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Effectiveness of neural mobilisation for the treatment of nerve-related cervicobrachial pain: a systematic review with subgroup meta-analysis

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Abstract

Neural mobilisations (NM) have been advocated for the treatment of nerve-related cervicobrachial pain; however, it is unclear what types of patients with nerve-related cervicobrachial pain (if any) may benefit. Medline, Web of Science, Scopus, PeDro, Cinahl, and Cochrane databases were searched from inception until December 2022. Randomised controlled trials were included if they assessed the effectiveness of NM in nerve-related cervicobrachial pain, and outcome measures were pain intensity and/or disability. Studies were classified according to their inclusion/exclusion criteria as *radiculopathy*, *Wainner cluster*, *Hall*, *and Elvey cluster* or *other*. Meta-analyses with subgroup analyses were performed. Risk of bias was assessed using Cochrane Rob2 tool. Twenty-seven studies were included. For pain and disability reduction, NM was found to be more effective than no treatment (pooled pain mean difference [MD] = −2.81, 95% confidence interval [CI] = −3.81 to −1.81; pooled disability standardized mean difference = −1.55, 95% CI = −2.72 to −0.37), increased the effectiveness of standard physiotherapy as an adjuvant when compared with standard physiotherapy alone (pooled pain MD = −1.44, 95% CI = −1.98 to −0.89; pooled disability MD = −11.07, 95% CI = −16.38 to −5.75) but was no more effective than cervical traction (pooled pain MD = −0.33, 95% CI = −1.35 to 0.68; pooled disability MD = −10.09, 95% CI = −21.89 to 1.81). For disability reduction, NM was found to be more effective than exercise (pooled MD = −18.27, 95% CI = −20.29 to −17.44). In most comparisons, there were significant differences in the effectiveness of NM between the subgroups. Neural mobilisations was consistently more effective than all alternative interventions (no treatment, traction, exercise, and standard physiotherapy alone) in 13 studies classified as *Wainner cluster*. PROSPERO registration: CRD42022376087.

Keywords: Cervicobrachial pain, Neural mobilisation

1. Introduction

Neck pain is among the top 10 causes of global disability and among the top 5 causes of disability in middle-income and high-income countries,[39] and the number of prevalent cases, incident cases, and years lived with disability continues to grow.[69] Fifty percent to 75% of patients will experience recurrent episodes in the following one to 5 years,[13,20] and 68% will endure chronic pain.[12] Nerve-related cervicobrachial pain is more common than neck pain alone (up to two-thirds of people with neck pain may experience nerve-related cervicobrachial pain) and is associated with higher levels of disability.[21,48] Pathophysiology and clinical presentation of nerve-related cervicobrachial pain differs between distinct subgroups. Nerve-related cervicobrachial pain secondary to painful cervical radiculopathy is caused by a lesion or disease involving the cervical nerve roots resulting in nerve conduction block and clinically manifests with pain and objective neurological deficits, such us dermatomal sensory loss, myotomal weakness, and hyporeflexia.[11,80,86,89] Radicular pain is most likely evoked by ectopic discharges generated at a highly excitable dorsal root or its ganglion.[11,45,51] Pain descriptors (eg, burning, shooting pain) suggest the involvement of a nerve root. Radicular pain can occur in the absence of loss of function.[11,40] Radiculopathy and radicular pain may coexist, resulting in a mixed pattern of symptoms.[40] Patients with nerve-related cervicobrachial pain may also present with signs of heightened neural mechanosensitivity, which manifests clinically by pain in response to limb movements causing nerve elongation and by local tenderness of nerve trunk palpation.[87,88] In this situation, in the absence of any nerve damage and presence of normal nerve function

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determined during bedside neurological integrity testing,[40,57,78] pain is most likely nociceptive, caused by the activation of peripheral nerve connective tissue nociceptors.[26,73] However, heightened neural mechanosensitivity may also coexist with nerve damage associated with conduction loss and neuropathic pain.[77,88]

Neural mobilisation (NM) has been advocated for the treatment of nerve-related cervicobrachial pain.[3,8] Neural mobilisation involves either active or passive specific movements of the limbs and/or the spine that aim to mobilise the nervous system itself or facilitate movement between neural structures and its surrounding tissues.[46] Biomechanically, NM may be divided into *tensioners*, where movements of 2 or more joints longitudinally load the neural tissue in opposite directions (eg, cervical contralateral side flexion and elbow/wrist extension), or *sliders*, where loading created by movement of one joint is counterbalanced by movement of other joints (eg, cervical contralateral side flexion and elbow/wrist flexion). In vivo studies in human participants[17,18,24] have shown that the former cause greater strain of the nerve and lower longitudinal excursion, whereas the latter cause lower strain and greater longitudinal excursion. Animal studies have shown that NM induces modulation of nerve mechanosensitive ion channel expression,[23] lowers concentrations of proinflammatory cytokines (TNF-α and IL-1β) at nerve branches and trunk,[94] and normalizes necrosis growth factor production at the dorsal root ganglion,[71] resulting in a reduction in hyperalgesia and allodynia. However, the effectiveness of NM in nerve-related cervicobrachial pain is still unclear. Previous systematic reviews[8,91] included studies where the effect of NM could not be isolated,[3,63] amalgamated in the same meta-analysis different comparator treatments,[3,16,54] or included patients with cervical somatic referred pain,[70] resulting in the collation of very heterogeneous samples and treatments in meta-analyses. Furthermore, despite evidence suggesting the presence of subgroups of patients with nerve-related cervicobrachial pain with different pathophysiology,[40] these have not been taken into account in previous reviews. Hence, it is not known what type of patient subgroups with nerve-related cervicobrachial pain (if any) may benefit from NM.

The primary aim of this systematic review was to assess the effectiveness of NM in patients with nerve-related cervicobrachial pain. The secondary aim was to explore if the effectiveness of NM varied between nerve-related cervicobrachial pain subgroups.

2. Methods

This systematic review followed PRISMA guidelines[58] and was registered in PROSPERO (registration number: CRD42022376087).

2.1. Search strategy and information sources

Medline, Web of Science, Scopus, PeDro, Cinahl, and Cochrane databases were searched for relevant studies from inception to July 2022 (and updated in December 2022) using the keywords shown in supplemental digital content (available at http://links.lww.com/PAIN/B927). Keywords in each row were combined using the Boolean operator "OR," whereas rows 1 and 2 were combined with the operator "AND." In addition, ANZCTR, ClinicalTrials.gov, and ISRCTN registers were searched using the keywords in row 1. The full search strategy can be found in supplemental digital content (available at http://links.lww.com/PAIN/B927). Search results were exported to Zotero software, version 5.0.96 (Corporation for Digital Scholarship, Vienna, VA) for processing. Reference lists of selected studies and previous reviews were also checked for further relevant studies.

2.2. Study selection and data extraction

Studies were included if they were randomised controlled trials, participants had nerve-related cervicobrachial pain, assessed the effectiveness of NM, and outcome measures were pain intensity and/or disability. Titles and abstracts of all studies were screened for relevance, and the full text of potentially relevant articles was evaluated by 3 reviewers (I.L., L.D. and I.V.). One reviewer (L.D.) performed data extraction using a predefined form, and a second reviewer (I.L.) checked extracted data for correctness and completeness. Extracted data included authors, year of publication, participant characteristics, inclusion/exclusion criteria for nerve-related cervicobrachial pain, interventions, outcome measures, and results. Details about interventions were extracted following TIDieR recommendations.[34] In studies where multiple comparisons were made, only those relevant to the aims of the systematic review were extracted. Where necessary, authors were contacted for further information or clarification.

2.3. Subclassification of studies

Three reviewers (I.L., B.T., and X.C.) independently classified studies according to the inclusion/exclusion criteria used to recruit participants. Studies were classified as having patients with painful *radiculopathy* if inclusion criteria included signs of conduction slowing or loss (eg, myotomal or dermatomal neurological deficit).[11,25,35,40,79] Studies were classified as *Wainner cluster* if their inclusion criteria was based on the reported specific cluster of signs by Wainner et al.,[93] where at least 3 of the following 4 tests had to be positive: upper limb neurodynamic test; ipsilateral cervical rotation range of movement $<60°$; distraction test; Spurling test. Studies were classified as *Hall and Elvey cluster* if their inclusion criteria made reference to the cluster of signs proposed by Hall and Elvey[29]: reduced active/passive cervical range of movement; evidence of heightened neural mechanosensitivity (positive upper limb neurodynamic test); and evidence of local cervical dysfunction (eg, through intervertebral movement testing). Studies not suitable for any of these subgroups (ie, the above criteria were not met) were classified as *other*.

2.4. Assessment of methodological risk of bias and publication bias

Two reviewers (I.L. and M.R.) independently assessed the risk of bias of each study using Cochrane's Risk-of-Bias 2 tool[31]; where necessary, a third party (J.R.) was involved. Following Cochrane algorithm for each of the assessed domains and overall judgement of risk of bias, studies were rated as *high risk of bias*, *some concerns*, or *low risk of bias*. Publication bias was evaluated through the identification of registered trials that had not been published; their authors were contacted to enquire about the reason for no publication.

2.5. Data items and synthesis methods

Meta-analyses were performed if 2 or more studies investigated the effectiveness of NM against the same comparator and used the same or comparable outcome measure. Statistical analysis was performed using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Posttreatment scores (mean and standard deviation (SD) of pain and disability for each group were inputted and expressed as mean difference (MD) between groups with a 95% confidence interval. For studies where posttreatment scores had been reported using median, range, and interquartile range, mean and standard deviation were calculated using *metacont* function in R software (version 4.2), based on the equations by Luo et al.[49] and Shi et al.[82] A random-effects model was used, and the magnitude of the summary MD was interpreted as small if below the minimally clinical important difference, moderate if just above the minimally clinical important difference, or large if greater than twice the minimally clinical important difference. Minimally clinical important differences of 10 points (0-100 scale) and 1.3 points (0-10 scale) were considered for disability (neck disability index[50]) and pain intensity,[14] respectively. When the available number of studies for a comparison was low (eg, two), we used the fixed-effects method for meta-analysis because a small number of studies can overinflate the effect size estimation if using a random-effects method.[27] Where different outcome measures were combined in the same meta-analysis (eg, Neck Disability Index and the Disabilities of the Arm, Shoulder and Hand questionnaires), the summary standardized mean difference (SMD) was calculated and interpreted as small (0.2-0.5), moderate (0.5-0.8), or large (>0.8).[15] The prediction interval (PI) was also calculated for each comparison and subgroup (if more than one study was available).[33] If a meta-analysis combined studies with different risk of bias, a sensitivity analysis was performed to assess the extent to which the magnitude of the summary standardized effect was affected by the inclusion of high-risk studies.

The statistical heterogeneity of effect sizes across studies was assessed with the Q-test and the I^2 index. Q-test was considered significant if P was <0.10 and statistical heterogeneity was considered substantial if I^2 was >60%. To assess whether the effectiveness of NM differed between patient subgroups with different pathophysiology, subgroup analyses were conducted, where studies were grouped according to the inclusion/exclusion criteria they used (ie, *radiculopathy*, Wainner cluster, *Hall and Elvey cluster* or *other*). Where meta-analysis was possible, the certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and rated as high, moderate, low, or very low. Certainty was downgraded one level each for serious study limitations (if >25% of participants were from studies classified as high risk; 2 levels if >50%), inconsistency (if statistical heterogeneity was significant and I^2 was >60%), indirectness (if >50% of participants were outside the target group), imprecision (if PI crossed zero or there were <100 participants), and publication bias (if there was evidence of publication bias).[38,83,92]

3. Results

3.1. Study selection

Study selection is summarized in the PRISMA flow diagram (**Fig. 1**). The search yielded 28,249 records, and after removal of duplicates, 16,376 records were screened, of which 112 full-text documents were reviewed. Finally, 27 studies (30 articles; in[59,66;36,37] and[61,62] 2 articles reported one study) met the inclusion/exclusion criteria and were included in the review. Eleven studies that were potentially relevant were excluded because they assessed only the immediate effects of a single treatment session,[16,52] the effect of NM could not be isolated because they included other manual therapy[3,9,56,81] or traction[74] treatments together with NM, compared different NM treatments between them,[6,19] included patients with somatic referred pain,[70] or treatment allocation was not randomised.[30] Several corresponding authors of studies[1,2,5,7,22,29,36,41,42,60,61,64,77,84] were contacted through email to request additional information or clarification about their study, which was obtained from 2 authors.[61,75]

3.2. Study characteristics

All included studies were randomised controlled trials assessing the effectiveness of NM; their characteristics can be found in supplemental digital content (available at http://links.lww.com/PAIN/B927). Most frequently, studies assessed the effectiveness of NM as an adjuvant to standard physiotherapy when compared with standard physiotherapy alone.[5,7,22,37,41,43,44,55,61,62,65,66,77,85] Other comparator interventions included cervical traction,[1,4,7,43,66] neck exercise,[28,60,64] Mckenzie manipulation/exercise,[44] Mulligan[84] and Maitland[52] cervical mobilisations, ultrasound,[16] laser,[2] and oral ibuprofen.[72] Three studies assessed the effectiveness of NM in comparison to no treatment.[54,67,68] Three studies allowed for multiple comparisons because they included 3 treatment groups.[7,44,66]

Neural mobilisation interventions included the following: a cervical lateral glide[16,42,67]; upper limb sliders,[7,28,43,52,61,62,70,74,77] tensioners,[2,4,36,37,42,53] or sliders and tensioners[1,59,65,66]; and cervical lateral glide and sliders[54] or tensioners[85]; in 6 studies, the type of NM used was unclear.[5,22,44,60,64,84] Most often, NM was passive,[2,5,7,16,36,37,41–43,54,55,59–62,66–70,74,77,84,85] and in a minority of cases active,[54] active or passive,[4,44] or both active and passive[28,65]; it was unclear in 4 studies.[1,5,22,64] In the majority of cases, NM was performed without symptom reproduction[2,16,54,59,66,68,72,75]; some reported performing it without or with minimal symptoms,[1,28,42,44,53] and 2 studies at the point of symptom reproduction[4,85]; tailoring was unclear in 14 studies.[5,7,22,36,37,41,43,54,60–62,64,65,67,84] Treatment was most often delivered by a clinician in person,[2,16,29,36,37,41–44,52,53,59–62,65–68,72,75,84,85] involved home exercises in one study,[54] and was unclear in 6.[1,4,5,7,22,64] Treatment frequency varied between 2,[54] 3,[2,36,37,41–43,59–62,66,75,85] 4,[4,64] 5,[22,28,67,68,72] 6,[7,53,65] and 7[44,84] days per week. Duration of treatment ranged between one,[1,28,84] one and a half,[44,53] 2,[7,54,60,85] 3,[36,37,41] 4,[2,4,22,43,59,61,62,65,66,75] 6,[67,68,72] 8,[43] and 12[64] weeks. In 2 studies,[16,52] only a single session of treatment was provided. In one study,[1] treatment frequency was not specified, and, in another,[5] neither frequency nor duration was specified.

According to the inclusion/exclusion criteria used to recruit their participants, one study[2] was classified as *radiculopathy* (their inclusion criteria included dermatomal numbness and/or myotome weakness), 15[1,4,7,22,36,37,44,59,61,62,64–70,74,77,84] as *Wainner cluster*, 4[16,28,52,85] as *Hall and Elvey cluster*, and 6[5,41,42,44,55,60] as *other*. Fifteen studies[2,4,5,22,29,42–44,56,59–62,65–68,72,75] measured changes in both pain and disability, whereas 9 measured only either pain[7,16,36,37,44,52,53,85] or disability.[1,64,84] Outcome measures for pain included the visual analogue scale (VAS)[2,5,22,29,36,37,41,44,54,55,85] and numeric pain rating scale (NPRS),[4,7,16,43,44,54,59–62,65–70,74,77] whereas disability was measured using the Neck Disability Index (NDI)[1,2,4,5,22,29,42–44,56,59–62,65,66,75,84] and the Disabilities of the Arm, Shoulder and Hand (DASH)[64,67,68,72] questionnaires.

The majority of studies measured only outcomes immediately post last treatment session,[1,2,4,7,16,22,29,36,37,42–45,52,59–62,64–70,74,77,84,85] with the exception of 3 that measured 1[52] and 2 weeks[54,60] post last treatment session. In one study,[5] the measurement time point was not clearly specified.

3.3. Methodological risk of bias and publication bias

Results of the methodological quality assessment can be found in **Figure 2**. Following assessment with Cochrane's Risk-of-Bias 2 tool, 12 studies[4,5,7,28,42,45,56,65,67,70,74,84] were classified as *high*

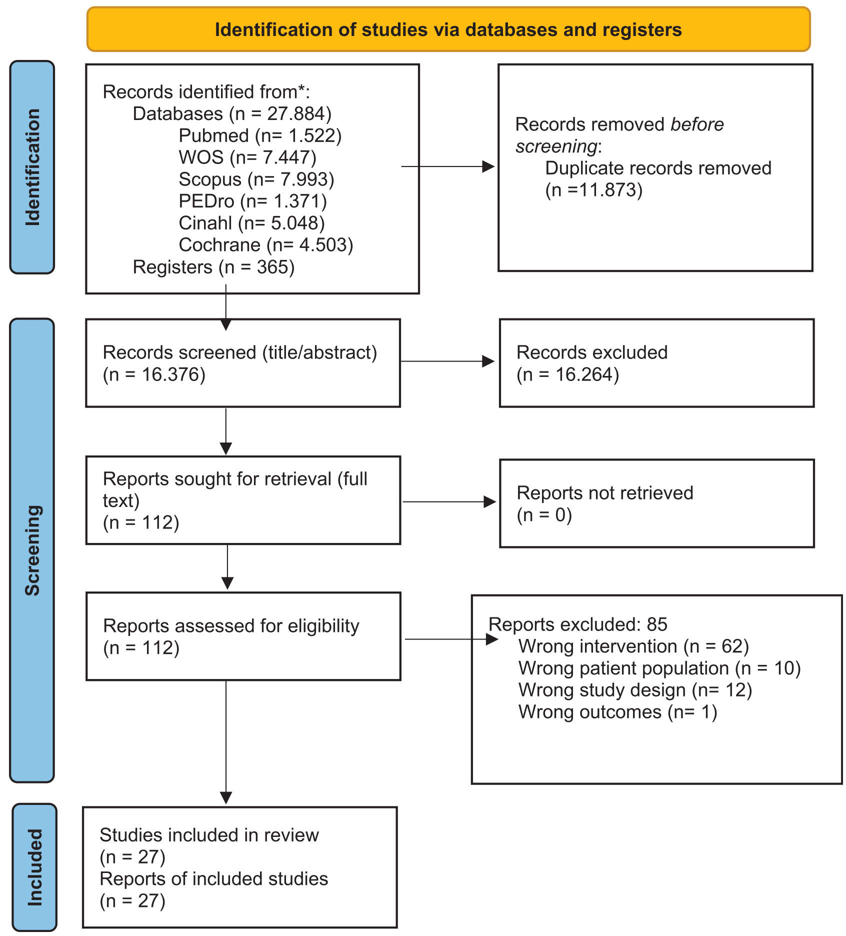

Figure 1. PRISMA flow diagram.

risk of bias and 15 studies[1,2,16,22,36,37,42,43,52,53,59–62,64,66,75,85] as *some concerns*. No study was classified as *low risk*. Seventeen studies[1,2,4,5,7,22,29,42–45,55,60,64,77,84,85] had inadequate or limited information regarding randomisation and allocation sequence concealment; only 2 studies[16,54] reported whether deviations from the intended intervention had arisen; there were some concerns or high risk of bias arising from missing outcome data in 17 studies.[1,2,4,5,29,42,43,45,59,60,64–68,72,84,85] Because the outcome measures of interest were patient reported pain and disability, outcome assessors (the patients themselves) could have been influenced by knowledge of the intervention received, which resulted in no study being labelled as *low risk* regarding measurement of the outcome. No study evidenced a prespecified analysis plan that was finalized before unblinded outcome data were available, hence, all studies were labelled as *some concerns* regarding selection of the reported result.

Regarding publication bias, 4 registered trials that had been concluded but not published were identified: NCT03652831 assessing the effect of NM as an adjuvant to conventional physiotherapy; CTRI/2008/091/000187 comparing the effect of NM vs manual therapy and vs conventional physiotherapy; CTRI/2011/06/001851 comparing the effect of NM vs conventional physiotherapy; and, CTRI/2020/04/024,509 comparing the effectiveness of NM vs traction. Authors were contacted, and only one reply was obtained (CTRI/2011/06/001851) with no clear information about the reasons for no publication.

3.4. Effects of interventions

3.4.1. Effectiveness of neural mobilisations vs no treatment

3.4.1.1. Pain

Three high risk studies[54,67,68] with a total of 159 participants compared the effectiveness of NM vs no treatment on pain intensity reduction in the short term. Findings of the meta-analysis are reported in **Figure 3** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). Neural mobilisation was found to be more effective than no treatment (pooled MD = −2.81; 95% CI = −3.81 to −1.81; $P < 0.00,001$; $I^2 = 79\%$; PI = −4.62 to −0.99; certainty of evidence: very low). However, although all 3 studies reported an effect in favour of NM, there were significant differences in the magnitude of the effect between the subgroups ($P = 0.04$). The effects reported in 2 studies[67,68] classified as *Wainner cluster* (pooled MD = −3.22; 95% CI = −4.14 to −2.30; $P < 0.00,001$; $I^2 = 77\%$; PI = −4.69 to 1.76; certainty of evidence: very low) were superior to those reported in one study[54] classified as *other* (MD = −1.6; 95% CI = −2.87 to −0.33; $P = 0.01$).

3.4.1.2. Disability

Three *high-risk* studies[54,67,68] with a total of 159 participants compared the effectiveness of NM vs no treatment on disability reduction in the short term. Findings of the meta-analysis are

Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Abhilash et al 2018	-	-	-	-	-	-
Abu Shady et al 2020	-	-	-	-	-	-
Anwar et al 2016	X	-	-	-	-	X
Anwar et al 2015	X	X	-	-	-	X
Barot et al 2020	X	-	+	-	-	X
Coppieters et al 2003	+	+	+	-	-	-
Dhuriya et al 2021	-	-	+	-	-	-
Gupta et al 2012	-	X	X	X	-	X
Ibrahim et al 2019 and Ibrahim et al 2021	+	-	+	-	-	-
Kayiran et al 2021	X	-	-	-	-	X
Khatwani et al 2015	-	-	-	-	-	-
Kim et al 2017	-	-	+	-	-	-
Kumar et al 2010	X	-	-	-	-	X
Marks et al 2011	+	-	+	-	-	-
Nar et al 2014	-	-	+	-	-	-
Nee et al 2012	+	+	+	X	-	X
Pallewar et al 2021 and Raval et al 2014	+	-	-	-	-	-
Pandey et al 2021	-	-	-	-	-	-
Rafiq et al 2021	+	-	+	-	-	-
Rajalaxmi et al 2020	-	-	-	-	-	-
Ranganath et al 2018	+	X	X	-	-	X
Rodríguez-Sanz et al 2017	+	-	-	X	-	X
Rodríguez-Sanz et al 2018	+	-	X	X	-	X
Sanz et al 2018	+	-	X	-	-	X
Savva et al 2021	-	-	+	-	-	-
Srinivasulu et al 2021	-	-	X	-	-	X
Sudhakar et al 2022	-	-	-	-	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Figure 2. Results of the methodological quality assessment using Cochrane's Risk-of-Bias 2.

reported in **Figure 4** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). Neural mobilisations were found to be more effective than no treatment (pooled SMD = −1.55; 95% CI = −2.72 to −0.37; $P = 0.01$; $I^2 = 90\%$; PI = −3.80 to 0.71; certainty of evidence: very low). However, there were significant differences between the subgroups ($P < 0.00,001$). Neural mobilisations were found to be more effective than no treatment in 2 studies[67,68] classified as *Wainner cluster* (pooled SMD = −2.12; 95% CI = −2.61 to −1.63; $P < 0.00,001$; $I^2 = 0\%$; PI = −2.61 to −1.64; certainty of evidence: low) but not more effective in 1 study[54] classified as *other* (SMD = −0.43; 95% CI = −1 to 0.14; $P = 0.14$).

3.4.2. Effectiveness of neural mobilisations vs cervical traction

3.4.2.1. Pain

Four studies[4,7,43,66] (2 *high risk of bias* and 2 *some concern*) with a total of 128 participants compared the effectiveness of NM vs traction on pain intensity reduction in the short term. Findings of the meta-analysis are reported in **Figure 5** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). There was no overall difference in the effectiveness of NM vs traction (MD = −0.33; 95% CI = −1.35 to 0.68; $P = 0.52$; $I^2 = 94\%$; PI = −2.54 to 1.88; certainty of evidence: very low). The sensitivity analysis removing 2 high-risk studies[4,7] yielded the same result ($P = 0.58$). However, the subgroup analysis revealed significant differences in the effectiveness of NM between different subgroups ($P < 0.00,001$), which remained significant following the removal of high-risk studies[4,7] ($P < 0.0001$). In 3 studies[4,7,66] (2 *high risk*, one *some concern*) classified as *Wainner cluster*, NM was found to be more effective than traction (pooled MD = −0.89; 95% CI = −1.31 to −0.47; $P < 0.0001$; $I^2 = 57\%$; PI = −1.59 to −0.2; certainty of evidence: low), whereas in 1 study[42] (*some concern*) classified as *other*, traction was found to be more effective than NM (MD = 1.33; 95% CI = 0.72-1.94; $P < 0.0001$).

3.4.2.2. Disability

Four studies[1,4,42,66] (1 *high risk of bias* and 3 *some concern*) with a total of 140 participants compared the effectiveness of NM vs cervical traction on disability reduction in the short term. Findings of the meta-analysis are reported in **Figure 6** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). There was no overall difference in the effectiveness of NM vs traction (pooled MD = −10.09; 95% CI = −21.89 to 1.81; $P = 0.10$; $I^2 = 97\%$; PI = −36.32 to 16.15; certainty of evidence: very low). The sensitivity analysis removing a high-risk study[4] yielded the same result ($P = 0.38$). However, there were significant differences in the effectiveness of NM between the subgroups ($P = 0.02$), although this was no longer significant ($P = 0.14$) after the removal of the high-risk study.[4] In 3 studies[1,4,66] (1 *high risk* and 2 *some concern*) classified as *Wainner cluster*, NM was more effective than cervical traction (pooled MD = −14.52; 95% CI = −28.54 to −0.50; $P = 0.04$; $I^2 = 96\%$; PI = −42.10 to 13.06; certainty of evidence: low), whereas in 1 study[42] (*some concern*) classified as *other*, cervical traction was found to be more effective than NM (MD = 2.67; 95% CI = 0.59-4.75; $P = 0.01$).

3.4.3. Effectiveness of neural mobilisations vs exercise

3.4.3.1. Pain

Two studies with a total of 78 participants compared the effectiveness of NM vs neck exercise on pain intensity reduction in the short term. No meta-analysis could be performed. Gupta and Sharma[28] (*high risk of bias*), classified as *Hall and Elvey cluster*, concluded that NM was significantly more effective than exercise but only reported the median of the pre-to-post treatment reduction in pain intensity on a 0 to 10 visual analogue scale (NM: 1.95; exercise: 0.30). Pandey et al.[60] (*some concern*), classified as *other*, also reported a greater reduction in pain intensity with NM than with cervical exercise on a 0 to 10 visual analogue scale (posttreatment pain mean ± SD: NM 0.12 ± 0.10, exercise 3.41 ± 1.59; $P = 0.021$).

3.4.3.2. Disability

Two *some concern* studies[60,64] (1[64] classified as *Wainner cluster* and 1[60] as *other*), with a total of 74 participants, compared the effectiveness of NM vs neck exercise on disability reduction in the short term. Findings of the meta-analysis are reported in **Figure 7** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). Both studies reported significant differences in favour of NM (pooled MD = −18.87; 95% CI = −20.29 to −17.44; $P < 0.00,001$; $I^2 = 26\%$; certainty of evidence: moderate). There were no significant differences ($P = 0.25$) between the subgroups, that is, the effectiveness of exercise in the study[64] classified as *Wainner cluster* (MD = 21.8; 95% CI = −26.95 to −16.65) was not

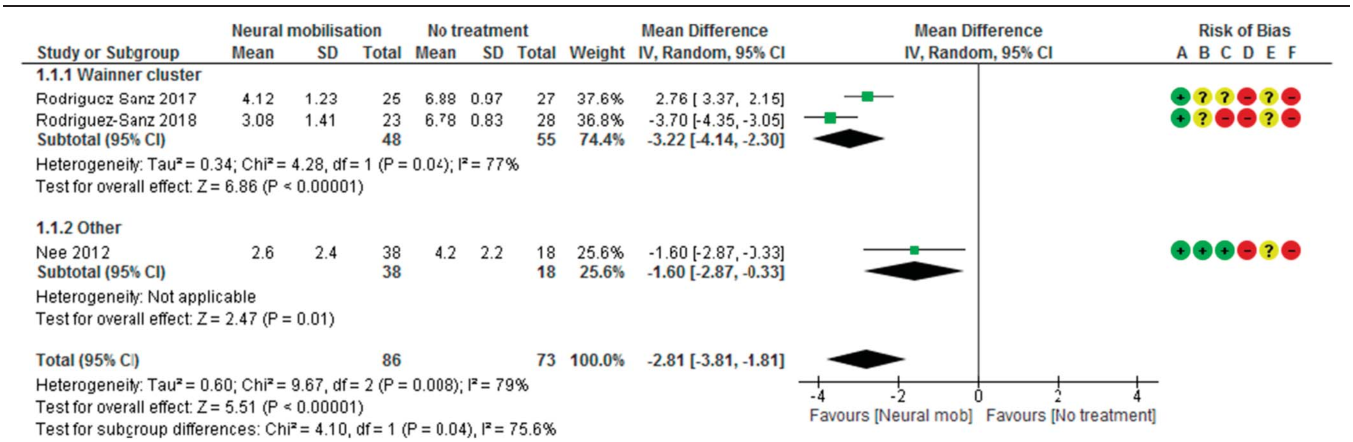

Figure 3. Effectiveness of NM vs no treatment on pain. Outcome measured immediately or 2 weeks post last treatment session (2-4 weeks after treatment commencement).

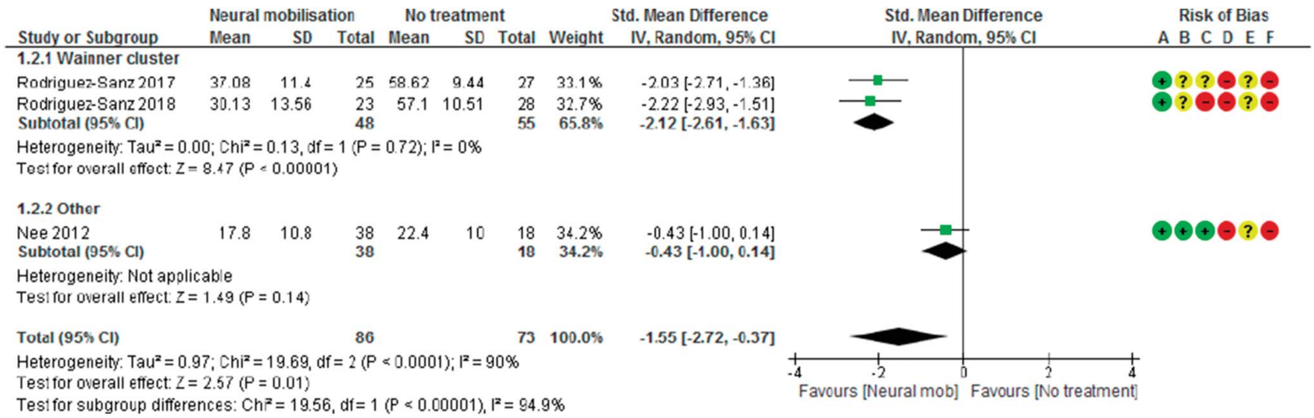

Figure 4. Effectiveness of NM vs no treatment on disability. Outcome measured immediately or 2 weeks post last treatment session (2-4 weeks after treatment commencement).

different ($P = 0.25$) to its effectiveness in the study[60] classified as *other* (MD = −18.63; 95% CI = −20.11 to −17.14).

3.4.4. Effectiveness of neural mobilisations plus standard physiotherapy vs standard physiotherapy alone

3.4.4.1. Pain

Thirteen studies[5,7,22,37,41,43,44,55,61,62,65,66,77,85] evaluated the effectiveness of NM as an adjuvant to standard physiotherapy when compared with standard physiotherapy alone on pain intensity reduction in the short term. Anwar et al.[5] (*high risk of bias*), classified as *other*, reported a significant effect in favour of adding NM to standard physiotherapy but only provided a *P* value with no other data and could not be included in the meta-analysis. Mean and standard deviation of posttreatment scores in the studies by Ibrahim et al.[37] and Rafiq et al.[61,62] were calculated using the sample size, range, median, and interquartile range reported in their articles. Hence, 12 studies[7,22,37,41,43,44,53,61,62,65,66,77,85] (4 *high risk of bias* and 8 *some concern*) with 475 participants were included in the meta-analysis. Findings of the meta-analysis are reported in **Figure 8** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). Neural mobilisation plus standard physiotherapy was found to be more effective than standard physiotherapy alone (pooled MD = −1.44; 95% CI = −1.98 to −0.89; $P < 0.00,001$; $I^2 = 94\%$; CI = −3.27 to 0.40; certainty of evidence: very low); differences were still significant ($P < 0.0001$) after the removal of 4 high-risk studies.[7,41,44,65] There were also significant differences between the subgroups in the added effect of NM to standard physiotherapy ($P < 0.001$); again, this was still significant ($P < 0.009$) after the removal of high-risk studies.[7,41,44,65] Greatest effect of NM was observed in a study[85] (*some concern*) classified as *Hall and Elvey cluster* (SMD = −2.4; 95% CI = −2.58 to −2.22; $P < 0.00,001$), and NM was also effective as an adjuvant to standard physiotherapy in the subgroup of 8 studies[7,22,37,43,61,62,65,66,77] (2 *high risk* and 6 *some concern*) classified as *Wainner cluster* (pooled MD = −1.59; 95% CI = −2.15 to −1.03; $P < 0.00,001$ $I^2 = 88\%$; PI= −3.23 to 0.03; certainty of evidence: low); however, NM was not found to be effective as an adjuvant to standard physiotherapy in the subgroup of 3 studies[41,44,53] (2 *high risk* and 1 *some concern*) classified as *other* (pooled MD = −0.59; 95% CI = −1.9 to 0.72; $P = 0.38$; $I^2 = 88\%$; PI = −2.42 to 1.20; certainty of evidence: very low).

Medium-term effects were evaluated only by one *some concern* study.[43] At 4 weeks postintervention, participants receiving standard physiotherapy plus NM reported statistically significant lower pain intensity than those receiving standard physiotherapy alone.

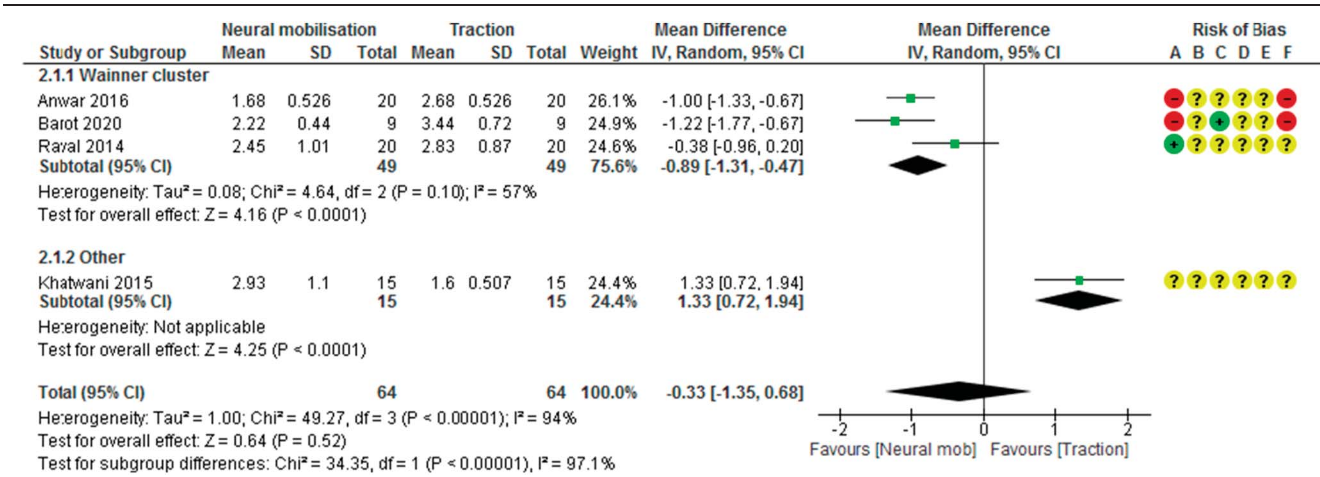

Figure 5. Effectiveness of NM vs cervical traction on pain. Outcome measured post last treatment session (2-4 weeks after treatment commencement).

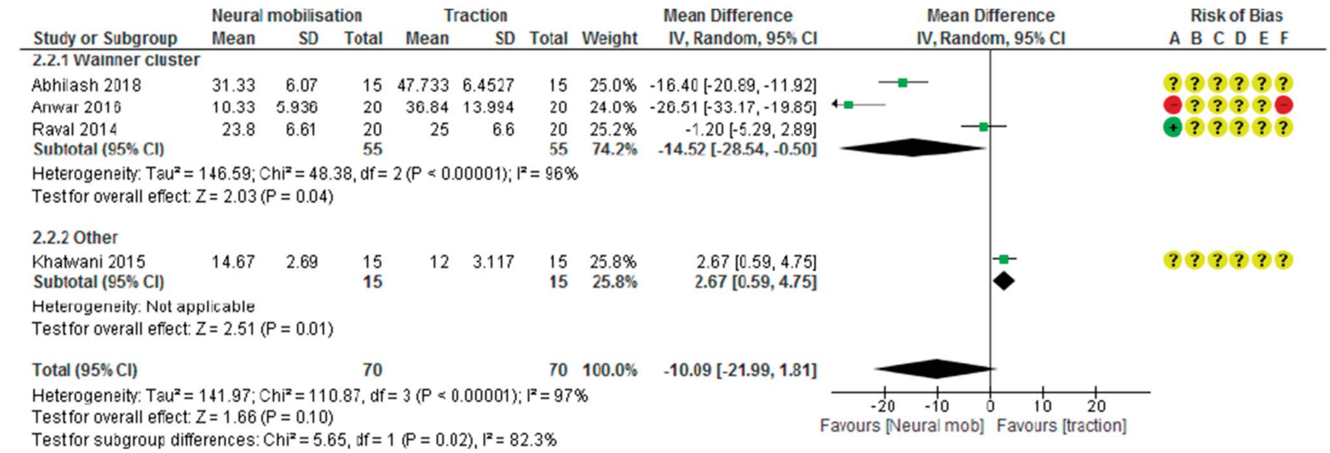

Figure 6. Effectiveness of NM vs cervical traction on disability. Outcome measured post last treatment session (2-4 weeks after treatment commencement).

3.4.4.2. Disability

Eight studies[5,22,41,43,61,62,65,66,75] evaluated the effectiveness of NM as an adjuvant to standard physiotherapy when compared with standard physiotherapy alone on disability reduction in the short term. Anwar et al.[5] (*high risk of bias*), classified as *other*, reported a significant effect in favour of adding NM to standard physiotherapy but only provided a *P* value with no other data and could not be included in the meta-analysis. Hence, 7 studies[22,41,43,61,62,65,66,75] (2 *high risk of bias* and 5 *some concern*) with 337 participants were included in the meta-analysis. Findings of the meta-analysis are reported in **Figure 9** and GRADE in supplemental digital content (available at http://links.lww.com/PAIN/B927). Neural mobilisation plus standard physiotherapy was found to be more effective than standard physiotherapy alone (pooled MD = −11.07; 95% CI = −16.38 to −5.75; $P < 0.0001$ $I^2 = 94\%$; PI= −25.07-2.94; certainty of evidence: very low), and differences were still significant (P = 0.0003) after the removal of 2 high-risk studies.[41,65] Neural mobilisation was found to be effective as an adjuvant to standard physiotherapy in a subgroup of 6 studies[22,43,61,62,65,66,75] (1 *high risk* and 5 *some concern*) classified as *Wainner cluster* (pooled MD = −12.25; 95% CI = −18.14 to −6.36; $P < 0.0001$ $I^2 = 95\%$; PI= −26.86-2.36; certainty of evidence: low) and not effective in a study[41] (*high risk*) classified as *other* (MD = −4.08; 95% CI = −10.07-1.91; $P = 0.18$); however, differences between the subgroups did not reach statistical significance ($P = 0.06$) (sensitivity analysis was not possible after the removal of the only study[41] classified as *other*).

Medium-term effects were evaluated only by 1 *some concern* study.[43] At 4 weeks post intervention completion, participants receiving standard physiotherapy plus NM reported statistically significant lower pain disability than those receiving standard physiotherapy alone.

3.4.5. Effectiveness of neural mobilisations vs other modalities

3.4.5.1. Pain

One study each compared the effectiveness of NM vs Mckenzie manipulation/exercise,[44] Maitland[52] cervical mobilisations, ultrasound,[16] laser,[2] and oral ibuprofen[72] on pain intensity. Kumar[44] (*high risk*), classified as *other*, found a Mckenzie cervical exercise and manipulation protocol more effective than NM. Marks et al.[52] (*some concern*), classified as *Hall and Elvey cluster*, reported no significant differences in pain reduction between Maitland cervical mobilisations and NM after a single session of treatment. Coppieters et al.[16] (*some concern*), classified as *Hall and Elvey cluster*, found a single session of NM to be more effective than ultrasound, whereas Abu Shady et al.[2] (*some concern*), classified as *radiculopathy*, found laser to be more effective than NM.

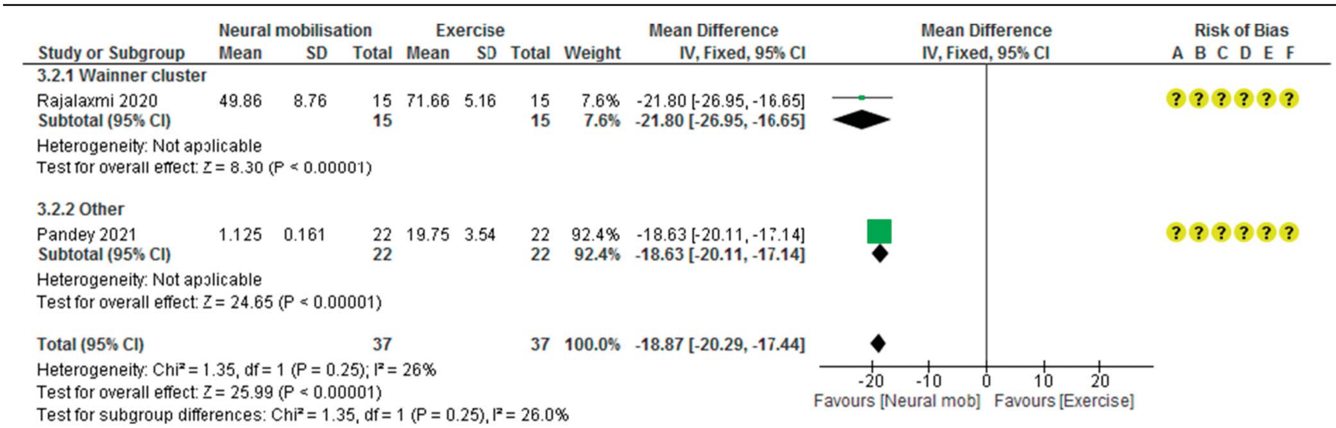

Figure 7. Effectiveness of NM vs neck exercise on disability. Outcome measured immediately or 2 weeks post last treatment session (2-12 weeks after treatment commencement).

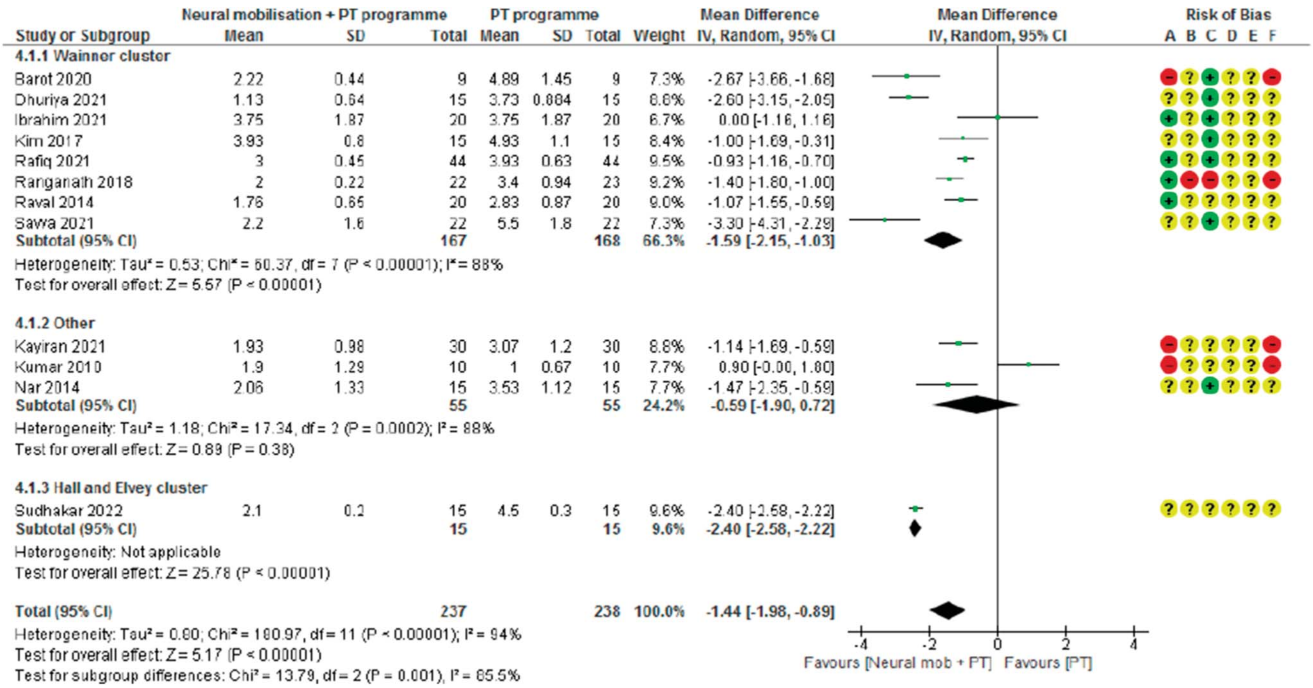

Figure 8. Effectiveness of NM plus standard physiotherapy vs standard physiotherapy alone on pain intensity. Outcome measured immediately post last treatment session (10 days to 4 weeks after treatment commencement).

Finally, Sanz et al.[72] (*high risk*), classified as *Wainner cluster*, reported greater effectiveness of oral ibuprofen when compared with NM.

3.4.5.2. Disability

One study each compared the effectiveness of NM vs Mulligan[84] cervical mobilisations, laser,[2] and oral ibuprofen[72] on disability reduction. Srinivasulu and Divya[84] (*high risk*), classified as *Wainner cluster*, found NM and Mulligan cervical mobilisations to be equally effective in the short term. Abu Shady et al.[2] (*some concern*), classified as *radiculopathy*, found laser to be more effective than NM in the short term, and Sanz et al.[72] (*high risk*), classified as *Wainner cluster*, found oral ibuprofen to be more effective than NM.

4. Discussion

This review is a comprehensive evaluation of the effectiveness of NM in nerve-related cervicobrachial pain, providing estimates of the effect of NM in comparison to no treatment, cervical traction, and cervical exercise, and as an adjuvant to standard physiotherapy when compared with standard physiotherapy alone. Furthermore, it is the first to assess if the effectiveness of NM may differ between different nerve-related cervicobrachial pain subgroups.

Where all study participants were considered together, regardless of subgroup, meta-analyses found NM to be more effective for pain and disability reduction than no treatment, with a large treatment effect. However, all 3 studies included were high risk of bias, mostly because the absence of intervention in the

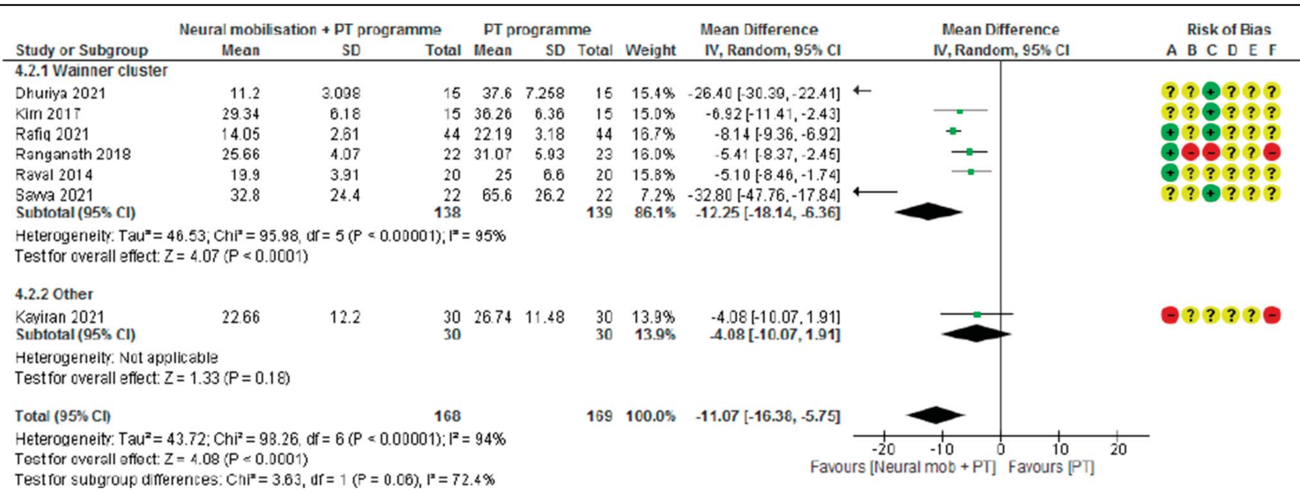

Figure 9. Effectiveness of NM plus standard physiotherapy vs standard physiotherapy alone on disability. Outcome measured immediately post last treatment session (10 days to 4 weeks after treatment commencement).

control group made a placebo effect in favour of NM more likely. When compared with cervical traction, NM was found to be equally effective both for disability and pain. The comparison with cervical exercise resulted in a large effect in favour of NM both for pain and disability reduction, although the number of studies available were limited. Greatest number of studies (13[5,7,22,37,41,43,44,55,61,62,65,66,77,85] in total) assessed the effect of NM when added to standard physiotherapy compared with standard physiotherapy alone. Both for pain and disability reduction, moderate size effects were observed in favour of adding NM to standard physiotherapy, and this finding was not affected by the exclusion of high-risk studies. We found very limited evidence for any other comparisons; NM was found to be more effective than ultrasound,[16] equally effective as Maitland and Mulligan cervical mobilisations[52,84] but less effective than laser,[2] oral ibuprofen,[72] and a Mckenzie cervical exercise and manipulation protocol.[44] All studies but one[43] (which showed favourable medium term effects of NM) assessed only short-term effects; hence, the medium-term and long-term effectiveness of NM is unknown.

Subgroup analyses were significant in most (5 out of 7) meta-analyses. This suggests that the effectiveness of NM may differ between different nerve-related cervicobrachial pain subgroups. Consistently, NM was more effective than all alternative interventions (no treatment, traction, exercise, and standard physiotherapy alone) in 13 [1,4,7,22,44,63,64,66–70,77] out of 14 studies classified as *Wainner cluster*, of which all but one[38] (that reported no difference) reported more favourable outcomes following NM. Effect sizes were small (pain) to moderate (disability) when compared with traction, moderate (pain and disability) when compared with standard physiotherapy alone, and large when compared with no treatment (pain and disability) and exercise (disability). To the contrary, in studies classified as *other*, findings differed between comparisons; NM showed a moderate effect on pain but no effect on disability when compared with no treatment, a large effect on disability in comparison to exercise, had no effect when added to standard physiotherapy in neither pain nor disability, and demonstrated inferior effectiveness than cervical traction on pain and disability. Nevertheless, only 7 studies[5,41,42,44,55,56,60] were classified as *other*; hence, only one study was available for most of these comparisons. We classified Nee et al.[54] as *other* because they only partially fulfilled the cluster by Hall and Elvey[29] since their criteria made no reference to cervical spine findings (ie, reduced neck movement and local cervical dysfunction), just to evidence of heightened neural mechanosensitivity through symptom reproduction and structural differentiation during upper limb neurodynamic testing.

Only 1 study,[85] classified as *Hall and Elvey cluster*, was included in the meta-analyses, showing a moderate effect on pain when added to standard physiotherapy. In other studies classified *Hall and Elvey cluster* but not included in the meta-analyses, NM was found to be more effective than ultrasound[16] and equally effective as Maitland mobilisations for pain reduction.[52] Therefore, it would appear that NM is consistently[1,4,7,22,44,61,62,64–70,77] more effective than no treatment, traction, exercise, and standard physiotherapy alone in patients with nerve-related cervicobrachial pain that fulfil the criteria by Wainner et al.,[93] with minor evidence[85] of its effectiveness in patients who fulfil the criteria by Hall and Elvey.[29] It is of note that the worst outcome for NM was observed in the only study classified as *radiculopathy,* where laser was found to be much more effective than NM. Although limited to a single study, this finding is in agreement with 2 previous studies[55,76] that have noted poorer outcome following NM in patients with characteristics compatible with radiculopathy. In a single arm study[76] assessing the effects of NM in patients with low back–related leg pain, only 15% of patients with signs of conduction loss (hypoesthesia, muscle weakness, or hyporeflexia) and 11% of patients with pain descriptors suggestive of neuropathic pain (12 or greater in the Leeds assessment of neuropathic symptoms and signs scale[10]) achieved a successful treatment outcome with NM, compared with 56% of those patients with heightened neural mechanosensitivity without conduction loss or neuropathic pain.[76] In another study on patients with nerve-related cervicobrachial pain, a baseline LANSS score of less than 12 (absence of neuropathic pain qualities) was a positive predictor of successful outcome.[55]

However, for most comparisons, sample sizes were small, there was considerable statistical heterogeneity, and PI crossed zero. Methodological quality assessment also classified a substantial number of studies as high risk of bias, most often because of bias arising from the randomization process and missing outcome data. Together, they caused downgrading of the evidence on GRADE assessment. For meta-analyses involving all patients, evidence was very low for all comparisons except for NM vs exercise, albeit only 2 studies were available for the latter comparison. Following recommendations by Cochrane[32] on the interpretation of evidence, this review concludes that, when patients with nerve-related cervicobrachial pain regardless of subgroup are considered, NM is likely to result in a moderate reduction in disability when compared with nonspecific active range of motion and isometric exercises of the neck and shoulder; scope for clinical recommendations for other comparisons is limited because of the high uncertainty of the evidence. For patients with nerve-related cervicobrachial pain that fulfil the criteria by Wainner et al.,[93] certainty of evidence was low for most comparisons and outcomes. Hence, this review concludes that, in this patient subgroup, NM may result in a large (when compared with no treatment), small (when compared with traction), or moderate (when compared with standard physiotherapy alone) reduction in pain and/or disability.

Two previous reviews[45,90] on the use of classification systems and diagnostic criteria for cervical radiculopathy in randomised controlled trials reported an inconsistent use of different clusters of signs and symptoms for its diagnosis, which varied considerably between the studies. Heterogeneity among study samples has been postulated as one of the reasons for conflicting results between the trials[47]; furthermore, identifying more homogenous subgroups of patients should enable target each subgroup with the intervention most likely to be effective.[76] The subclassification we used was based on available evidence and previous recommendations. Although the cluster of signs proposed by Wainner et al.[93] has been frequently used to diagnose cervical radiculopathy,[22,36,37,65,66,75,84] we did not adopt this classification following recommendations from Bogduk[11] and the International Association for the Study of Pain[35, 79] that radiculopathy is characterized by neurological deficits in a dermatomal or myotomal distribution. None of the cluster signs by Wainner et al.[93] are indicative of a loss of function, they rather indicate a gain of function as pain provocative manoeuvres. In comparison to the cluster by Wainner et al.,[93] the cluster proposed by Hall and Elvey[29] does not incorporate compression (Spurling test) and distraction manoeuvres of the cervical spine, rather it requires the detection of cervical somatic dysfunction through cervical spine palpation. Therefore, we considered that these could represent 2 different subgroups of patients with nerve-related cervicobrachial pain that may respond differently to NM, although it is likely that overlapping exists. Studies that did not fit in these classification categories were classified as *other*. Studies in this latter category had no specific feature in common, only the fact that they could not be included in the former subgroups, making this *other* category rather heterogeneous. Such heterogeneity may also explain the fact that the effectiveness of NM in this subgroup varied considerably between the studies.

Findings of this review suggests that effectiveness of NM may differ between nerve-related cervicobrachial pain patient subgroups of different pathophysiology and clinical presentation. Neural mobilisations may be more effective than no treatment, traction, exercise, and standard physiotherapy alone in patients who fulfil the cluster by Wainner et al.[93]; however, certainty of the evidence is low. Research comparing the effectiveness of NM in different patient subgroups is required. Researchers should ensure adequate sample sizes and take steps to overcome the methodological flaws identified in this review.

4.1. Limitations of the review

GRADE assessment resulted in the downgrading of evidence by 2 to 3 levels in most comparisons. It is of note that in comparisons where there was significant statistical heterogeneity, in addition to its effects on the rating of inconsistency, this may have also affected the rating in imprecision (through its effect on the PI), resulting in a 2-level downgrading.

Data extraction was performed by a single reviewer. Although a second reviewer revised extracted data for correctness and completeness, this reviewer was not blind to the work of the first reviewer.

We classified studies according to the information articles provided about the criteria used to include participants in their study. We assumed that those studies that stated their participants had fulfilled a specific criterion (eg, Hall and Elvey's[29]), did in fact follow the guidance outlined in the criteria, albeit specific detail was at times lacking.

Evaluation of the relationship between patient characteristics and effectiveness of NM is based on an indirect interpretation of the results of the studies through subgroup meta-analysis. Furthermore, subgroup meta-analyses performed involved a small number of studies, and, at times, the result was highly dependent on the findings of 1 or 2 studies. Nevertheless, the conclusions of this review are based on the findings of several subgroup meta-analyses, which together point to the importance of patients' pain phenotype in the effectiveness of NM.

Conflict of interest statement

I. Lascurain-Aguirrebeña has checked all authors' COIs and the COI statement in the text of the manuscript is in agreement with the COI statement on the ICJME forms. The remaining authors have no conflicts of interest to declare.

Acknowledgements and conflicts of interest

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