



The effectiveness of lower body quadrant neural A24 mobilization in healthy and back pain population: An upgraded meta-analysis

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Introduction

Low back pain (LBP) is the most common pain syndrome in Europe, affecting around 50 % of European citizens [1]. It is not considered a disease and may be a consequence of various known or unknown dysfunctions or pathological conditions [2]. LBP can be accompanied by pain in the legs and be associated with neurological symptoms in the lower limbs [2]. Worldwide, the prevalence of chronic LBP increased from 1.4 to 15.6 % over the last two decades [3]. In Portugal, its prevalence is estimated to be around 36.6% [4] and recently, the leading cause of disease burden in both genders has changed from stroke and ischemic heart disease to LBP [5]. Furthermore, chronic LBP is one of the main causes of years lived with disability in Portugal, having increased from 15.9% in 1990 to 16.7% in 2016 [5]. Pain severity and its association with disability is different between individuals; while some may present little discomfort to daily live functions, others may be highly compromised with restrictions in relationships, work, and social activities [6].

A therapeutic intervention that has been shown positive effects in decreasing pain and improving functioning is neural mobilization (NM) [7–14], which consists of a combination of articular movements that promote the gliding or the tensioning of the peripheral nervous system and that can be performed both passively by the health professional or actively by the individual [15]. It is believed to facilitate the nerve gliding in relation to adjacent tissues, to facilitate neural vascularity, and to improve the axoplasmic flow, which in turn results in improved neural functioning and, consequently, in improved motor and sensory function [16]. One study, for example, showed that neurodynamic nerve gliding provided a slightly greater increase in hamstring extensibility and passive stiffness when compared to static stretching, possibly by decreasing nerve tension and increasing strain in connective tissues [10].

Neto et al. published in 2017 a systematic review with meta-analysis that aimed to verify the effectiveness of NM in pain and disability of individuals with LBP, and in the flexibility of healthy individuals [17]. Considering this meta-analysis was published in 2017 (4 years ago) with few studies, and that those that were included were published no later than May 2015, the intention was, therefore, to update this study with the inclusion of new randomized controlled trials (RCTs).

This study was carried out within the curricular unit Statistical Methods in Health Sciences of the Doctoral Program in Rehabilitation Sciences at the University of Aveiro, and the objective was to update the meta-analysis "Effects of lower body quadrant neural mobilization in healthy and low back pain populations: A systematic review and meta-analysis" [17] in order to verify if there was any change in the results previously found with the inclusion of new individual studies.

Methods:

i) Search strategy and study selection

An electronic search of scientific articles was conducted by two researchers. One author (FB) searched for articles with healthy individuals and a second author (EPN) searched for articles with low back pain individuals in PubMed and Web of Science databases. The search terms were chosen based on the PICO strategy, and are well specified in Appendix 1 of the supplementary material. As an update, were considered publications between May 2015 till March 2021. This search was complemented by manually detecting references from bibliography. Each author identified studies by title and abstract and removed duplicated articles. Posteriorly, the two authors read the entire manuscripts and gave recommendations for inclusion.

Keywords: disability evaluation, flexibility, low back pain, neural mobilization, pain, range of motion

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Supplementary material:

Conflict of interest: authors declare no conflict of interests.

First published: 22JUN2021



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ii) Inclusion and exclusion criteria

The criteria used to search for articles were established in accordance with the PICO strategy below: Population – Healthy and LBP patients over 18 years.

Intervention - Any form of NM applied in the lower body quadrant (sliding or tensioning).

Comparison-A control intervention, no intervention, or placebo.

Outcomes – Pain intensity (measured with a visual analog scale or a numeric rating scale); disability (measured by the Oswestry Disability Index – ODI or the Roland and Morris Disability Questionnaire – RMDQ), and lower limb flexibility (measured by the straight leg raise test–SLR, the active knee extension test–AKE or the passive knee extension test–PKE).

Types of study and its characteristics – studies must be written in English or Portuguese, be a randomized controlled trial (RCT), published from May 2015 and include any form of NM technique in the lower body quadrant in humans.

iii) Data extraction

Data extraction from de new articles included were performed by two authors. FB extracted information from articles with healthy individuals and EPN from articles with LBP individuals. From each study was extracted a qualitative summary (Tables 1 and 2 – supplementary material): bibliographic information; characteristics of the participants; characteristics of NM interventions (technique type, number of sessions, number of repetitions, and duration); type of control condition and respective frequency and duration); outcomes measured (pain, disability, lower limb flexibility); measuring instruments for the evaluation of primary outcomes; and a quantitative summary (Tables 3 – 5, supplementary material): mean difference, standard deviation, sample size, effect size (between groups or within groups) and the respective standard error. All outcomes were continuous and effect sizes were determined using the following data: sample sizes, means, and standard deviations (SD), both at baseline and post-treatment, for all groups (i.e., treatment and control). Only one study [18] did not present data from results in the baseline and presented three moment assessments (4, 8 and 12 days after intervention). Therefore, we have considered as the initial evaluation the data referring to the second evaluation moment, that is, 4 days after the intervention. Regarding the post-intervention data, those obtained 12 days after its application were considered.

iv) Data synthesis

In the original article, the authors considered conducting a paired analysis (within group data) for "pain" because they considered that in one of the studies [19] there was a difference between the groups in the baseline, which would be a potential risk of bias in the case of a comparative analysis between independent groups. However, for this update it was decided to carry out an independent analysis (between groups data) with the exclusion of this study, to make the statistical analysis more robust and reliable. For the other dependent variables ("flexibility" and "disability") were also considered analyses for independent groups as the original article. For the new included studies in this upgrade, mean difference and its standard deviation were calculated for each group (experimental and control) [20] and posteriorly, effect sizes were determined by the standardized mean difference with Hedges' g correction for small samples [21], and classified according to Cohen's guidelines [22] as small (0.20), medium (0.50), and large (0.80) effects. For studies included in the original article [17], were utilized the existing effect sizes, although standard error was calculated (SE=(upper limit-lower limit)/3.92) for each of them [20]. For each effect size, 95% confidence intervals (CI) were calculated. Analyses were conducted using the R Version 1.4.1106. Statistical heterogeneity was inspected using Cochran's Q statistic for which a significant pvalue (<0.1) [23] and I2 statistic that ranges from 0 to 100%, with values of 25%, 50%, and 75% reflecting low, moderate and high statistical heterogeneity, respectively [24,25]. A publication bias analysis was considered for the meta-analysis that had the "flexibility" as the dependent variable, so visual inspections of the data were carried out through the forest, funnel, radial and baujat plots, as well as through the Egger's regression test, Begg and Mazumdar's rank correlation test and Rosenthal's Fail Safe Number [26–29]. The funnel plot is an informal method for detecting potential publication bias. It can be said that there is a potential publication bias when the graph is asymmetric with a gap. When any asymmetry was identified in the funnel plot, it was tested by a simple linear regression: the Egger's Regression Test. If the alpha value is equal to zero, it means that the funnel plot is in fact symmetric [26,27]. The Rosenthal's Fail-Safe Number (N) was calculated to verify what would be the number of articles with a null effect to be added to the analysis so that the combined effect was no longer statistically significant [29,30].

Results:

i) Search results

Six studies were included in this meta-analysis upgrade: four for the dependent variable "flexibility", two for the dependent variable "pain", and one for the dependent variable "disability". One of the studies, provided data for both "pain" and "disability".

ii) Summary of quantitative analysis (individual studies)

(See Tables 3 – 5 in Supplementary Data)

iii) Effects of neural mobilization on flexibility

Five additional studies were included in this upgraded meta-analysis. The results of NM effects on flexibility are demonstrated in Figure 1. Total of nine studies showed a significant medium effect size (k = 9; g = 0.78; 95% CI = 0.47 – 1.09; z = 4.94; p < 0.0001) supporting the use of NM to enhance flexibility in healthy population. Heterogeneity was significant (p = 0.02; I² = 56%), so the random effect model was considered. The greatest effect size (g = 1.71) was found by Areeudomwong et al. (2016) that compared the application of neurodynamic sliders technique with placebo intervention in a group of healthy male footballers [31]. The risk of potential publication bias was assessed by visual inspection of the funnel plot and radial plot (See Figures 5 and 6 – in Supplementary Data), and it was complemented with the Egger's (p = 0.47) and Begg and Mazundar's tests (p=0.53), which support that the null hypothesis of symmetry cannot be rejected. Based on Rosenthal's fail-safe number in this new meta-analysis (N = 177), which is slightly higher than the calculated cut-off (N = 55), it is estimated that 177 additional studies would be required to transform the original effect size.

Original meta-analysis [17] found the largest effect size by Castellote-Caballero et al. (2013) [32], so the authors decided to remove this study from the analysis to verify if it would influence or alter the effect size and significance of results, but it did not. In this upgrade, we performed an additional meta-analysis without the trial conducted by Areeudomwong et al. (2016) to also determine the influence of this study in the global effect size (k = 8; g = 0.66; 95% CI = 0.46 - 0.86; z = 6.50; p < 0.0001). Results from both meta-analyses were very similar in their effect sizes. Taking into account that heterogeneity was not significant without this study (p = 0.15; I² = 35%), the fixed effect model was considered for this analysis, so it is possible to realize that the heterogeneity was derivate from this effect size, and it can be verified through a baujat plot (See Figure 7–Supplementary Data).

Study	TE	seTE	SMD - Hedges`g	SMD - Hedges`g	95%-CI	Weight
Castellote-Caballero et al., 2013	1.38	0.334		1.38	[0.73; 2.04]	11.0%
Castellote-Caballero et al., 2014	0.64	0.197		0.64	[0.26; 1.03]	16.2%
Méndez-Sánchez et al., 2010	0.75	0.643		0.75	[-0.51; 2.01]	4.7%
Sharma et al., 2016	0.90	0.231		0.90	[0.45; 1.36]	14.8%
Webright et al., 1997	0.14	0.347		0.14	[-0.55; 0.82]	10.6%
Arreudomwong et al., 2016	1.71	0.371		1.71	[0.98; 2.44]	9.9%
Ganesh et al., 2017	0.81	0.380		0.81	[0.07; 1.56]	9.6%
Vinod Babu et al., 2015	0.30	0.224		0.30	[-0.14; 0.74]	15.1%
Satkunskiene et al., 2020	0.63	0.437		0.63	[-0.22; 1.49]	8.2%
Random effects model				0.78	[0.47; 1.09]	100.0%
Prediction interval					[-0.11; 1.67]	
Heterogeneity: $I^2 = 56\%$, $\tau^2 = 0.116$	8, p =	0.02				
			-2 -1 0 1 2			

Figure 1 - Forest plot (dependent variable "flexibility"). TE – estimate of treatment effect; seTE – standard error of treatment estimate; SMD – Standardized mean difference; CI – Confidence interval.

Study	TE	seTE	SMD - Hedges`g	SMD - Hedges`g	95%-CI	Weight
Castellote-Caballero et al., 2013	1.38	0.334		1.38	[0.73; 2.04]	9.3%
Castellote-Caballero et al., 2014	0.64	0.197	- 	0.64	[0.26; 1.03]	26.8%
Méndez-Sánchez et al., 2010	0.75	0.643		0.75	[-0.51; 2.01]	2.5%
Sharma et al., 2016	0.90	0.231		0.90	[0.45; 1.36]	19.5%
Webright et al., 1997	0.14	0.347		0.14	[-0.55; 0.82]	8.6%
Arreudomwong et al., 2016	1.71	0.371		1.71	[0.98; 2.44]	0.0%
Ganesh et al., 2017	0.81	0.380		0.81	[0.07; 1.56]	7.2%
Vinod Babu et al., 2015	0.30	0.224	+ 	0.30	[-0.14; 0.74]	20.7%
Satkunskiene et al., 2020	0.63	0.437	++	0.63	[-0.22; 1.49]	5.4%
Fixed effect model				0.66	[0.46; 0.86]	100.0%
Prediction interval					[0.05; 1.30]	
Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.048$	30, p =	0.15				
			-2 -1 0 1 2			

Figure 2 - Forest plot (dependent variable "flexibility") excluding Areeudomwong et al. (2016). TE – estimate of treatment effect; seTE – standard error of treatment estimate; SMD – Standardized mean difference; CI – Confidence interval.

iv) Effects of neural mobilization on pain

The results of NM effects on pain are demonstrated in Figure 3 and two additional studies were included in this upgraded meta-analysis. Total of seven studies showed a significant high effect size (k = 6 g = 0.52; 95% CI = 0.29 – 0.75; z = 4.45; p < 0.0001). Heterogeneity was not significant (p = 0.87; I² = 0%), so the fixed effect model was considered.

Study	TE	seTE	SMD - Hedges`g	SMD - Hedges`g	95%-CI	Weight (fixed)	Weight (random)
Cleland et al., 2006 Colakovic et al., 2013 Dwornik et al., 2009 Nagrale et al., 2012 Plaza-Manzano et al., 2020 Tambekar et al., 2016	0.17 0.54 0.64 0.38 0.64 0.67	0.360 0.260 0.220 0.260 0.360 0.370		0.17 0.54 0.64 0.38 0.64 - 0.67	[-0.54; 0.88] [0.03; 1.05] [0.21; 1.07] [-0.13; 0.89] [-0.07; 1.35] [-0.06; 1.40]	10.6% 20.3% 28.3% 20.3% 10.6% 10.0%	10.6% 20.3% 28.3% 20.3% 10.6% 10.0%
Fixed effect model Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p =	0.87		0.52 0.52	[0.29; 0.75] [0.29; 0.75] [0.20; 0.85]	100.0% 	 100.0%

Figure 3 - Forest plot (dependent variable "pain"). TE – estimate of treatment effect; seTE – standard error of treatment estimate; SMD – Standardized mean difference; CI – Confidence interval.

v) Effects of neural mobilization on disability

The results of NM effects on disability are demonstrated in Figure 4 and only one additional study was included in this upgraded meta-analysis. Total of four studies showed a significant high effect size (k=4; g = 1.30; 95% CI=0.75-1.86; z=4.71; p<0.0001). Heterogeneity was not significant in Cochran's test (p= 0.12); but considering a moderate heterogeneity (I²=49%), a random effect model was considered.



Figure 4 - Forest plot (dependent variable "disability"). TE – estimate of treatment effect; seTE – standard error of treatment estimate; SMD – Standardized mean difference; CI – Confidence interval.

Discussion:

This study performed an upgraded of three meta-analyses from Neto et al. (2017) regarding the effectiveness of NM in healthy and in LBP individuals. Six new studies were included in this update: four studies for the dependent variable "flexibility", two studies for the dependent variable "pain", and only one study for the dependent variable "disability". The main findings were: i) NM intervention either alone or combined with other techniques decreased pain and disability levels in LBP individuals; ii) NM intervention increased flexibility in healthy individuals; iii) there is a large variability in NM interventions, regarding duration, frequency, and type of technique applied to individuals.

NM techniques have a medium effect size (g = 0.78) in increasing flexibility in healthy individuals and this upgraded meta-analysis, with a total of 9 studies, showed that this result was reinforced with the four new included studies.

In the pain meta-analysis, with a total of 6 studies, the effect size remained significant and medium (g = 0.52), but decreased in relation to the original meta-analysis (g = 1.30)[17]. This is due to the fact that it was opted for this update, unlike the original authors, to carry out an analysis for independent groups (between groups data vs within group data) for the dependent variable pain. The study of Dwornik et al. (2009) gives a contribute to this result, as its weight is bigger than the other studies (28.3%).

In disability, with a total of 4 studies, this upgrade reinforced the beneficial effects of NM in LBP individuals (g = 1.30).

Limitations are focused on the number of studies in each meta-analysis, but although these global effect sizes are derived from few studies, NM applied in lower body quadrant is still an important target for future investigation in LBP population and healthy individuals. A relevant aspect to be considered is the great variability regarding the dosimetry of application of the neural mobilization technique in the included

studies. With the data that currently exist, it has not yet been possible to establish a standardization regarding the number of sets, repetitions, and the most suitable duration of application of the technique. In the study of Ganesh [18], for example, it is not clear the number of sessions performed with the intervention group compared to the control group (6 days / week for 2 weeks), which makes it difficult to identify the dosimetry associated with the intervention outcome. More studies need to be carried out in order to identify the best application dose of this technique for specific populations.

Another relevant point to consider is the fact that interventions applied to control groups in the various individual studies vary greatly from study to study, which makes it difficult to carry out a comparative analysis between studies in a more standardized way. In studies involving individuals with low back pain, for example, interventions associated with control groups encompass very different modalities, such as passive vertebral mobilization [33], stretching [19], motor control exercises and lumbar stabilization [34,35]. Furthermore, the applied neural mobilization technique is different between studies. Some studies used global neural mobilization techniques [33,35], while others used specific nerve mobilization techniques for the sciatic nerve [19,34]. This is another factor that makes a real comparison between the effects of each study difficult, considering that different techniques were applied to the target population.

It is also worth noting that in the studies included in the group of healthy individuals, the primary outcome (flexibility) was measured by tests that were slightly different from each other. Some studies used the Passive Straight Leg Raise (SLR) test [10,18,36], while other studies used the Passive Knee Extension (PKE)[31,37].

Despite recognizing the importance of standardizing measurement instruments for conducting a metaanalysis, it was decided to include these studies, considering the variability between them. However, for future studies, a more specific definition of assessment methods is recommended as an inclusion criterion for individual studies.

This study was developed within a curricular unit in the Doctoral Program in Rehabilitation Sciences at the University of Aveiro.

Conclusion

The results found remained and we conclude that MN has a significant effect on the treatment of people with low back pain and on the flexibility of healthy people. However, due to the small number of studies included in each of the meta-analyses and the great methodological variability identified between the studies, further research in this area is necessary to increase the robustness of the results and the meta-analysis itself. Thus, more RCTs with comparisons between groups are necessary for a better and more solid conclusion about NM in people with low back pain.

Financial support:

One of the investigators (EPN) have a scholarship from Fundação para Ciência e a Tecnologia – FCT (2020.08869.BD). CINTES-IS.UA – Center for Health Technology and Services Research at the University of Aveiro.

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