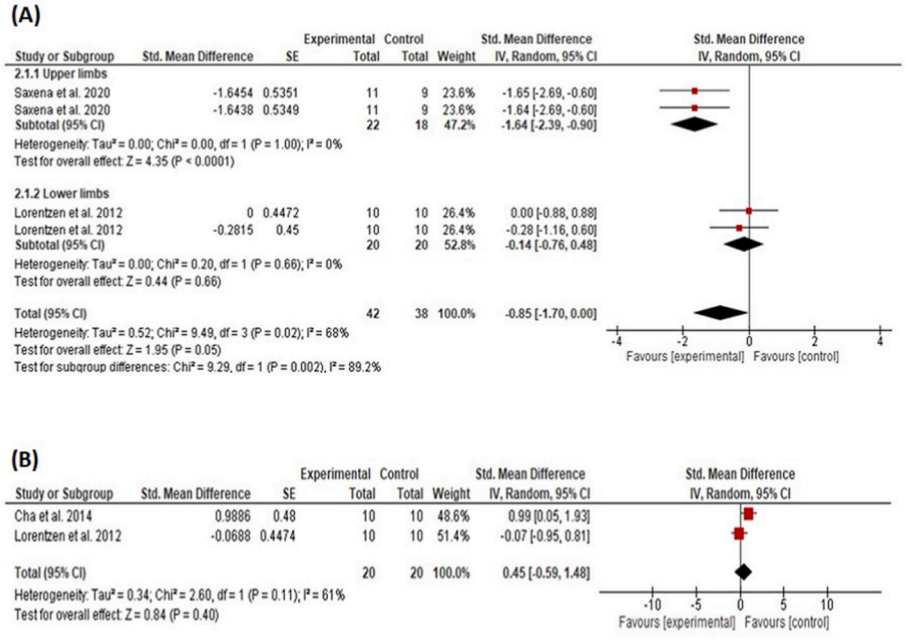

Fig. 4. Forest plot of the meta-analysis in people with diseases of the nervous system. A: level of spasticity; B: knee range of motion.

3.5. Spasticity and range of motion

As regards participants with diseases of the nervous system, pooled data demonstrated an overall beneficial effect, favouring the use of NM to decrease spasticity (two studies: SMD = −0.85; 95% CI = −1.70, 0.00; p = 0.05; I^2 = 68%), especially for upper limb muscles (Fig. 4A), with no

Table 2
The overall certainty of the evidence (GRADE, Grading of Recommendations Assessment, Development, and Evaluation).

Summary of findings			The certainty of the evidence (GRADE approach)					
Condition and outcomes	Nº of studies	Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Level of evidence	Importance
Autoinflammatory or autoimmune disorders								
Pain intensity	3	102	Very serious (−2)	No	Serious (−1)	Serious (−1)	Very low	Critical
Inflammatory biomarkers	2	30	Very Serious (−2)	No	No	Serious (−1)	Very low	Critical
Diseases of the nervous system								
Spasticity	2	30	Very serious (−2)	Serious (−1)	No	Serious (−1)	Very low	Critical
Range of motion	2	30	Very serious (−2)	Serious (−1)	No	Serious (−1)	Very low	Critical

Note: We did not rate publication bias due to the scarce number of studies.

effect on knee range of motion (two studies: SMD = −0.45; 95% CI = −0.59, 1.48; p = 0.40; I^2 = 61%) (Fig. 4B). The certainty of evidence (very low) was downgraded due to risk of bias, inconsistency, and imprecision (Table 2). Therefore, it is not clear whether NM may have an impact on these outcomes.

4. Discussion

Our results showed, with very low certainty of evidence, that NM could be effective at improving pain intensity in adults with arthritic disorders and reducing spasticity in people with brain or spinal cord injury. The scarce available evidence indicates that NM is not effective at evoking changes in inflammatory biomarkers or in functional-related outcomes in this population.

Current literature recommends NM to manage pain intensity in chronic primary musculoskeletal pain, e.g., neck, arm, and low-back pain [15,42], with some conflicting findings [43]. NM has also been proposed as a valid therapeutic option for improving pain-related measures in painful peripheral neuropathies [16] and in conditions associated with chronic secondary musculoskeletal pain [44,45]. The present results indicate that NM, alone or within a multimodal protocol, may help to reduce pain in people with autoimmune or autoinflammatory disorders [31,33–35,38,39], and in patients with multiple sclerosis [32]. However, the real impact of NM remains uncertain due to the very low quality of the evidence. It has been argued that the type of NM technique may influence the results [15]. In this systematic review, both passive sliding and active tensioning techniques demonstrated similar effects on pain intensity. Peripheral and central mechanisms, i.e., changes in blood flow, local sensitivity, sensorimotor function [46,47], cortical activity [48], intraneural oedema [49], and inflammation [50] may explain the beneficial effects of the use of NM in individuals where persistent inflammation is an important source of pain [50]. However, none of the included studies demonstrated changes in inflammatory biomarkers after a 4- to 8-week treatment protocol using NM [37,38]. This, together with the heterogeneity of trials in terms of participants, interventions, type of disease, and control groups, makes it difficult to reach a conclusion. Therefore, further research is needed to understand the exact effect of NM on chronic musculoskeletal pain associated with local or systemic inflammation or with a neurological condition.

For individuals with diseases of the nervous system, we found that passive NM of the upper or lower limbs may be superior to other forms of manual therapy for decreasing spasticity. This finding, however, needs to be interpreted with caution since it is based on only two studies (including 30 participants with brain or spinal cord injury) [30,40] with very low certainty of evidence. Spasticity is common in neurological diseases and often leads to a reduced range of movement and high levels of disability [4]. Existing scientific evidence is not sufficient to recommend any non-pharmacological intervention to manage spasticity-related problems [51]. NM techniques have been successfully used to improve the extensibility of the musculoskeletal and peripheral nervous systems [40], and decrease the sensitivity to mechanical pressure and light touch in neurological patients [17,32]. In fact, NM seems to modify the electromyographic activity of spastic muscles even when applied to the non-affected limb [52,53]. A plausible explanation is the ability of NM to reduce the cross-sectional area of the nerve [52] and decrease peripheral and central sensory deficits [54], which ultimately improves neural function at the whole system level [52].

In the studies included in this review, NM was no better than control interventions at increasing joint mobility [30,36]. How to improve the restricted range of movement associated with spasticity has mostly been investigated in neurological diseases [51]. NM can modify the mechanical properties of muscle [55] and, therefore, influences joint range of movement. Preliminary findings from two case report studies demonstrated the effect of combining NM with botulinum toxin injections, which increased upper and lower limb range of movement in stroke survivors [56,57]. Similar effects have been shown with the isolated use of active sliding and tensioning exercises [58], or with passive NM [59], in other chronic conditions. Overall, there is insufficient and low-quality evidence on the possible impact of NM on joint mobility.

This systematic review has some limitations that need to be considered. First, there is a paucity of information on the topic. We only included 11 studies, which represents a potential risk of bias due to the small number of participants and the inability to assess the publication bias. Second, the heterogeneity among trials in terms of conditions, outcome measures, intervention protocols, and control groups, makes it difficult to interpret the results. Additionally, two of the studies referred to the same population [33,35], hence repeated data was considered only once. Lastly, we aimed to examine the effect of NM on conditions that evoke chronic secondary musculoskeletal pain, following a recent diagnostic taxonomy [5]. However, it should be acknowledged that neurological diseases, e.g., stroke, multiple sclerosis, brain injury, and spinal cord injury, can also eventually lead to central neuropathic pain [24]. Despite this, none of the assessed studies included participants with a diagnosis of neuropathic pain.

5. Conclusion

The present systematic review suggested positive effects of NM on reducing pain intensity and the level of spasticity in people with disorders associated with chronic secondary musculoskeletal pain from persistent inflammation or a disease of the nervous system. Current findings must be interpreted with caution given the small number of studies and the very low quality of evidence.

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CRediT authorship contribution statement

Ramón González-Matilla: Conceptualization, Methodology, Investigation, Writing – original draft. **Vanesa Abuín-Porras:** Conceptualization, Methodology, Writing – original draft, Supervision. **María Jesús Casuso-Holgado:** Methodology, Formal analysis, Writing – original draft. **Inmaculada Riquelme:** Writing – original draft. **Alberto Marcos**

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Declaration of competing interest

All the authors declare that there are no conflicts of interest.
PROSPERO database registration code: (CRD42020188805).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2022.101618.

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