Autonomic Effects of Spinal Manipulative Therapy: Systematic Review of Randomized Controlled Trials

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Abstract

Objective: The purpose of this study was to systematically review the effects of spinal manipulative therapy (SMT) on autonomic nervous system (ANS)-mediated outcomes, in both symptomatic and healthy populations, and to assess the quality of evidence for the most prevalent outcomes with the Grading of Recommendations, Assessment, Development and Evaluation approach.

Methods: PubMed, Cochrane Library, PEDro, Web of Science, and EMBASE were searched from their inception to March 2014. Randomized controlled trials involving SMT, such as mobilization and manipulation, that reported at least 1 outcome related to the ANS, with placebo, control groups, or other SMT techniques as comparators, with either healthy or symptomatic samples were included. The Physiotherapy Evidence Database scale and the Grading of Recommendations, Assessment, Development and Evaluation approach were used to assess risk of bias and the quality of evidence, respectively.

Results: Eighteen trials were included in this systematic review. Passive accessory intervertebral mobilization produced sympathoexcitation independently of the treated region (cervical, thoracic, or lumbar spine); although sustained natural apophyseal glides did not influence the ANS, conflicting results were observed regarding manipulation techniques. The overall quality of evidence for all analyzed outcomes ranged from low to very low quality.

Conclusion: There is evidence pointing toward the existence of sympathoexcitatory short-term effects following passive accessory intervertebral mobilization mobilizations, but not for sustained natural apophyseal glide mobilizations. There is conflicting evidence regarding the ability of manipulation to elicit sympathoexcitation. However, the low quality of the evidence precludes a definitive conclusion of such effects. Based on the current evidence, there is uncertainty regarding the true effect estimates of SMT on ANS-mediated outcomes. (J Manipulative Physiol Ther 2019;42:623-634)

Key Indexing Terms: *Autonomic Nervous System; Manipulation, Spinal; Systematic Review*

Introduction

Spinal manipulative therapy (SMT) is widely used in the management of multiple musculoskeletal conditions. For this purpose, a number of SMT approaches have been developed, including manipulation (MANIP) techniques and mobilization (MOB) techniques.[1,2]

Whereas high-velocity, low-amplitude, and grade V manipulation are described as MANIP techniques, passive accessory intervertebral mobilization (PAIVM) techniques, Sustained Natural Apophyseal Glides (SNAGS) and Natural Apophyseal Glides (NAGS) are within the scope of MOB techniques.[1,3,4] Recent evidence has shown that both MOB (PAIVM and SNAGS) and MANIP induce positive clinical effects in patients with neck pain,[5] cervicogenic dizziness,[6] cervicogenic headache,[7] and low back pain.[8-11]

It is currently recognized that the clinical effects of SMT are deemed to be mediated by peripheral, spinal, and supraspinal mechanisms.[12] A body of evidence suggests that the activity of the sympathetic nervous system plays a role in the cascade of neurophysiological events that lead to SMT-induced hypoalgesia.[13-26] According to these studies, SMT delivered to the vertebral column would generate a

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rapid hypoalgesic effect owing to the activation of descending pain pathways projecting from the dorsal periaqueductal gray area, which, in turn, would be responsible for eliciting sympathoexcitation.[27]

Several outcomes that indirectly measure the ANS function have been reported in randomized controlled trials, such as skin conductance (SC), skin temperature (ST), and heart rate (HR). Although increased SC and HR denotes enhanced activity of the sympathetic nervous system,[13,18-21] increased ST denotes upregulation of the parasympathetic nervous system.[13,18,20,21] Although a growing number of studies have found that SMT indeed affects the ANS, there is no established consensus regarding the ability of such techniques to modulate autonomic activity and whether this effect is responsible for the observed clinical benefits. A systematic review has demonstrated increased sympathetic activity concurrently with hypoalgesic effects after SMT.[15] Nonetheless, this review included only studies that performed MOB at the cervical spine. The latest systematic review on the effect of SMT on sympathetic nervous system[28] gave some important insights into the role of vertebral MOB on sympathoexcitation in both healthy and symptomatic populations. However, studies investigating the effects of MANIP were excluded. Moreover, some methodological aspects must be highlighted: a best-evidence synthesis approach based solely on risk of bias of individual study assessments was used to determine the level of evidence. This is not in line with current recommendations from the Cochrane Collaboration, which defines the quality of evidence based not only on the interaction between risk of bias, but also directness of evidence, precision of effect estimates, consistency of results among individual studies, and risk of publication bias.[29,30] Therefore, the method used for estimating the level of evidence might have overestimated the findings. Furthermore, outcomes were not assessed individually; rather, the level of evidence was determined based on a composite of the available outcomes in each study. Besides, by adopting this approach, it is impossible to determine whether the outcomes have similar behaviors among different conditions and interventions, which is of special interest in a systematic review.

The purpose of this study was to systematically review the effects of both MOB (PAIVM and SNAGS) and MANIP techniques versus controls on ANS-mediated outcomes in randomized controlled trials that assessed both symptomatic and healthy populations.

Methods

Literature Search Strategy

This systematic review followed the Preferred Reporting Item for Systematic Reviews and Meta-Analyses recommendations[31] and was prospectively registered at the International Prospective Register of Systematic Reviews (registration number: CRD42014008747). Five electronic databases (PubMed, Cochrane Library, PEDro, Web of Science, and EMBASE) were searched from their inception to March 2014. The search strategy for PubMed is depicted in Appendix A. The reference list of each included study was also screened. There were no language or geographic restrictions in the search strategy, but only studies in English, Spanish, or Portuguese were included in the analysis.

Eligibility Criteria

Only randomized controlled trials were included in this review. Studies should report at least 1 outcome related to the autonomic nervous system. Studies with either healthy or symptomatic samples were included. All types of manual techniques applied to the spinal column were included, including MOB (PAIVM, natural apophyseal glides, and SNAGS) and MANIP techniques.

Studies were excluded if the intervention technique was not clearly applied to the spinal column, if the technique was not specifically directed to spinal joints (eg, myofascial release), if an apparatus was used to perform the technique (ie, if the technique was instrument-assisted), and if the full-text paper was not available. When the full-text article could not be retrieved, the authors were contacted via e-mail and the paper was requested. Papers whose authors did not reply were excluded.

Study Selection

Two independent reviewers (F.X.A. and R.F.A.) selected the studies to be included according to the eligibility criteria described earlier. After the electronic search, titles and abstracts were screened and, when relevant, the full paper was read. Differences were solved by consensus. When consensus was not reached, a third author arbitrated (G.E.F).

Data Extraction

Data were extracted independently by 2 investigators (F.X.A. and R.F.A.) and inputted to a standardized spreadsheet (Table 1). Author, year, sample size, experimental procedure, comparators, and outcomes were extracted from each study. Extracted data were double-checked by each reviewer. Differences were solved by consensus. A third reviewer (G.E.F) was consulted in the absence of consensus.

Risk of Bias Assessment

The Physiotherapy Evidence Database (PEDro) scale, which is an 11-item scale designed for rating risk of bias of

randomized controlled trials, was used. Each satisfied item (except for item 1, which, unlike other scale items, pertains to external validity and is not included in the final score) contributes 1 point to the total score.[32] This instrument has shown a fair to good reliability,[32] with an intraclass correlation coefficient ranging from 0.68[32] to 0.91[33] and is a useful instrument to measure the methodological quality of physical therapy trials.[34] The rating was performed independently by 2 reviewers (F.F.S and G.E.F). Disagreements were solved by consensus.

Data Analysis and Quality of Evidence

Owing to marked heterogeneity between outcome measures, comparators, reporting methods, and interventions among studies, meta-analysis was not possible. Therefore, a descriptive approach was adopted. To compare treatment effects, only immediate post-treatment comparisons were considered for analysis. In studies that performed more than 1 treatment session, only values recorded after the first session were considered.

The overall quality of evidence for each individual outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach,[35] as suggested by the Cochrane Collaboration[36] and as realized previously.[37] In this assessment tool, the overall evidence was downgraded depending on the presence of[1] within-study limitations (risk of bias),[2] inconsistency of results (heterogeneity),[3] indirectness of evidence (conclusions drawn based on indirect populations, interventions, comparators, or outcomes),[4] imprecision of the effect estimates (inadequate descriptive statistics to determine results precision), and[5] risk of publication bias. Additionally, 3 factors could increase the quality of evidence[1]: large magnitude effect across studies,[2] presence of a dose-response gradient, and[3] all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect.

Following the GRADE working group recommendations, the decision to downgrade the quality of the evidence for a given outcome owing to risk of bias was not based on the quantitative results of the PEDro scale[30]; rather, the judgment process involved the assessment of individual items in relation to a particular outcome. When an outcome was assessed by only 1 study, the overall quality was initially considered to be low and the presence of high risk of bias downgraded the quality of evidence to very low.

For each individual outcome, 4 levels of quality could be attributed: high, moderate, low, and very low. In high-quality evidence, there are consistent, direct, and precise findings among at least 75% of the participants from studies with low risk of bias and with no suspected publication bias. In this scenario, further research is unlikely to change either the estimate or confidence in the results. In moderate evidence, 1 of the domains is not met and further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. In low-quality evidence, 2 of the domains are not met and further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. In very low-quality evidence, 3 of the domains are not met and the results are very uncertain.

Results

Description of Studies

Between February and March 2014, the electronic search returned 2065 titles. After elimination of 81 duplicates, 1984 titles were screened for eligibility. Of these, 1960 were excluded after title and abstract reading. Twenty-four trials were selected for full-text read, among which 10 studies were excluded.[38-47] Reference lists of selected papers yielded 4 additional references and, therefore, 18 trials were included in this systematic review. The flow diagram is depicted in Figure 1. Included trials were conducted between 1993 and 2013, comprising a total of 1055 participants. Spinal manipulative therapy was delivered to the cervical spine in 10 studies,[13,18,20,25,26,48-52] in the thoracic spine in 5 studies,[19,53-56] and in the lumbar spine in 3 trials.[21,24,57] Ten trials had a crossover design with adequate washout period.[18,20,25,26,48,50-53,56] Three studies comprised a symptomatic population,[13,25,55] and 15 studies were conducted with asymptomatic participants.[18-21,24,26,48-54,56,57] Mobilization techniques were performed in 12 studies,[13,18-21,24-26,50-52,56] and MANIP techniques were performed in 6 trials.[48,49,53-55,57] Two studies[48,53] were not included in the quality assessment because between-group comparisons were lacking, and 1 study[57] compared SMT (lumbar manipulation at the L4-L5 segment) to another intervention (McKenzie's lumbar extension exercise).

Effect of MOB Techniques Versus No Treatment. Skin conductance was assessed in healthy participants in 7 trials (n = 302).[18,20,21,24,51,52,56] Two trials[21,21] did not find statistically significant differences between PAIVM MOB and control groups, and 5 trials[18,24,51,52,56] demonstrated that the intervention significantly increased SC compared with no treatment. There is very low-quality evidence (GRADE) that PAIVM MOB increased SC (ie, promoted sympathoexcitation) compared with no treatment in healthy participants (Table 2). A single study[25] with low risk of bias demonstrated that SC significantly increased in patients with neck pain compared to a control group. There is low-quality evidence (GRADE) that PAIVM MOB increased SC compared to no treatment in patients with neck pain (Table 2).

Five trials[18,20,51,52,56] (n = 208) investigated the effect of PAIVM MOB on ST in healthy participants. Most trials

Table 1. *Summary of Included Studies*

Author (Year)	Participants	N (IG/CG/PG)	Study Design	Region	Intervention Group	Comparison Group	ANS-Mediated Outcome	PEDro SCORE	Results
La Touche et al (2013)[13]	Patients with chronic craniofacial pain	32 (16/16)	RCT	Upper cervical (C0-C3)	AP upper cervical PAIVM MOB; 0.5Hz	Placebo	SC, ST, HR, RR	9	SC: PAIVM MOB > Placebo (increase) ST: PAIVM MOB = Placebo HR: PAIVM MOB > Placebo (increase) RR: PAIVM MOB > Placebo
Puhl et al (2012)[54]	Asymptomatic	36 (18/18)	RCT	Upper thoracic (T1-T6)	Thoracic MANIP	Placebo	ENPC	6	ENPC: MANIP = Placebo
Moutzouri et al (2012)[21]	Asymptomatic	45 (15/15/15)	RCT	Lumbar (L4)	L4 SNAG MOB	Placebo/control	SC	7	SC: SNAG MOB = Placebo = Control
Perry et al (2011)[57]	Asymptomatic	50 (25/25)	RCT	Lumbar (L4-L5)	Lumbar L4-L5 MANIP	McKenzie's lumbar extension exercise	SC	6	SC: MANIP > Control (increase)
Sillevis et al (2010)[55]	Patients with chronic neck pain	100 (50/50)	RCT	Thoracic (T3-T4)	Upper thoracic (T3-T4) MANIP	Placebo	PD	4	PD: MANIP > Placebo (decrease)
Jowsey and Perry (2010)[19]	Asymptomatic	36 (18/18)	RCT	Thoracic (T4)	Grade III rotatory PA T4 PAIVM MOB; 0.5 Hz	Placebo	SC	7	SC: PAIVM MOB > Placebo (increase; side-specific)
Perry and Green (2011)[57]	Asymptomatic	45 (15/15/15)	RCT	Lumbar (L4-L5)	Grade III unilateral PA PAIVM MOB; Left L4-L5 facet joint; 2 Hz	Placebo/control	SC	9	SC: PAIVM MOB = Placebo = Control
Moulson et al (2006)[20]	Asymptomatic	48 (16/16/16) [a]	RCT (cross-over)	Cervical (C5-C6)	C5-C6 SNAG MOB	Placebo/control	SC, ST	7	SC: SNAG MOB = Placebo > Control (increase) ST: SNAG MOB = Placebo = Control (increase)
Budgell and Polus (2006)[53]	Asymptomatic	56 (28/28) [a]	RCT (cross-over)	Upper thoracic (T1-T4)	Prone upper thoracic MANIP	Placebo	HR, HRV	3	No intergroup comparison HR: Decrease in MANIP and placebo; HRV (absolute; LF; LF/HF): Decrease in MANIP and placebo HRV (normalized); decrease in MANIP
Gosling et al (2005)[49]	Asymptomatic	30 (10/10/10)	RCT	Upper cervical (C1-C2)	Right side MANIP	Left side MANIP/control	ELPCT	4	ELPCT: MANIP > Control (side-specific; decrease)

Sterling et al (2001)[25]	Patients with mid-lower neck pain	90 (30/30/30) [a]	RCT (cross-over)	Cervical (C5-C6)	Grade III PA C5-C6 PAIVM MOB	Placebo/control	SC, CT	7	SC: PAIVM MOB > Placebo/Control (increase) ST: PAIVM MOB > Placebo/control (decrease)
Budgell and Hirano (2001)[48]	Asymptomatic	48 (24/24) [a]	RCT (cross-over)	Upper cervical (C1-C2)	Supine upper cervical rotatory MANIP (C1-C2)	Placebo	HR, HRV	3	No intergroup comparison HR: MANIP = Placebo HRV (normalized; absolute; LF/HF): MANIP > Placebo (increase)
Vicenzino et al (1998)[26]	Asymptomatic	72 (24/24/24) [a]	RCT (cross-over)	Cervical (C5-C6)	Grade III C5 left lateral glide PAIVM MOB	Placebo/control	HR, RR, BP	5	HR: PAIVM MOB > Placebo/Control RR: PAIVM MOB > Placebo/Control BP: PAIVM MOB > Placebo/Control
McGuiness et al (1997)[50]	Asymptomatic	69 (23/23/23) [a]	RCT (cross-over)	Cervical (C5)	Grade III central PA C5 PAIVM MOB	Placebo/control	HR, RR, BP	5	HR: PAIVM MOB > Placebo/Control (increase) RR: PAIVM MOB > Placebo/Control (increase) BP: PAIVM MOB > Placebo/Control (increase)
Chiu and Wright (1996)[18]	Asymptomatic	48 (16/16/16) [a]	RCT (cross-over)	Cervical (C5)	Grade III central PA C5 2Hz PAIVM MOB	Grade III central PA C5 0.5Hz PAIVM MOB/ control	SC, ST	5	SC: PAIVM MOB > Control ST: PAIVM MOB = Control
Vicenzino et al (1994)[52]	Asymptomatic	136 (34/34/34/34) [a]	RCT (cross-over)	Cervical (C5-C6)	Grade III left lateral glide C5-C6 2HZ PAIVM MOB; Right upper limb in ULNTT1 (LG1)	Grade III left lateral glide C5-C6 2HZ PAIVM MOB; Right upper limb in ULNTT2b (LG2b)/Placebo/ control	SC, ST	5	SC: PAIVM MOB > Placebo/Control (increase) ST: PAIVM MOB = Placebo = Control
Slater et al (1994)[56]	Asymptomatic	66 (22/22/22) [a]	RCT (cross-over)	Thoracic (T6)	Grade IV unilateral PA T6 PAIVM MOB in Sympathetic Slump	Placebo/control	SC, ST	5	SC: PAIVM MOB > Placebo/Control (increase) ST: PAIVM MOB = Placebo > Control (decrease)

Note. ">" denotes that there were statistically significant differences for a treatment arm; "=" denotes that there were no significant differences among treatment arms.

ANS, autonomic nervous system; *AP*, anteroposterior; *BP*, blood pressure; *CG*, control group; *ELPCT*, edge light pupil cycle time; *ENPC*, epinephrine, norepinephrine plasma concentration; *HR*, heart rate; *HRV*, heart rate variability; *IC*, intervention group; *LF/HF*, low-frequency/high-frequency ratio; *MANIP*, manipulation; *MOB*, mobilization; *PAIVM*, passive accessory intervertebral mobilization; *PC*, placebo group; *PD*, pupil diameter; *RCT*, randomized controlled trial; *RR*, respiratory rate; *SC*, skin conductance; *SNAG*, Sustained Natural Apophyseal Glide; *ST*, skin temperature; *ULNTT*, upper limb neural tension test.

[a] Number of experimental conditions in crossover trials.

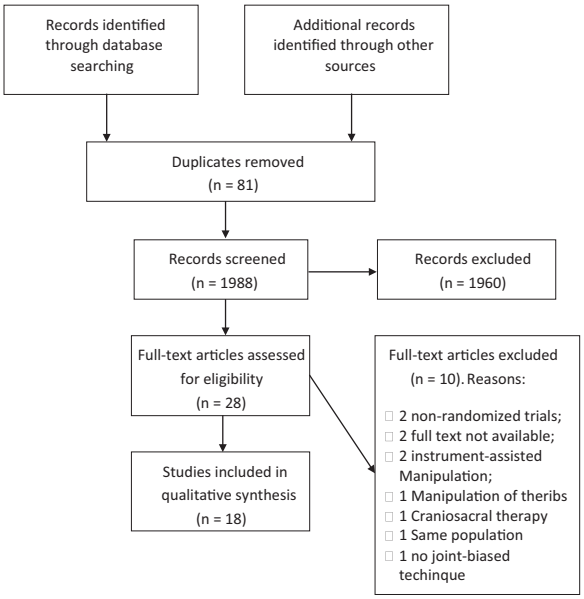

Fig 1. *Preferred Reporting Item for Systematic Reviews and Meta-Analyses flow diagram.*

reported no significant difference between PAIVM MOB and control in altering ST. There is very low-quality evidence (GRADE) that PAIVM MOB did not change ST compared to no intervention in healthy individuals (Table 2). A single trial with low risk of bias[25] reported a significant decrease in ST (ie, promoted sympathoexcitation) in the treatment group compared to no treatment in patients with neck pain. There is low-quality evidence (GRADE) that PAIVM MOB significantly decreased ST compared to no intervention in individuals with neck pain (Table 2). Two studies[26,50] (n = 94) reported a significant increase in HR (ie, promoted sympathoexcitation) following PAIVM MOB compared to no treatment. There is low-quality evidence (GRADE) that PAIVM MOB increased HR in healthy individuals (Table 2).

Effect of MOB Techniques Versus Placebo. The effects of MOB techniques compared to placebo were investigated in 9 trials[19-21,24,26,50-52,56] conducted in healthy individuals (n = 366), 1 trial carried out in patients with craniofacial pain,[13] (n = 32) and 1 trial[25] in patients with neck pain (n = 60). The effect of MOB in SC was analyzed in 7 studies (n = 306).[19-21,24,51,52,56] Four trials[19,51,52,56] found a significant increase in SC for PAIVM MOB group compared to placebo, whereas no differences were found in 1 trial.[24] Overall, there is low-quality evidence (GRADE) that SC is significantly increased immediately after PAIVM MOB techniques compared with placebo in healthy individuals (Table 3). Sustained natural apophyseal glides MOB did not change ST compared with placebo in 2 trials.[20,21] There is low-quality evidence that SNAGS MOB did not affect SC in healthy individuals (Table 3). One study with low risk of bias[13] found significantly increased SC after treatment compared with placebo in patients with craniofacial pain. There is low-quality evidence (GRADE) that PAIVM MOB significantly increased SC in patients with craniofacial pain. A single study in patients with neck pain[25] with low risk of bias found a significant increase in SC in comparison to placebo. Evidence that PAIVM MOB significantly increased SC in patients with neck pain compared with placebo was rated as low-quality (GRADE) (Table 3).

Four trials[20,51,52,56] (n = 210) investigated whether MOB influenced ST compared with placebo. All trials failed to detect significant differences between MOB and placebo for this outcome. There is very low-quality evidence (GRADE) that PAIVM and SNAG MOB did not significantly change ST compared to placebo in healthy individuals (Table 3). A single study[13] including patients with craniofacial pain did not find significant differences between PAIVM MOB and placebo groups. There is low-quality evidence (GRADE) that PAIVM MOB did not significantly change ST compared to placebo (Table 3). A single study[25] on participants with neck pain reported a decrease in ST in the PAIVM MOB group compared to placebo. There is low-quality evidence (GRADE) that PAIVM MOB decreased ST in patients with neck pain compared to placebo (Table 3).

HR was investigated in 2 studies with healthy volunteers,[26,50] and 1 study[13] performed in patients with craniocervical pain. In healthy participants (n = 94), PAIVM MOB significantly increased HR compared to placebo. There is low-quality evidence (GRADE) that PAIVM MOB increased HR compared to placebo (Table 3). There is also low-quality evidence (GRADE) from a trial with a low risk of bias[25] that PAIVM MOB increased HR in patients with craniofacial pain (Table 3).

The Effect of MANIP Versus No Treatment. Only 1 study compared MANIP with no treatment in healthy persons.[49] This single study (n = 30), with high risk of bias, demonstrated a significant decrease in edge light pupil cycle time. There is very low-quality evidence (GRADE) that MANIP decreased edge light pupil cycle time in healthy participants (Table 4).

The Effect of MANIP Versus Placebo. One study[54] (n = 36) found that MANIP did not result in significant differences compared to placebo for epinephrine and norepinephrine plasma concentration. There is low-quality evidence (GRADE) that MANIP did not change plasma concentrations of epinephrine and norepinephrine (Table 5).

An individual study[55] (n = 100) assessed the effects of MANIP on pupil dilation in patients with chronic neck pain and found that MANIP did not significantly alter the outcome, whereas participants in the placebo group showed a significant decrease in pupil diameter (ie, parasympathetic excitation). There is low-quality evidence

Table 2. *Mobilization Versus No Treatment*

Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Direction of Outcome
Skin conductance (healthy)							
302 (7 RCTs)	Serious [a]	Serious [b]	Not serious	Serious [c]	None	Very low	Increase
Skin conductance (neck pain)							
60 (1 RCT)	Not serious	-	-	-	-	Low	Increase
Skin temperature (healthy)							
208 (5 RCTs)	Serious [a]	Serious	Not serious	Serious [c]	None	Very low	No change
Skin temperature (neck pain)							
60 (1 RCT)	Not serious	-	-	-	-	Low	Decrease
Heart rate variability (healthy)							
94 (2 RCTs)	Serious [a]	Not serious	Not serious	Serious [c]	None	Very low	Increase

RCT, randomized controlled trial.
[a] Most studies did not grant allocation concealment nor provide information regarding group comparisons at baseline.
[b] Two trials (30%) reported nonsignificant findings.
[c] More than 40% of the included studies did not provide adequate descriptive statistics to determine the precision of the results.

(GRADE) indicating that MANIP did not alter pupil diameter (Table 5).

Discussion

This systematic review aimed to summarize the current evidence of the effects of SMT on ANS-mediated outcomes. This is the first systematic review on this topic that used the GRADE approach to determine the quality of evidence for each individual outcome. The results of this review indicate that, when compared to control interventions, PAIVM MOB induced sympathoexcitation. This is suggested by the fact that PAIVM MOB increased SC and HR in healthy volunteers. Compared to placebo, PAIVM MOB increased SC, while no effect was observed in studies that performed SNAGS MOB. It was also observed that ST did not change in healthy participants and in patients with craniofacial pain, but decreased in patients with chronic neck pain. Moreover, HR increased in both healthy participants and patients with craniofacial pain, evincing the occurrence of sympathoexcitation. Manipulation compared to no intervention resulted in decreased edge light pupil cycle time, whereas MANIP compared to placebo demonstrated no effect on epinephrine and norepinephrine plasma concentration and pupil dilation.

Previous systematic reviews have suggested that spinal mobilization produces sympathoexcitation.[15,28] Similarly, our results indicate that PAIVM MOB indeed promotes sympathoexcitation. However, unlike previous studies, this review demonstrated that there were conflicting results regarding the ability of MANIP to elicit sympathoexcitation, and that SNAGS MOB consistently did not influence the ANS.

At the present time, the long-term effects of SMT on ANS-mediated outcomes have not been studied yet. La Touche et al[13] analyzed the immediate effects on clinical and ANS-related outcomes after each of the 3 treatment sessions. The authors demonstrated progressive improvement in the visual analog scale and pressure pain threshold, but no increments were noted for SC, HR, and ST during the subsequent sessions. The results of this study indicate that sympathoexcitation may be a transient occurrence not linked to the clinical improvements observed between sessions.

In a recent review by Kingston et al,[28] strong evidence that PAIVM MOB promotes sympathoexcitation was shown, but the quality of the evidence was based solely on risk of bias of individual studies. Concomitantly, due to the adopted cutoff of 6 points in the PEDro scale, all the included studies were classified as having low risk of bias. The use of the PEDro scale as the sole instrument to determine the quality of the evidence may overestimate inferences and conclusions of systematic reviews and meta-analyses.[58] Moreover, this approach is not recommended by the Cochrane Collaboration,[29] which advocates a domain-based evaluation with open and systematic judgment, in which subjectivity plays an important role.[29,36] In our review, the absence of capital items in several included studies, such as allocation concealment and blinding of the outcome assessor (88% and 39% of the included studies did not grant allocation concealment and blinding of the outcome evaluator, respectively) was determinant to downgrade the quality of evidence due to high risk of bias.

Several issues in individual studies precluded pooling of the results, such as the absence of adequate reporting of

Table 3. *MOB Versus Placebo*

Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Direction of Outcome
Skin conductance (healthy)							
210 (5 RCTs) PAIVM MOB	Serious [a]	Not serious	Not serious	Serious [2]	None	Low	Increase
62 (2 RCTs) SNAG MOB	Serious [a]	Not serious	Not serious	Serious [b]	None	Low	No change
Skin conductance (craniofacial pain)							
32 (1 RCT)	Not serious	-	-	-	-	Low	Increase
Skin conductance (neck pain)							
60 (1 RCT)	Not serious	-	-	-	-	Low	Increase
Skin temperature (healthy)							
144 (3 RCTs) PAIVM MOB	Serious [a]	Not serious	Not serious	Serious [b]	None	Very low	No change
32 (1 RCT) SNAG MOB	Serious [a]	Not serious	Not serious	Serious [b]	None	Very low	No change
Skin temperature (craniofacial pain)							
32 (1 RCT)	Not serious	-	-	-	-	Low	No change
Skin temperature (neck pain)							
60 (1 RCT)	Not serious	-	-	-	-	Low	Decrease
Heart rate (healthy)							
94 (2 RCTs)	Serious [c]	Not serious	Not serious	Not serious	None	Low	Increase
Heart rate (craniofacial pain)							
32 (1 RCT)	Not serious	-	-	-	-	Low	Increase

MOB, mobilization; *PAIVM*, passive accessory intervertebral mobilization; *RCT*, randomized controlled trial; *SNAG*, Sustained Natural Apophyseal Glide.

[a] Most studies (40%) did not grant allocation concealment nor provide information regarding group comparisons at baseline.

[b] More than 40% of the included studies did not provide adequate descriptive statistics to determine the precision of the results.

[c] No study performed concealed allocation nor report baseline group comparisons.

Table 4. *Manipulation Versus No Treatment*

Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Direction of Outcome
Edge light pupil cycle time (healthy)							
20 (1 RCT)	Serious [a]	-	-	-	-	Very low	Decrease

RCT, randomized controlled trial.

[a] Most did not grant concealed allocation nor outcome assessor blinding.

point and variability measures,[18,25,26,51,56] and data presented only in mean differences within and between groups.[19,20,21,57] Inadequate reporting makes the interpretation of studies difficult if not impossible.[34] The inappropriateness of pooling due to poor reporting downgraded the evidence for imprecision in several outcomes.[36]

Implications for Future Research

More studies with high methodological quality and proper data reporting are necessary. Future research should address patient samples with long-term follow-up, which might provide more relevant insights into the role of SMT-related sympathoexcitation in clinical outcomes.

Table 5. *Manipulation Versus Placebo*

Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Direction of Outcome
Norepinephrine/epinephrine plasmatic concentration (healthy)							
36 (1 RCT)	Not serious	-	-	-	-	Low	No change
Pupil diameter (chronic neck pain)							
100 (1 RCT)	Serious [a]	-	-	-	-	Very low	No change

RCT, randomized controlled trial.
[a] Did not grant outcome assessor blinding.

In this sense, within-variables correlation would be a suitable approach to determine the amount as well as the direction of the relation between these outcomes. Another ANS-mediated outcome, such as the HR variability, should be addressed in future studies, since it provides consistent information on either sympathetic or vagal activity.[59] Future studies should also report accuracy measures, such as the standard error of measurement. For instance, only 2 included studies explicitly reported standard error of measurement values.[19,20] This will aid readers in determining whether or not the reported results can be explained by the experimental manipulation itself (ie, the treatment provided). Finally, future studies should directly compare ANS effects of MOB and MANIP in addition to the effects of different manual therapy approaches.

Limitations

This systematic review has some limitations. Fifteen of the 18 included trials enrolled asymptomatic participants, and consequently, generalization to clinical populations is limited. The language restriction in inclusion criteria defined a priori could be pointed to as a source of selection bias. However, our search strategy did not find any randomized controlled trial assessing the effect of SMT on ANS-mediated outcomes published in languages other than English. The marked heterogeneity between outcome measures, comparators, reporting methods, and interventions among studies prevented the realization of meta-analysis. Moreover, as many studies reported only percentage of change and the variability measurements were poorly reported, it was impossible to report point estimates and 95% confidence intervals for each outcome of each study.

Conclusion

There is evidence pointing toward the existence of short-term sympathoexcitatory effects following PAIVM MOB, but not for SNAGS MOB. There is conflicting evidence regarding the ability of MANIP to elicit sympathoexcitation. It is unwise to draw conclusions about the true effect exerted by SMT on ANS-mediated outcomes, given the low to very low quality of evidence. Future studies must reduce risk of bias by adopting simple and achievable procedures, such as allocation concealment and blinding of the outcome assessor. Enhancing the quality of individual studies will improve the confidence on effect estimates and provide more accurate insights into the mechanisms of SMT.

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Contributorship Information

Concept development (provided idea for the research): F.X.A., G.E.F., R.F.A., F.F.S., R.D.M.P., M.F.S.
Design (planned the methods to generate the results): F.X.A., G.E.F.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): F.X.A., G.E.F.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): F.X.A., G.E.F., R.F.A., F.F.S.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): F.X.A., G.E.F., F.F.S.
Literature search (performed the literature search): F.X.A., R.F.A.
Writing (responsible for writing a substantive part of the manuscript): F.X.A., G.E.F.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): F.X.A., G.E.F., R.D.M.P., M.F.S.

Appendix A. PubMed Search Strategy

Outcome

((((“autonomic nervous system”[MeSH Terms] OR (“autonomic” All Fields] OR “nervous”[All Fields] OR “system”[All Fields]) OR “autonomic nervous system”[All Fields]) OR (“sympathetic nervous system"[MeSH Terms] OR (“sympathetic”[All Fields] OR “nervous”[All Fields] OR “system”[All Fields]) OR “sympathetic nervous system”[All Fields]) OR (“parasympathetic nervous system”[MeSH Terms] OR (“parasympathetic”[All Fields] OR “nervous”[All Fields] OR “system”[All Fields]) OR “parasympathetic nervous system”[All Fields]))

Intervention

((“manipulation, spinal”[MeSH Terms] OR (“manipulation”[All Fields] OR “spinal” All Fields]) OR “spinal manipulation"[All Fields] OR (“spinal”[All Fields] OR “manipulation”[All Fields])) OR (Spinal[All Fields] OR “mobilisation”[All Fields])) OR (“musculoskeletal manipulations”[MeSH Terms] OR (“musculoskeletal”[All Fields] OR “manipulations"[All Fields]) OR “musculoskeletal manipulations”[All Fields] OR (“manual”[All Fields] OR “therapy”[All Fields]) OR “manual therapy”[All Fields])))

Problem

((“cervical vertebrae”[MeSH Terms] OR (“cervical”[All Fields] OR “vertebrae”[All Fields]) OR “cervical vertebrae”[All Fields] OR (“cervical”[All Fields] OR “spine”[All Fields]) OR “cervical spine” [All Fields]) OR ((“thorax” [MeSH Terms] OR “thorax"[All Fields] OR “thoracic"[All Fields]) OR (“spine”[MeSH Terms] OR “spine”[All Fields])) OR (“lumbar vertebrae”[MeSH Terms] OR (“lumbar”[All Fields] OR “vertebrae”[All Fields]) OR “lumbar vertebrae”[All Fields] OR (“lumbar”[All Fields] OR “spine” All Fields]) OR “lumbar spine”[All Fields]) OR (“spine”[MeSH Terms] OR “spine”[All Fields])))

Study Design

randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized controlled trials [MeSH Terms] OR random allocation [MeSH Terms] OR double blind method [MeSH Terms] OR single blind method [MeSH Terms] OR clinical trial [Publication Type] OR clinical trials [MeSH Terms] OR (clinical* [Text Word] AND trial* [Text Word]) OR single* [Text Word] OR double* [Text Word] OR treble* [Text Word] OR triple* [Text Word] OR placebos [MeSH Terms] OR placebo* [Text Word] OR random* [Text Word] OR research design [MeSH Terms] OR follow-up studies [MeSH Terms] OR prospective studies [MeSH Terms] OR control* [Text Word] OR prospectiv* [Text Word] OR volunteer* [Text Word]

Practical Applications

- The included studies suggest that PAIVM MOBS, but not SNAGS MOBS, are associated with autonomic-mediated effects, regardless of spinal region. There is conflicting evidence regarding the ability of MANIP to elicit sympathoexcitation.
- The findings suggest that autonomic mediated effects might be dependent on SMT type/application, as well as on the mechanical properties of different SMT approaches.
- These autonomic effects are associated with clinical improvements in some studies.
- It is unwise to draw ultimate conclusions about the true effect exerted by SMT on ANS outcomes, given the low to very low quality of evidence.

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