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Research

Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial

Ronaldo Fernando de Oliveira [a], Leonardo Oliveira Pena Costa [a], Leonardo Penteado Nascimento [b], Lívia Leticia Rissato [c]

[a] Masters and Doctoral Programs in Physical Therapy, Universidade Cidade de São Paulo, São Paulo, Brazil; [b] Escola de Osteopatia de Madrid Internacional, São Paulo, Brazil; [c] Physical Therapy Department, UBS Santo Antônio do Aracanguá, Santo Antônio do Aracanguá, Brazil

KEY WORDS

Randomised controlled trial
Low back pain
Spinal manipulation
Manual therapy
Manipulative therapy

ABSTRACT

Question: In people with chronic low back pain, what is the average effect of directing manipulation at the most painful lumbar level compared with generic manipulation of the spine? **Design**: Randomised controlled trial with concealed allocation, a blinded assessor and intention-to-treat analysis. **Participants**: 148 people with non-specific chronic low back pain with a minimum level of pain intensity of 3 points (measured from 0 to 10 on the Pain Numerical Rating Scale). **Interventions**: All participants received 10 spinal manipulation sessions over a 4-week period. The experimental group received treatment to the most painful segment of the lower back. The control group received treatment to the thoracic spine. **Outcome measures**: The primary outcome was pain intensity, measured at the end of the intervention (Week 4). Secondary outcomes were: pain intensity at Weeks 12 and 26; pressure pain threshold at Week 4; and global perceived change since onset and disability, both measured at Weeks 4, 12 and 26. **Results**: Each group was randomly allocated 74 participants. Data were collected at all time points for 71 participants (96%) in the experimental group and 72 (97%) in the control group. There were no clinically important between-group differences for pain intensity, disability or global perceived effect at any time point. The estimate of the effect of directing manipulation at the most painful lumbar level, as compared with generic manipulation, on pain intensity was too small to be considered clinically important: MD 0 (95% CI −0.9 to 0.9) at Week 4 and −0.1 (95% CI −1.0 to 0.8) at Week 26. **Conclusion**: No clinically important differences were observed between directed manipulation and generic manipulation in people with chronic low back pain. **Trial Registration**: NCT02883634. **[de Oliveira RF, Costa LOP, Nascimento LP, Rissato LL (2020) Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. *Journal of Physiotherapy* 66:174–179]**

Introduction

Chronic low back pain is highly associated with disability and costs to society.[1,2] There is a wide range of interventions that are used to manage chronic low back pain[3–7] such as exercise, pain education[8] and spinal manipulation.[9] The benefits of spinal manipulation include reductions in pain and disability, and these benefits are comparable with most recommended therapies for chronic low back pain in both the short and long term.[10,11] The most recent overview of clinical practice guidelines for people with low back pain[12] found that a third of the existing guidelines recommend spinal manipulation as a component of a multimodal program for patients with chronic low back pain.[3,13] However, as the site of pain is usually very sensitive, there is still debate about the need for specific manipulation (ie, at the site of the painful vertebral segment).[14–22]

Directed and generic manipulative therapy have been investigated recently in several studies,[14,18,19,21,23] which show that generic manipulation (ie, manipulation of a vertebral segment distant from the painful vertebral segment) can also have positive effects in some musculoskeletal conditions. The main studies[14,18,19] point to thoracic manipulation as a non-specific form of treatment in people with neck pain[14,18,19] and chronic low back pain.[15] Only one of those studies measured the immediate effects of thoracic manipulation (generic) or lumbar manipulation (directed) in people with chronic low back pain.[15] This trial did not detect differences between the directed and generic manipulation groups. However, in this clinical trial,[15] only one manipulation was performed as treatment and only short-term results were measured. Thus, there is a need to investigate whether this effect remains in the long term and whether more spinal manipulative therapy sessions would yield greater results.

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Therefore, the research question for this randomised controlled trial was:

> In people with chronic low back pain, what is the average effect of directing manipulation at the most painful lumbar level compared with generic manipulation of the spine?

Methods

Design

This was a prospectively registered, two-arm, randomised controlled trial with concealed allocation, a blinded assessor and intention-to-treat analysis. Participants were recruited in the main public outpatient physiotherapy clinic of a rural city in the state of Sao Paulo, Brazil. People who met the eligibility criteria were informed about the study aims. All eligible people who agreed to participate in the study signed a consent form. Eligibility was firstly determined by the outcome assessor (RFO) and double checked by the therapist (LLR) just before randomisation. Randomisation was performed by a researcher (LOPC), who was not involved in data collection, by generating a randomly ordered list of allocation codes using commercial software[a] at a 1:1 ratio. To conceal the allocation list, the randomisation codes were placed in sealed and opaque envelopes that were numbered consecutively.[24] The experimental group received manipulation directed at the vertebral level indicated by the therapist's assessment, whereas the control group received manipulation in the middle thoracic region. Participants received the 4-week course of study interventions in the same clinic, after which outcomes were assessed. The assessor responsible for collecting outcome data (RFO) was blinded to participant allocation. Due to the nature of the interventions, the therapist responsible for delivering manipulative treatment (LLR) was not blinded to randomisation. Participants were not informed about the type of manipulative treatment they received, but due to the nature of the interventions, this would not have been sufficient to blind the participants.

Participants

People of any gender were recruited consecutively if they were aged 18 to 80 years and were seeking care of non-specific chronic low back pain (duration $>$ 12 weeks).[3] They had to have a minimum level of pain intensity of 3 points on the 11-point Pain Numerical Rating Scale.[25] However, they were excluded from participating if they were pregnant or had spinal stenosis, vertebral fracture, cancer, advanced osteoporosis, or any haemorrhagic diseases.[26]

Intervention

Participants were treated by a physiotherapist (LLR) with 11 years of experience in clinical practice, intensive training in spinal manipulative therapy and a degree in osteopathy. This therapist took the medical history and performed the clinical examination of all participants included in the study.

To identify the participant's symptoms and the specific vertebral level to be manipulated, Maitland's posterior-anterior central vertebral pressure and posterior-anterior unilateral vertebral pressure mobilisations were used.[27] The posterior-anterior central vertebral pressure was performed with the patient in prone and making contact between the pisiform bone and the spinous process of the vertebra to be evaluated. For the posterior-anterior unilateral vertebral pressure, the therapist made contact on the transverse process of the vertebra with the thumbs overlapping each other and performing a perpendicular force of about 4 kg. Following assessment, the therapist defined the ideal level to be manipulated based on the participant's referred pain and assessment of vertebral levels.[28] In the cases where more than one vertebral level was symptomatic, the therapist nominated the most painful level.

At the end of the assessment, the therapist opened the randomisation envelope containing the participant's group allocation. Participants allocated to the experimental group received 'directed manipulation' (ie, a high-velocity thrust manipulation based on the vertebral level assessment made by the therapist). Participants allocated to the control group received 'generic manipulation' (ie, the most symptomatic vertebral level was disregarded and the high-velocity thrust manipulation was instead applied to the mid-thoracic region, close to the T5-T6 level). All participants underwent a 4-week treatment program, comprising three sessions a week for the first 2 weeks and two sessions a week for the final 2 weeks, totalling 10 manipulation sessions.[28]

Outcome measures

Participants were re-assessed immediately after treatment (Week 4), as well as at Weeks 12 and 26.

Primary outcome

The primary outcome measure was pain intensity assessed by the Pain Numerical Rating Scale,[29] measured at Week 4.

Secondary outcomes

Pain intensity was also assessed at Weeks 12 and 26, again using the Pain Numerical Rating Scale, as a secondary outcome measure. Disability was measured at Weeks 4, 12 and 26 using the Roland-Morris Disability Questionnaire. Global perceived change since onset was measured at Weeks 4, 12 and 26 using the Global Perceived Effect Scale. Pressure pain threshold was measured at Week 4 using a pressure algometer. The instruments used to measure these outcomes are described in detail in Table 1.

Data analysis

The required sample size was calculated as 148 participants (74 per group), allowing for statistical power of 80%, an alpha of 5%, and a dropout rate of up to 15%. The current statistical tests have power to detect a between-group difference of 1 point for pain intensity (with an estimated standard deviation of 1.84 points) and 4 points for disability (with an estimated standard deviation of 4.9 points). The estimates used in the sample size calculation were based on results from several previously published low back pain clinical trials.[28,38,39]

Participant characteristics were reported using descriptive statistical tests. The effects of treatment (ie, mean between-group differences) and 95% confidence intervals were calculated via mixed linear models using 'time versus group' interaction terms. These interaction terms are equivalent to the between-group differences. Missing data were handled using linear mixed models[40] (ie, imputation methods were not needed). An estimation approach was used to interpret the findings[41] rather than using statistical significance. All analyses were conducted using commercial software[a] and followed the principle of intention to treat.

Results

Flow of participants through the trial

Participants were recruited between February 2017 and December 2018. The characteristics of the participants at baseline are presented in Table 2 and in the first two columns of data in Tables 3 and 4. The participants were mostly women (78%), with a mean age of 44 years, a median duration of symptoms of 6 months (IQR 3 to 24 months), and moderate levels of pain intensity and disability. Demographic variables and clinical measures were similar at baseline. Among the 157 patients assessed for eligibility, nine were excluded, of whom six did not meet the inclusion criteria and three declined to participate in the study. The detailed flowchart is presented in Figure 1.

Table 1
Detailed description of the instruments used in outcome measurement.

Instruments	Description
Pain Numerical Rating Scale	Pain intensity is assessed on an 11-point Likert scale from 0 'no pain' and 10 'the worst possible pain'. The Pain Numerical Rating Scale is a responsive instrument that has excellent reproducibility.[24] This outcome was measured at Weeks 0, 4, 12 and 26. At each measurement, participants were asked about the mean pain intensity over the previous 7 days.
Global Perceived Effect Scale	The Global Perceived Effect Scale is used to compare the participant's current state to that of the time of onset of symptoms using a 11-point Likert scale ranging from −5 'much worse' through to 0 'no different' and up to +5 'fully recovered'. It is a tool that has excellent reliability.[24,30] This outcome was measured at Weeks 0, 4, 12 and 26. At each measurement, participants were asked, 'Compared to the beginning of this episode, how would you describe your lower back today?'
Roland-Morris Disability Questionnaire	The Roland-Morris Questionnaire is composed of 24 statements regarding daily activities that people may find difficult due to low back pain. For each statement, participants were asked to answer 'yes' or 'no' to indicate whether they found the activity difficult over the last 24 hours. The final score was obtained by adding the 'yes' answers, so higher scores indicate greater disability. It is recommended as a core outcome measurement instrument for low back pain[29,31] and has been translated, adapted and tested for use in Brazil.[32,33] This outcome was measured at Weeks 0, 4, 12 and 26.
Pressure algometer	The pressure pain threshold was measured by the blinded assessor using a pressure algometer[a], which measures the pressure and/or force applied to any segment of the body.[34,35] To measure the pressure pain threshold, the assessor positioned the algometer perpendicular to the skin, applying pressure at a constant velocity of approximately 5 Newtons/second. Measurement was performed on three points with participants lying in prone. Two points were laterally marked at 5 cm from the spinous processes of L4 and L5.[16] A third point was marked on the middle of the tibialis anterior muscle bilaterally.[36] The objective was to verify the presence of generalised pain that is expected to be present as a consequence of chronic low back pain, with measurements performed bilaterally.[36,37] Participants were instructed to push the algometer button when the sensation of pressure or discomfort became a clear sensation of pain. The measurements (in Newtons) were performed three times on each marked region, with a 30-second interval between them.[15] For any patient who did not report pain with a force application of 2,000 kPa, the test was interrupted and this value was used.[36] To ensure participants' understanding of procedures, two demonstrations were performed by applying the algometer to the dominant forearm muscles. Pressure algometry was measured at Weeks 0 and 4. At each measurement, the mean pressure pain thresholds were recorded for the anterior tibialis muscle bilaterally and the lumbar regions.

[a] Kratos DDK, Kratos Ltd, Sao Paulo, Brazil.

Adherence to the trial protocol

In the experimental group, three participants were not followed up at Weeks 4, 12 and 26. In the control group, two participants were not followed up at Weeks 4, 12 and 26. These five participants who were not assessed dropped out of the study during the intervention period without providing a reason. Adherence to the 10 planned treatment sessions was high in both groups, with a mean of 8.7 (SD 2.6) sessions in the experimental group and 8.8 (SD 2.5) sessions in the control group.

Effect of intervention

Both groups showed a decrease in pain intensity (Table 3). The estimate of the effect of directing manipulation at the most painful lumbar level, as compared with generic manipulation, on pain intensity was too small to be considered clinically important: MD 0 (95% CI −0.9 to 0.9) at Week 4 and −0.1 (95% CI −1.0 to 0.8) at Week 26. None of the between-group differences for any of the remaining outcomes were large enough to be considered clinically important (Tables 3 and 4). For individual participant data, see Table 5 on the eAddenda.

A total of four patients from the control group experienced temporary exacerbation of symptoms compared with no one from the experimental group.

Table 2
Baseline characteristics of participants.

Characteristic	Exp (n = 74)	Con (n = 74)
Age *(y)*, mean (SD)	45 (13)	45 (14)
Weight *(kg)*, mean (SD)	79 (15)	74 (12)
Height *(cm)*, mean (SD)	164 (9)	162 (7)
Gender, n (%)		
female	57 (77)	58 (78)
male	17 (23)	16 (2)
Symptom duration *(months)*, median (IQR)	6 (3 to 24)	6 (3 to 24)
Use of medication for back pain, n (%)	16 (22)	13 (18)
Recent exacerbation of pain, n (%)	33 (45)	39 (53)
Physically active, n (%)	14 (19)	16 (22)
Smoker, n (%)	10 (14)	8 (11)
Marital status, n (%)		
single	10 (14)	6 (8)
married	54 (73)	56 (76)
divorced	7 (10)	7 (10)
widowed	3 (4)	5 (7)
Education status, n (%)		
elementary/primary education	27 (37)	26 (35)
secondary education	29 (39)	36 (49)
undergraduate degree	16 (22)	9 (12)
postgraduate student	2 (3)	3 (4)

Discussion

This trial estimated the effects of 10 sessions of vertebral manipulation applied at a directed or generic vertebral level on pain intensity, disability, pressure pain threshold, and global perceived change in patients with chronic low back pain at 4, 12 and 26 weeks after randomisation. No clinically important differences were observed for the outcomes of pain intensity, disability, global perceived effect and pressure pain threshold. Participants in both groups experienced a large reduction in pain intensity after receiving the interventions. Baseline pain intensity was quite high and the improvements that were observed may have also been due to regression to the mean and other contextual effects that are always involved during treatment.

A strength of the present study is that 10 sessions of spinal manipulation were performed, which is more in line with clinical practice for spinal treatment; in contrast, the only study[15] that contrasted the same interventions examined the effect of only a single manipulation. Furthermore, all necessary precautions were taken to ensure that the present study had the lowest possible risk of bias, including adequate randomisation procedures, concealed allocation, a blinded assessor, similarity of groups at baseline, and intention-to-treat analysis. A weakness of the study is that it was not possible to blind the therapist, due to the nature of the interventions.

The physiological effects of vertebral manipulation are not yet fully understood. Nevertheless, there is a proposed model for a possible mechanism of effect.[42] This model suggests that a mechanical stimulus would generate neurophysiological effects that would produce symptom relief.[43] These neurophysiological effects include peripheral mechanisms, spinal cord mechanisms and supraspinal mechanisms.[42,43] Regarding the peripheral mechanisms, musculoskeletal injuries may induce inflammatory responses in the affected region, initiating a healing process that may influence pain processing. Thus, stimulation from spinal manipulation could modulate this pain processing.[42–44] With regards to spinal cord mechanisms, decreased activation of the dorsal horn of the spinal cord occurs after

Table 3
Mean (SD) for outcomes for each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

Outcome	Groups								Difference within groups				Difference between groups			
	Week 0		Week 4		Week 12		Week 26		Week 4 minus Week 0		Week 12 minus Week 0		Week 26 minus Week 0		Week 4 minus Week 0	Week 12 minus Week 0	Week 26 minus Week 0
	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp minus Con	Exp minus Con	Exp minus Con
Pain intensity *(0 to 10)*	6.3 (1.6)	6.2 (1.8)	3.3 (2.2)	3.1 (2.3)	3.6 (2.8)	3.6 (3.1)	4.4 (2.8)	4.3 (3.2)	−3.1 (2.3)	−3.1 (1.9)	−2.7 (2.8)	−2.6 (2.8)	−1.9 (3.1)	−1.8 (3.2)	0.0 (−0.9 to 0.9)	−0.1 (−1.0 to 0.8)	−0.1 (−1.0 to 0.8)
Disability *(0 to 24)*	8.8 (5.6)	8.8 (6.0)	3.4 (5.1)	3.4 (5.6)	3.7 (5.5)	3.5 (5.9)	3.4 (5.6)	4.1 (6.6)	−5.4 (4.9)	−5.4 (5.3)	−5.2 (5.6)	−5.3 (5.5)	−5.5 (6.0)	−4.7 (6.1)	0.1 (−1.7 to 1.5))	0.1 (−1.6 to 1.7)	−0.9 (−2.5 to 0.7)
Global perceived change *(−5 to 5)*[a]	−0.9 (2.2)	−0.4 (2.3)	2.4 (2.1)	3.0 (1.7)	2.4 (2.4)	2.7 (2.6)	2.7 (2.3)	2.5 (2.7)	3.4 (2.8)	3.4 (2.6)	3.4 (3.1)	3.1 (3.1)	3.6 (3.2)	2.9 (3.4)	−0.1 (−1.0 to 0.8)	0.3 (−0.7 to 1.2)	0.8 (−0.2 to 1.7)

Shaded cell = primary outcome.
Exp = experimental group, Con = control group.
[a] Global perceived change since onset of the pain.

spinal manipulation. Thus, a spinal cord stimulus would overstimulate the central nervous system with sensory stimuli from muscle proprioceptors.[42,43,45] Finally, regarding the supraspinal mechanisms, structures such as the anterior cingulate cortex, amygdala, periaqueductal grey matter and rostral ventromedial medulla modulate the pain experience. Therefore, vertebral manipulation would generate a central nervous system effect, reducing the activation of these structures.[42,43]

Regarding the specificity of vertebral manipulation, the present study shows the importance of the concept of regional interdependence.[22] This concept refers to the fact that a segment near the affected location could cause effects at a distance.[15,22] Classic examples of regional interdependence include the effects of hip strengthening when treating knee injuries,[46] thoracic manipulation for neck pain[14,18,19] and neck manipulation for patients with temporomandibular disorders.[23] Based on the current findings, it appears that there is no need to be specific about vertebral levels when applying manipulation in patients with chronic low back pain. These findings corroborate those of other studies that used thoracic spine manipulation as non-specific treatment for other conditions such as neck pain.[14,19]

This trial compared the effects of spinal manipulation in participants with non-specific chronic low back pain. Although there are studies evaluating the effect of manipulation in patients with acute and subacute low back pain,[47,48] there are still no studies comparing the effect of directed and generic manipulation in these patients. Therefore, it is unknown if the same results would have been found in participants with acute and subacute low back pain.

This study has important implications for clinical practice. Although no clinically important differences were detected, there were improvements in both pain and disability. Based on these findings, shared decision-making in the selection of treatments should be encouraged by considering either the patient's preferences and perspectives as well as the therapist's skills and preferences. Based on the results of this trial, the therapist may choose his/her preferred therapy: non-specific or specific manipulation. In the case of patients with severe low back pain, for example, the therapist's decision would be to manipulate a site away from the painful segment. Also, the therapist's ability with either technique may be considered. Therapists may choose to manipulate the patient specifically at the most affected level or not, according to the technique in which he/she is most skilled and has the most experience. Furthermore, the length of time for evaluation in the case of choosing specific manipulation should be considered. For specific vertebral manipulation, the therapist needs to perform several palpation tests that require different patient positioning. In non-specific manipulation, many of these procedures are unnecessary. With regards to patients, they may feel more comfortable with manipulation away from the painful region. Their preference can be respected by giving the option of manipulation either in the thoracic or in the lumbar spine.

Future studies are needed to evaluate the combined effect of thoracic and lumbar manipulation in patients with chronic low back pain. Finally, the mechanisms by which the improvement of patients with back pain occurs need to be further investigated, as the current model for these mechanisms is still not well explained.

What was already known on this topic: In people with chronic low back pain, the benefits of spinal manipulation may include reductions in pain and disability. Although spinal manipulation is usually applied at the most affected vertebral level, generic manipulation (ie, manipulation of a vertebral segment distant from the painful vertebral segment) can also have positive effects in some musculoskeletal conditions.

What this study adds: In people with chronic low back pain, improvements in pain, disability and global perceived effect were similar, regardless of whether spinal manipulation was applied at the most affected vertebral level or at a distant vertebral level. If spinal manipulation is to be used, selection of the vertebral level may be based on factors such as the patient's preference or the therapist's familiarity with applying manipulation at lumbar or thoracic levels.

Table 4
Mean (SD) for pressure pain threshold for each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

Pressure pain threshold *(kPa)*	Groups				Difference within groups		Difference between groups
	Week 0		Week 4		Week 4 minus Week 0		Week 4 minus Week 0
	Exp (n = 71)	Con (n = 72)	Exp (n = 71)	Con (n = 72)	Exp	Con	Exp minus Con
Lumbar	744 (346)	797 (370)	873 (382)	919 (393)	128 (331)	122 (232)	6 (−88 to 101)
Tibialis anterior	770 (337)	844 (329)	847 (354)	895 (300)	77 (257)	50 (220)	27 (−52 to 106)

Small anomalies in subtraction are due to the effects of rounding. Negative between-group differences favour the experimental group.
Con = control group, Exp = experimental group, kPa = kilopascals.

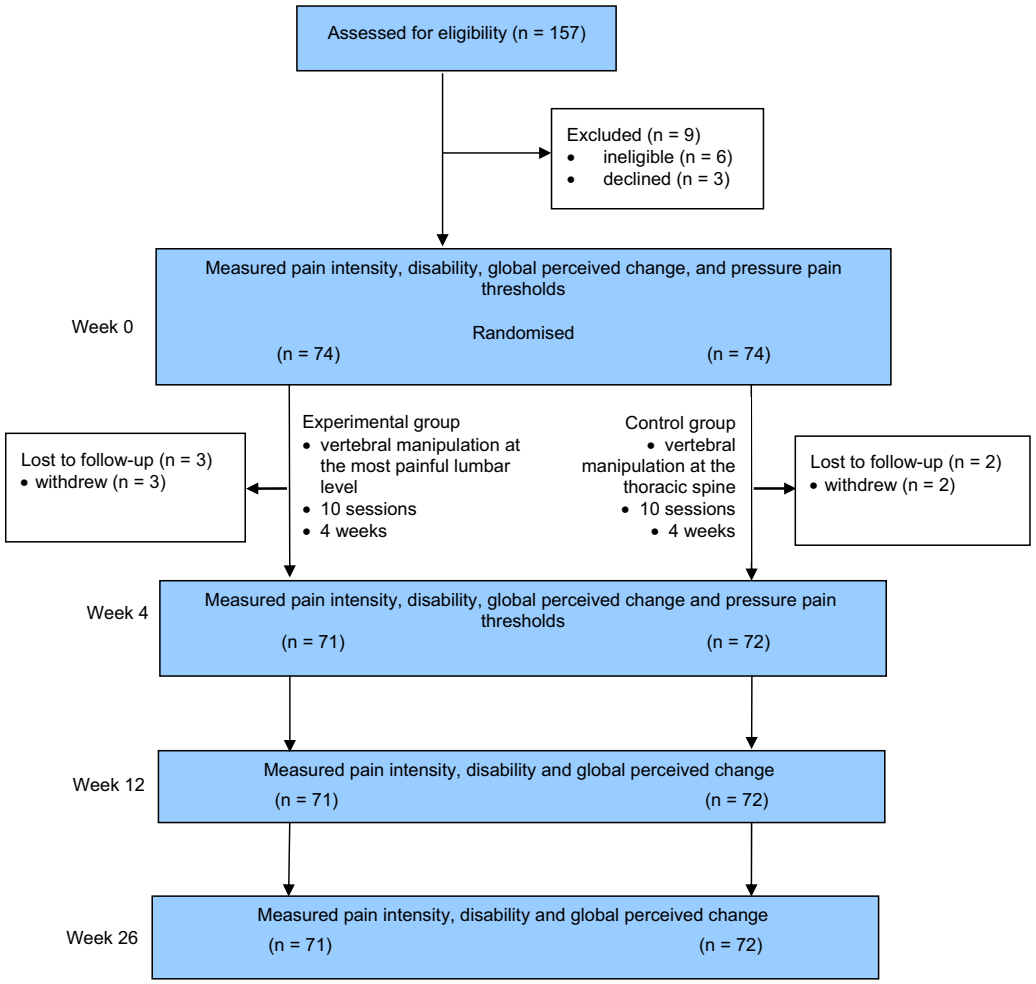

Figure 1. Flow of participants through the trial.

Footnotes: [a] SPSS® Version 19, IBM, Armonk, USA.

eAddenda: Table 5 can be found online at https://doi.org/10.1016/j.jphys.2020.06.007.

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Competing interests: Nil.

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Correspondence: Leonardo Oliveira Pena Costa, Masters and Doctoral Programs in Physical Therapy, Universidade Cidade de São Paulo, Brazil. Email: lcos3060@gmail.com

References

1. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J.* 2008;8:8–20.
2. Hush J, Elkins M. Virtual Special Issue on low back pain. *J Physiother.* 2018;64:208–209.
3. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J.* 2006;15:S192–S300.
4. Buchbinder R, van Tulder M, Oberg B, Costa LM, Woolf A, Schoene M, et al. Low back pain: a call for action. *Lancet.* 2018;391:2384–2388.
5. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. *Lancet.* 2018;391:2356–2367.

6. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet*. 2018;391:2368–2383.
7. Ferreira G, Costa LM, Stein A, Hartvigsen J, Buchbinder R, Maher CG. Tackling low back pain in Brazil: a wake-up call. *Braz J Phys Ther*. 2019;23:189–195.
8. Tegner H, Frederiksen P, Esbensen BA, Juhl C. Neurophysiological pain education for patients with chronic low back pain: a systematic review and meta-analysis. *Clin J Pain*. 2018;34:778–786.
9. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. *Spine*. 2011;36:E825–E846.
10. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2019;364:l689.
11. Senna MK, Machaly SA. Does maintained spinal manipulation therapy for chronic nonspecific low back pain result in better long-term outcome? *Spine*. 2011;36:1427–1437.
12. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CW, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J*. 2018;27:2791–2803.
13. Koes BW, van Tulder MW, Ostelo R, Kim Burton A, Waddell G. Clinical guidelines for the management of low back pain in primary care: an international comparison. *Spine*. 2001;26:2504–2513.
14. Cross KM, Kuenze C, Grindstaff TL, Hertel J. Thoracic spine thrust manipulation improves pain, range of motion, and self-reported function in patients with mechanical neck pain: a systematic review. *J Orthop Sports Phys Ther*. 2011;41:633–642.
15. de Oliveira RF, Liebano RE, Costa Lda C, Rissato LL, Costa LO. Immediate effects of region-specific and non-region-specific spinal manipulative therapy in patients with chronic low back pain: a randomized controlled trial. *Phys Ther*. 2013;93:748–756.
16. Farasyn A, Meeusen R. The influence of non-specific low back pain on pressure pain thresholds and disability. *Eur J Pain*. 2005;9:375–381.
17. Fernandez-Carnero J, Fernandez-de-las-Penas C, Cleland JA. Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia. *J Manipulative Physiol Ther*. 2008;31:675–681.
18. Gonzalez Rueda V, Lopez de Celis C, Barra Lopez ME, Carrasco Uribarren A, Castillo Tomas S, Hidalgo Garcia C. Effectiveness of a specific manual approach to the suboccipital region in patients with chronic mechanical neck pain and rotation deficit in the upper cervical spine: study protocol for a randomized controlled trial. *BMC Musculoskelet Disord*. 2017;18:384.
19. Gonzalez-Iglesias J, Fernandez-de-las-Penas C, Cleland JA, Alburquerque-Sendin F, Palomeque-del-Cerro L, Mendez-Sanchez R. Inclusion of thoracic spine thrust manipulation into an electro-therapy/thermal program for the management of patients with acute mechanical neck pain: a randomized clinical trial. *Man Ther*. 2009;14:306–313.
20. Kardouni JR, Pidcoe PE, Shaffer SW, Finucane SD, Cheatham SA, Sousa CO, et al. Thoracic spine manipulation in individuals with subacromial impingement syndrome does not immediately alter thoracic spine kinematics, thoracic excursion, or scapular kinematics: a randomized controlled trial. *J Orthop Sports Phys Ther*. 2015;45:527–538.
21. Mansilla-Ferragut P, Fernandez-de-Las Penas C, Alburquerque-Sendin F, Cleland JA, Bosca-Gandia JJ. Immediate effects of atlanto-occipital joint manipulation on active mouth opening and pressure pain sensitivity in women with mechanical neck pain. *J Manipulative Physiol Ther*. 2009;32:101–106.
22. McDevitt A, Young J, Mintken P, Cleland J. Regional interdependence and manual therapy directed at the thoracic spine. *J Man Manip Ther*. 2015;23:139–146.
23. Oliveira-Campelo NM, Rubens-Rebelatto J, Marti NVFJ, Alburquerque-Sendi NF, Fernandez-de-Las-Penas C. The immediate effects of atlanto-occipital joint manipulation and suboccipital muscle inhibition technique on active mouth opening and pressure pain sensitivity over latent myofascial trigger points in the masticatory muscles. *J Orthop Sports Phys Ther*. 2010;40:310–317.
24. Herbert R. *Practical Evidence-based Physiotherapy*. Second Edition. London, United Kingdom: Elsevier Butterworth Heinemann; 2005.
25. Costa LO, Maher CG, Latimer J, Ferreira PH, Ferreira ML, Pozzi GC, et al. Clinimetric testing of three self-report outcome measures for low back pain patients in Brazil: which one is the best? *Spine*. 2008;33:2459–2463.
26. Kuchera ML. Applying osteopathic principles to formulate treatment for patients with chronic pain. *J Am Osteopath Assoc*. 2007;107:ES28–ES38.
27. Cook CE. *Orthopedic Manual Therapy: An Evidence-Based Approach*. Second Edition. New Jersey: Pearson; 2011.
28. Ferreira ML, Ferreira PH, Latimer J, Herbert RD, Hodges PW, Jennings MD, et al. Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: a randomized trial. *Pain*. 2007;131:31–37.
29. Chiarotto A, Boers M, Deyo RA, Buchbinder R, Corbin TP, Costa LO, et al. Core outcome measurement instruments for clinical trials in nonspecific low back pain. *Pain*. 2018;159:481–495.
30. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol*. 2010;63:760–766 e761.
31. Chiarotto A, Maxwell LJ, Terwee CB, Wells GA, Tugwell P, Ostelo RW. Roland-Morris Disability Questionnaire and Oswestry Disability Index: which has better measurement properties for measuring physical functioning in nonspecific low back pain? Systematic review and meta-analysis. *Phys Ther*. 2016;96:1620–1637.
32. Costa LO, Maher CG, Latimer J, Ferreira PH, Pozzi GC, Ribeiro RN. Psychometric characteristics of the Brazilian-Portuguese versions of the Functional Rating Index and the Roland Morris Disability Questionnaire. *Spine*. 2007;32:1902–1907.
33. Nusbaum L, Natour J, Ferraz MB, Goldenberg J. Translation, adaptation and validation of the Roland-Morris questionnaire - Brazil Roland-Morris. *Braz J Med Biol Res*. 2001;34:203–210.
34. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. *Pain*. 1987;30:115–126.
35. Kinser AM, Sands WA, Stone MH. Reliability and validity of a pressure algometer. *J Strength Cond Res*. 2009;23:312–314.
36. O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J*. 2011;20:2120–2125.
37. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. *Nat Rev Rheumatol*. 2010;6:599–606.
38. Costa LOP, Maher CG, Latimer J, Hodges PW, Herbert RD, Refshauge KM, et al. Motor control exercise for chronic low back pain: a randomized placebo-controlled trial. *Phys Ther*. 2009;89:1275–1286.
39. Macedo LG, Latimer J, Maher CG, Hodges PW, McAuley JH, Nicholas MK, et al. Effect of motor control exercises versus graded activity in patients with chronic nonspecific low back pain: a randomized controlled trial. *Phys Ther*. 2012;92:363–377.
40. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. *J Clin Epidemiol*. 2002;55:329–337.
41. Herbert R. Research Note: Significance testing and hypothesis testing: meaningless, misleading and mostly unnecessary. *J Physiother*. 2019;65:178–181.
42. Bialosky JE, Beneciuk JM, Bishop MD, Coronado RA, Penza CW, Simon CB, et al. Unraveling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther*. 2018;48:8–18.
43. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009;14:531–538.
44. Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *J Manipulative Physiol Ther*. 2006;29:14–21.
45. Pickar JG, Wheeler JD. Response of muscle proprioceptors to spinal manipulative-like loads in the anesthetized cat. *J Manipulative Physiol Ther*. 2001;24:2–11.
46. Fukuda TY, Rossetto FM, Magalhaes E, Bryk FF, Lucareli PRG, de Almeida Carvalho NA. Short-term effects of hip abductors and lateral rotators strengthening in females with patellofemoral pain syndrome: a randomized controlled clinical trial. *J Orthop Sports Phys Ther*. 2010;40:736–742.
47. Schneider M, Haas M, Glick R, Stevans J, Landsittel D. Comparison of spinal manipulation methods and usual medical care for acute and subacute low back pain: a randomized clinical trial. *Spine*. 2015;40:209–217.
48. Paige NM, Miake-Lye IM, Booth MS, Beroes JM, Mardian AS, Dougherty P, et al. Association of spinal manipulative therapy with clinical benefit and harm for acute low back pain: systematic review and meta-analysis. *JAMA*. 2017;317:1451–1460.