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Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic nonspecific low back pain: a pilot randomized, controlled trial

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ABSTRACT

Objectives: The *long-term* goal of our study is to improve the understanding of the biological mechanisms associated with spinal manipulative therapy (SMT) in low back pain.

Methods: This project involved a pilot randomized, blinded clinical trial (ClinicalTrials.gov registration number NCT03078114) of 3-week SMT in chronic nonspecific low back pain (CNSLBP) patients. We recruited 29 participants and randomly assigned them into either a SMT (n = 14) or sham SMT (n = 15) group. Pre- and postintervention, we quantified the effect of SMT on clinical outcomes (Numeric Pain Rating Scale and Oswestry Disability Index) and pressure pain threshold (PPT) at local (lumbar spine), regional (lower extremity), and remote (upper extremity) anatomical sites.

Results: We observed a significant main effect for time signifying reduced hypersensitivity (increased PPT) at local (p = .015) and regional (p = .014) locations at 3 weeks. Furthermore, we found significant main effects of time indicating improvements in pain (p < .001) and disability (p = .02) from baseline among all participants regardless of intervention. However, no between-group differences were observed in PPT, clinical pain, or disability between the SMT and sham SMT groups over 3 weeks.

Conclusions: After 3 weeks of SMT or sham SMT in CNSLBP patients, we found hypoalgesia at local and remote sites along with improved pain and low back-related disability.

Level of Evidence: 1b

KEYWORDS

Spinal manipulation; lumbar spine; manual therapy; low back pain; pressure pain threshold; chronic; treatment outcome

Introduction

Low back pain affects up to 85% of the adult population imposing an economic burden of $86 billion annually *or* 1% of the United States gross domestic product [1–3]. Chronic low back pain (pain duration > 3 months), although only accounting for 5% of those with low back pain, represents 75% of the total treatment costs [1,2]. Present clinical practice guidelines recommend spinal manipulative therapy (SMT) as a *primary* intervention for low back pain [4–6]. SMT may reduce pain and disability in chronic low back pain patients [7,8]. A systematic review concluded that improvement in pain and function following SMT, in comparison with other interventions, might *not* be considered clinically relevant due to limited level of improvement and small effect size [9]. However, in comparison to other therapies, the practical benefits of SMT for managing chronic low back pain may include cost effectiveness, relative safety, and/or clinician or patient preferences [9].

Researchers have investigated changes in pressure pain threshold (PPT) in an attempt to understand *how* and *why* SMT impacts peripheral and/or central biological pathways in low back pain; however, the findings have not been conclusive [10–12]. PPT testing may be used as an indirect measure of peripheral and/or central sensitization for musculoskeletal pain [13]. Peripheral and central sensitization may be differentiated by comparing experimental pain responses at sites *local* and *remote* to the primary area of injury [14,15]. Peripheral mechanisms such as sensitization of tissue nociceptors may elucidate *local* tissue hyperalgesia, while central sensitization reflects widespread hyperalgesia at *remote* anatomical locations [15]. SMT may influence peripheral tissue hyperalgesia through decreased sensitivity within muscles spindles [11,16] and/or central sensitization of dorsal horn neurons through the descending inhibitory pain mechanism (DIPM) via the periaqueductal gray (PAG) region [10,17–21]. Depending on the measurement site, the examined effect of SMT on PPT in *chronic* LBP patients may reflect *local, regional* or *remote* neurophysiological mechanisms [11,12]. Past studies have reported mixed results on changes in PPT after SMT related to the anatomical site of the applied mechanical stimuli in healthy and low back pain subjects [22–26]. Studies in *healthy, asymptomatic* subjects examining the effects of SMT on PPT reported *significant* changes in

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PPT at local, regional, and remote sites [23] along with conflicting results reporting *no significant* change in PPT at a local site [24]. Investigations in *low back pain* patients evaluating the effects of SMT on PPT described *no significant* changes in PPT at regional locations [22,26], while other studies reported *significant* changes in PPT at a local site [22,25]. Presently, it is unclear whether SMT can reduce PPT in chronic low back pain, and if it does, which pain pathway, local or central, is responsible for changes in PPT. Until these questions are answered, it is neither possible to establish objective neurophysiological evidence of the mechanisms of SMT, nor to gain ubiquitous acceptance of SMT among the scientific and healthcare communities [27,28].

The goal of our study is to further the understanding of the biological effects associated with SMT. As our *primary* objective, we examined the effect of SMT on PPT at different anatomical sites and specific clinical outcomes. Our *central* hypothesis was that SMT would reduce hypersensitivity to mechanical stimuli applied at local, regional and remote sites and improve clinical outcomes in chronic nonspecific low back pain (CNSLBP) patients.

Methods

Research design

This project involved a pilot randomized, blinded clinical trial of 3-week spinal manipulative therapy in individuals with CNSLBP (Figure 1). Subjects were randomly assigned to spinal manipulation (SMT) or sham spinal manipulation (sham SMT) groups. We enrolled 29 ($n = 29$) subjects out of 51 patients who were assessed for inclusion/exclusion criteria. Clinical evaluations and analyses were performed at the University of Saint Mary research lab. Prior to starting treatment, each subject underwent physical and neurological examinations. Physical examination procedures included vital signs, orthopedic testing, palpation, and range of motion testing. Neurological examination comprised testing of muscle strength, deep tendon reflexes, pathological reflexes, and sensation.

Participants

We recruited persons with CNSLBP between January 2016 and April 2016 from campuses of two universities. Subjects were screened for fulfilling the

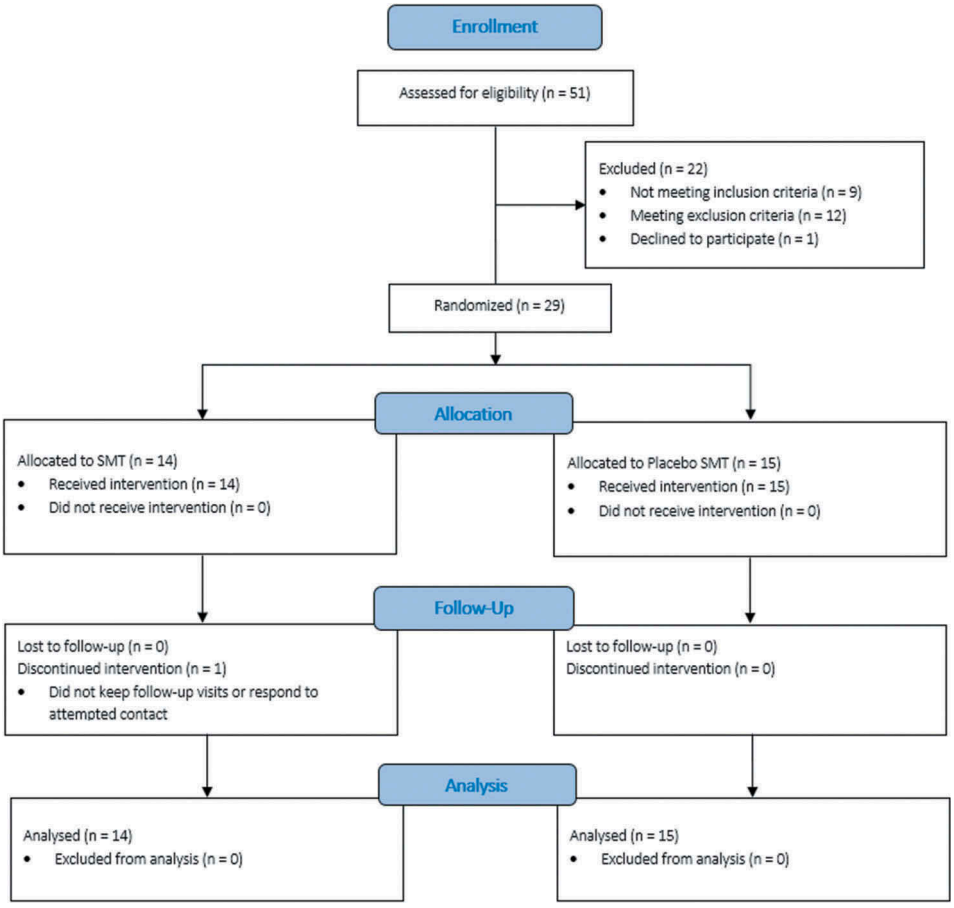

Figure 1. CONSORT diagram of enrollment, allocation, follow-up, and analysis for the study. SMT = spinal manipulative therapy. CONSORT = Consolidated standards of reporting trials.

inclusion and exclusion criteria. If a subject met these criteria, they were asked to sign an informed consent form approved by the human protection committees of the University of Saint Mary and University of Kansas Medical Center. In addition, we registered this study through ClinicalTrials.gov (registration number NCT03078114). Patients with low back pain were included in this study if they met the following criteria: (1) chronic nonspecific (> 12 weeks duration) low back pain rated ≥ 3/10 at its worst over the past 24 h on a numeric rating scale (NRS) (0 = no pain at all, 10 = worst pain imaginable); (2) male or female subjects between the ages of 18 and 60 years; (3) ability to read and understand English; and (4) currently not involved in litigation. Chronic low back pain patients were excluded if they reported any contraindications for SMT (Appendix 1).

Randomization and blinding

A computerized random number generator created a random allocation sequence list. Using this list, subjects were randomly allocated to either SMT or sham SMT group. This list was stored in a locked file cabinet with access limited to research personnel. After subject enrollment, a designated research assistant opened the correct numbered, sealed, opaque envelope. Each subject was assigned a unique identification number and the research assistant registered the subject's name and identification number in a log. This was the only information connecting the patient's identifying information with study records. Clinicians delivering the intervention were aware of group assignment, but the assessor was blinded to group allocation. A single assessor, with 22 years of experience as a licensed chiropractor, evaluated all outcome measures. Also, subjects were blinded to group allocation and advised to avoid discussing study details with the outcome assessor.

Procedures for clinical assessment

After signing an informed consent, investigators collected information regarding medications, past medical history, education, and demographic data from each subject. We gathered information related to attendance, medications, adverse events, and treatment sessions during the trial. The study coordinator monitored data quality on a weekly basis. In the event of improper data collection, there was immediate resolution of the recognized irregularity. A clinician performed a standard physical examination including vital signs and mobility testing. In addition, subjects underwent a neurological examination.

During the baseline evaluation, subjects completed clinical outcome measures capturing pain and self-reported disability. Information related to pain and disability was ascertained through the Numerical Pain Rating Scale (NPRS) and Oswestry Disability Index (ODI). Clinical changes over 3 weeks (assessed at prefirst intervention and 3 weeks on visit 7) on measures of pain (NPRS) and disability (ODI) served as clinical outcomes. We used the NPRS for screening (inclusion criteria) and as a clinical outcome measure. However, as described by Bialosky et al. (2014), we used the 11-point scale (0–10) during the screening procedure, whereas we used the 101-point (0–100) for measuring clinical outcomes [29]. While using the NPRS, subjects rated their pain intensity using an 101-point scale, with '0' indicating no pain and '100' indicating the worst pain imaginable [30]. The reliability and validity of NPRSs has been established in the scientific literature [31,32]. Scientific literature has established that a change of 1.25 points (on an 11-point NPRS scale) meets the minimal clinically important difference (MCID) for low back pain patients [33]. Alternatively, a 27.9% (raw change/baseline × 100) change in the NPRS realizes the MCID for CLBP patients [34]. The ODI is an efficient (~ 10 min) and generalizable outcome measure [35]. The reliability and validity of the ODI has been reported in the scientific literature [36–39]. The ODI has been found the most sensitive index to detect an improvement in disability associated with manual therapy, yielding large-sized improvements across many studies [30,36,37,40]. Also, MCID change score thresholds for the ODI range from 5 to 10 points [33,41,42].

Assessment of pain sensitivity

During the first visit, CNSLBP subjects underwent *pre* and immediately *posttreatment* pressure pain threshold (PPT) assessment. In addition, subjects underwent a third PPT assessment at the 1-week follow-up visit (visit 7) that occurred 3 weeks after the initial session. We determined PPT by applying pressure with a digital algometer (Wagner Instruments, Greenwich, Connecticut) to three anatomical regions allocated as local, regional, or remote. The digital algometer had a 1 cm^2 rubber-tipped probe that was applied perpendicular to skin at a rate of 1 kg per second (kg/s) [24]. Marks were placed on the belly (middle third) of the dominant tibialis anterior muscle (regional) [22] and dominant lateral epicondyle of the elbow (remote) [43]. Also, we marked a point 5 cm lateral to the spinous process of L5 (local) on the dominant side [22]. These three anatomical landmarks for pressure application were chosen based on high reliability values reported from previous studies [22,43]. Scientific literature has reported using dominant regions [29] for PPT testing, while a systematic review by Millan et al. [11] reported that SMT consistently demonstrates a bilateral hypoalgesic effect. Thus, we selected the dominant-side for PPT testing.

Subjects were asked to say 'stop' the moment the sensation changed from feeling *pressure* to feeling *pain*. The pain threshold was defined as the least pressure intensity at which subject's perceived pain. The pressure threshold in kilograms (kg) causing the perception of pain

was recorded for data analysis. Three measurements were collected for each anatomical region with 30 s of rest in between pressure applications. The mean value of the three threshold measurements was used for data analysis [22,24]. Before testing, each subject received three practice measurements with pressure applied to the dorsal aspect of their dominant hand [24]. Previous scientific literature has demonstrated the interrater (ICC = 0.94–0.97), intrarater (ICC = 0.79–0.90), and test–retest (ICC = 0.76–0.79) reliability of PPT measurements [22,44,45]. Prior to data collection, an assessor blinded to group allocation undertook training with the digital algometer to ensure adherence to the specified rate of pressure application and cessation of pressure [24,45]. PPT has been used in previous clinical trials as an outcome measure for response to spinal manipulation [11,12,25,26,29,43,46,47]. Previous scientific literature has established that a 15% reduction in PPT may be considered a clinically relevant change [48,49].

Treatment protocols

After completion of the screening and baseline assessments, both the SMT and sham SMT groups commenced the assigned treatment protocols. The SMT and sham SMT procedures were administered and supervised by licensed clinicians. Subjects received three treatments per week for 2 consecutive weeks (six treatments) with one additional follow-up visit less than 1-week postintervention (visit 7). A written log of attendance, medications, health changes, and injuries/adverse events was maintained for each subject.

Manual interventions

SMT involved the patient lying supine with the spine in a position of lateral bending and rotation followed by a high-velocity low-amplitude force applied to the lumbopelvic region (Appendix 2). This SMT procedure has demonstrated clinical efficacy in previous clinical trials involving low back pain patients [50–53]. This treatment protocol adheres to current United States clinical practice guidelines for managing low back pain with SMT [54,55]. Thus, a 2-week (six treatments) intervention appears sufficient to determine the potential effects of SMT in chronic nonspecific low back pain patients. As reported in previous studies [29,56,57], each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides.

Previous clinical trials have used placebo SMT or sham SMT as a comparison group [29,58,59]. Sham SMT placed the patient in the supine position, but without accompanying lateral bending and rotation of the spine (neutral spine position) followed by a high-velocity low amplitude force applied to the table [29]. As reported in previous studies [29,56,57], each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides. Thus, each participant (SMT and sham SMT) received four high-velocity low-amplitude thrusts (two left-sided and two right-sided) regardless of whether or not cavitation ('popping') occurred during the procedure [29,57]. Both the lumbopelvic SMT and sham SMT procedures were administered by two licensed clinicians (physical therapist and/or chiropractor) with greater than 8 years of manual therapy experience.

Data analyses

We conducted our statistical analyses according to the intention-to-treat analysis principle [60–63]. If data points were missing, we imputed the subject's missing data by baseline observation carried forward (BOCF) or last observation carried forward (LOCF) methods, dependent upon whether or not we captured postintervention data prior to the dropout [60–62]. We used individual *t* tests and chi-square tests to assess for postrandomization group differences in demographic measures, clinical measures, and pain sensitivity measures. We set our significance at .05 and performed analyses using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL).

Our primary aim consisted of investigating the effect of SMT on PPT in CNSLBP patients. We checked for normality (Kolmogorov-Smirnov Test), homogeneity of variance (Levene's Test), and sphericity (Mauchly's Test), making the appropriate statistical corrections (i.e. Greenhouse-Geisser) as indicated by the data. Based on meeting the assumption of normality, we used a mixed analysis of variance to test for a group (SMT, sham SMT) × time (prefirst intervention, immediately postfirst intervention to 3 weeks) interaction for pressure pain threshold. Interaction terms may be considered comparable to the *between*-group differences or the effect of the intervention. If testing revealed a significant group × time interaction, we performed contrasts to determine *within*-group changes. We tested *within*-group pressure pain threshold differences using a paired-samples *t* test. We repeated these same measures for each pressure pain testing location (lumbar paraspinal musculature, elbow lateral epicondyle, and tibialis anterior muscle).

Our secondary aim consisted of investigating the effect of SMT on clinical outcomes in CNSLBP patients. We checked for normality (Kolmogorov-Smirnov Test), homogeneity of variance (Levene's Test), and sphericity (Mauchly's Test), making the appropriate statistical corrections (i.e. Greenhouse-Geisser) as indicated by the data. Based on meeting the assumption of normality, we used a mixed analysis of variance to test for a group (SMT, sham SMT) × time (prefirst intervention to 3 weeks) interaction for clinical outcomes (NPRS and ODI). If testing revealed a significant group × time interaction, we performed contrasts to determine *within*-group changes. We tested

within-group (pre- and postintervention) clinical differences using a paired-samples *t* test.

Sample size estimation

Our primary aim was to examine the changes after SMT in pressure pain threshold examined at three different body sites. Bialosky et al. [57] reported an effect size (Cohen's *d*) of 1.20 on thermal pain threshold measured on the upper limb after spinal manipulation in comparison to a control group. We assumed that the pressure pain threshold measured at the upper limb may show similar changes after our SMT intervention compared to the control group. Assuming 80% statistical power and .05 alpha level, a sample size of 12 was required for each group in our study. Presuming a drop-out rate of 20%, we needed to recruit a total of 30 subjects.

Results

Baseline demographics and characteristics

We screened 51 individuals for the study and 29 ($n = 29$) signed the informed consent form (Figure 1). Within our sample 38% of the subjects were females with a mean age of 23.86 (SD = 5.74) years (Table 1). Individual groups did not differ by baseline demographic measures, clinical measures, or pain sensitivity measures.

Pain sensitivity

We did not observe group (SMT, sham SMT) by time (prefirst intervention, immediately postfirst intervention to 3 weeks) differences in PPT assessed at the dominant-side lumbar paraspinal musculature ($p = .913$) (Table 2). However, we observed a significant main effect for time with PPT at the lumbar paraspinal musculature ($p = .015$) *Post-hoc* pairwise comparisons revealed significant ($p = .044$) within-group differences from prefirst intervention to 3 weeks (Figure 2). We did not observe group (SMT, sham SMT) by time (prefirst intervention, immediately postfirst intervention to 3 weeks) differences in PPT assessed at the dominant-side lateral epicondyle ($p = .571$) nor did we observe a main effect for time ($p = .109$). We did not observe group (SMT, sham SMT) by time (prefirst intervention, immediately postfirst intervention to 3 weeks) differences in PPT assessed at the dominant-side tibialis anterior muscle ($p = .675$). However, we observed a significant main effect for time with PPT at the tibialis anterior muscle ($p = .014$). *Post-hoc* pairwise comparisons revealed significant ($p = .014$) within-group differences from immediately postfirst intervention to 3 weeks.

Clinical outcomes

We did not observe a significant group (SMT, sham SMT) by time (baseline to 3 weeks) interaction for low

Table 1. Baseline comparison of intervention groups.

	SMT	Sham	Total Sample	p Value for Difference
Gender (% female)	6/14 (43)	5/15 (33)	11/29 (38)	.60
Age (years)	24.29 (7.33)	23.47 (3.94)	23.86 (5.74)	.71
Education (years)	17.00 (1.92)	17.20 (1.47)	17.10 (1.68)	.76
Duration of LBP (months)	45.07 (29.77)	43.00 (27.40)	44.00 (28.07)	.85
ODI	15.93 (6.23)	15.07 (7.68)	15.48 (6.91)	.74
NPRS	41.64 (12.70)	36.87 (17.25)	39.17 (15.15)	.41
PPT local	3.39 (2.02)	3.36 (1.36)	3.37 (1.68)	.96
PPT regional	4.36 (1.78)	4.88 (1.71)	4.63 (1.74)	.44
PPT remote	2.95 (1.33)	3.19 (1.55)	3.08 (1.35)	.64

All data reported as mean (standard deviation) values. LBP = low back pain. ODI = Oswestry Disability Index (0–100% with smaller numbers indicating less disability). NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). PPT = pressure pain threshold expressed in kg/cm^2. Local = lumbar paraspinal musculature. Regional = tibialis anterior muscle. Remote = elbow lateral epicondyle.

Table 2. Changes in PPT.

	Time	PPT Lumbar Paraspinal Musculature (Local)	PPT Tibialis Anterior Muscle (Regional)	PPT Lateral Epicondyle (Remote)
SMT	Prefirst intervention	3.39 (2.02)	4.36 (1.78)	2.95 (1.33)
	Immediately postfirst intervention	3.54 (1.95)	4.28 (2.05)	2.66 (1.02)
	3 weeks postfirst intervention	3.88 (1.74)*	5.12 (2.11)$^{\delta}$	3.13 (1.32)
Sham	Prefirst intervention	3.36 (1.36)	4.88 (1.71)	3.19 (1.39)
	Immediately postfirst intervention	3.42 (1.49)	4.78 (1.99)	3.02 (1.64)
	3 weeks postfirst intervention	3.78 (1.59)*	5.34 (2.35)$^{\delta}$	3.17 (1.23)
Total sample	Prefirst intervention	3.37 (1.68)	4.63 (1.74)	3.08 (1.35)
	Immediately postfirst intervention	3.48 (1.70)	4.54 (2.00)	2.85 (1.36)
	3 weeks postfirst intervention	3.83 (1.64)	5.23 (2.20)	3.15 (1.25)

All data reported as mean (standard deviation) values. We observed a significant main effect of time for PPT at the lumbar paraspinal and tibialis anterior testing locations, but neither outcome was dependent upon group assignment. PPT = pressure pain threshold expressed in kg/cm^2. *significant *within*-group differences ($p < .05$) between prefirst intervention and 3 weeks. $^{\delta}$significant *within*-group differences ($p < .05$) between postfirst intervention and 3 weeks.

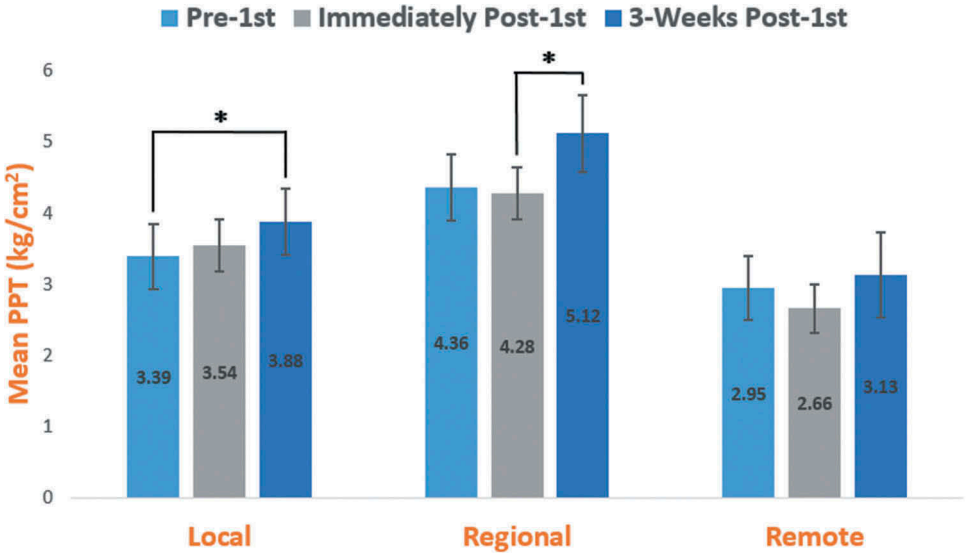

Figure 2. Change in PPT from prefirst intervention to immediately postfirst intervention and 3 weeks postfirst intervention for the *SMT* group at local, regional, and remote testing locations. We observed a significant main effect of time at the local and regional testing sites, but neither outcome was dependent upon group assignment. SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = lumbar paraspinal musculature. Regional = tibialis anterior muscle. Remote = elbow lateral epicondyle. Error bars = standard error. *significant *within*-group differences ($p < .05$).

back pain over the 3 weeks of the study ($p = .458$). However, we observed a significant main effect for time with low back pain ($p < .001$). Regardless of group assignment, we observed a mean decrease in low back pain of 11.31 (SE = 2.63) across subjects in the study. We did not observe a group (SMT, sham SMT) by time (baseline to 3 weeks) interaction for low back pain-related disability ($p = .829$). However, we observed a significant main effect for time with disability ($p = .02$). Regardless of group assignment, we observed a mean decrease in low back pain-related disability of 2.56 (SE = 1.04) across participants in the study.

Additional outcomes

We recorded additional clinical information including adverse events, change in medication, spinal joint cavitation, onset of new injuries/exacerbations, and believability of group assignment. A single adverse event of transient (< 48 h) local, mild joint discomfort was reported in the SMT group, while participants in the sham SMT group related no adverse events during the clinical trial. In addition, no changes in medication were conveyed for participants in either group throughout the study. We calculated the mean number of interventions for each group (SMT $\bar{x}$=5.7 and sham SMT $\bar{x}$=6.0), with an independent samples *t* test indicating no significant difference ($p = .336$) between the groups. As reported by clinician perception, spinal joint cavitation occurred at 61.25% (49/80 occasions) and 2.22% (2/90 occasions) frequencies in the SMT and sham groups, respectively. We arrived as these values based upon the product of the group size and the number of treatment sessions that each subject attended throughout trial. For example, the sham SMT group consisted of 15 subjects ($n = 15$) with each participant attending six treatment sessions during trial (i.e. 15 subjects × 6 visits each = 90 occasions). For the sham SMT group, 8/15 (53.3%) of subjects reported an exacerbation of low back pain related to activity at 3-week follow-up session, while only 3/13 (23.1%) of subjects in the SMT group reported an exacerbation during the trial. Based upon a two-sample test for proportions, there was no significant difference ($p = .778$) between the groups for subjects who felt they received an active form of treatment. Within the SMT group, 38.5% of participants believed that they received an active form of therapy, while 33.3% of subjects in the sham group thought that they received active treatment. Thus, our results indicate that we achieved adequate blinding for both groups and knowledge of treatment did not likely affect outcomes since both groups were similar in perception that they received an active form of intervention.

Discussion

Pain sensitivity

As outlined, our primary aim was to investigate the effect of SMT on PPT in chronic nonspecific low back pain patients, thereby exploring the neurophysiological mechanisms associated with SMT. We tested PPT at three anatomical locations including the lumbar paraspinal musculature [22] (local), tibialis anterior muscle [22] (regional), and lateral epicondyle of the elbow [43] (remote). The application of mechanical stimuli across multiple anatomical regions following SMT may help to differentiate the biological pathways, peripheral and/or central, associated with pain modulation following SMT. The current investigation embodied a novel design by

examining the effects of SMT on PPT across *multiple* anatomical testing locations (local, regional, and remote) in *chronic* nonspecific low back pain patients.

Based upon our findings, both SMT and sham SMT reduced hypersensitivity (increased PPT) at a local and regional locations from preintervention to 3 weeks. Our results are similar to previous studies [23,25,43,64] that reported reduced hypersensitivity to mechanical stimuli following SMT. Yu et al. [23] reported that lumbopelvic SMT performed on *asymptomatic* volunteers produced an immediate, significant reduction in hypersensitivity at local, regional, and remote anatomical locations, thus signifying local and widespread hypoalgesia.

Depending on the measurement site, the examined effect of SMT on pressure pain threshold in CLBP patients may reflect local tissue, spinal cord and/or supraspinal biological pathways [12]. Previous studies testing the consequences of *lumbopelvic* manipulation on pain sensitivity have reported applying stimuli to *local, regional*, and/or *remote* anatomical locations [22,24–26,29,56,57]. Coronado et al. [12] published a systematic review and meta-analysis that concluded future research designs should include *multi-regional* application of stimulus following SMT to differentiate local, specific effects versus general hypoalgesia. Hypoalgesia at a *local* testing site following SMT might modulate pain via stimulation of peripheral muscle spindles and/or central segmental reflex pathways [11,65]. A *regional* testing site might be considered an anatomical region within the same or overlapping dermatomes as those influenced by SMT [56]. For example, testing for hypoalgesia following lumbopelvic manipulation only in anatomical locations innervated by lumbosacral nerve roots [22,29]. George et al. [56] reported that pain sensitivity testing *only* at remote anatomical locations cannot distinguish whether or not the hypoalgesia following SMT is a large, general effect or a specific effect localized to the spinal levels associated with the manipulation. Also, paraspinal muscle reflexes along with motoneuron excitability may be influenced by SMT, perhaps affecting reflex neural output to spinal musculature [11,16]. Thus, modulation of PPT at regional sites following SMT seems likely modulated through central neural mechanisms; however, peripheral mechanisms may also influence the regional pain effects of SMT [11,16]. A systematic review and meta-analysis concluded that increased PPT at *remote* anatomical sites suggests a general or widespread effect of SMT on central sensitization [12]. In addition, evidence from fMRI imaging suggests that reduced PPT (i.e. hyperalgesia) at a *remote* site indicates a *central*, rather than peripheral, cause for CLBP [66].

To the best of our knowledge, this paper represents the first investigation reporting the effects of SMT on PPT across local, regional, and remote locales in CNSLBP patients. In addition to quantifying the immediate (< 30 min) effects of SMT on PPT, our novel design measured the effects of repeated (6 interventions) SMT on PPT at 3 weeks. In our study, we did not find immediate or 3-week hypolagesia at a remote testing site, implying that SMT may not have a significant widespread hypoalgesic effect on CNSLBP patients [56]. In addition, our findings of 3-week hypoalgesia at local and regional sites advocates that SMT may diminish sensitivity within local muscles spindles and/or influence the dorsal horn by means of the removal of subthreshold mechanical stimuli via pain gate mechanisms [10,11,15,16,29]. Based upon previous scientific literature [11,15,29], our findings of local and regional hypoalgesia infer a *primarily* central-mediated analgesic effect of SMT at the spinal cord, but peripheral mechanisms cannot be excluded from modulating spinal pain. Similar to our results, a previous study reported a local hypoalgesic effect following lumbopelvic SMT in *healthy* subjects, but no significant widespread hypoalgesic effect on a remote testing site (cervical spine) [56].

Hypolagesia at 3 weeks post-SMT suggests a prolonged analgesic effect beyond the brief, immediate period postintervention reported by previous investigations [23,25,56]. Boal and Gillette [67] suggested that SMT may produce hypoalgesia through stimulation of mechanosensitive afferents that modulate pain via central-mediated pathways. Long-term depression (LTD), initiated by the activation of mechanosensitive afferents, may reverse long-term potentiation (LTP) in dorsal horn neurons through neuronal plasticity [67]. LTD may influence dorsal horn neurons for protracted time intervals, thereby mitigating spinal pain for minutes or hours, and perhaps even for days or weeks [67]. Accordingly, our findings of SMT-induced hypolagesia at 3 weeks implies that manual therapy may modulate pain for an extended period of time through central-mediated neuronal plasticity.

However, interpretation of our results requires a caution. It appears that our SMT and sham SMT had a similar effect on PPT at 3 weeks postintervention. The sham SMT has been previously reported effective in blinding participants [29]. Bialosky et al. [29] compared the effects of SMT in low back pain patients to placebo SMT, 'enhanced' placebo SMT, and control groups. Although not significant, Bialosky et al. [29] reported limited, immediate hypoalgesia to mechanical stimuli applied to the posterior superior iliac spine after low back pain subjects received SMT, sham SMT and enhanced sham SMT. The sham SMT used for our experimental design aimed to apply a thrust into the table with the spine positioned in neutral (without trunk lateral bending), unlike the SMT procedure that applied a thrust into rotation with accompanying trunk

lateral bending. Bialosky et al. [29] conceded that the sham SMT applied a *mechanical load* to the spine. Scientific models associated with SMT postulate that a *mechanical stimulus* may elicit a cascade of potential neurophysiological effects, thereby accounting for the therapeutic benefits associated with manual therapy [13,16,68]. Our findings that both SMT and sham SMT produced hypoalgesia at sites local and distant to the region of pain indicated that the application of a *mechanical load* to the spine elicited a neurophysiological response, but suggests less importance on *how* the force is applied.

Our outcomes indicate a small, but potentially clinically relevant change in PPT following SMT in CNSLBP patients. At 3 weeks postintervention, the SMT group demonstrated a 14.5% (± 1.74 SE) increase (hypoalgesia) in PPT at the local site, and a 17.4% (± 2.35 SE) increase in PPT at the regional location (Figure 3). Consequently, the regional PPT testing location reached the 15% change in threshold established as clinically relevant for patient populations, while the local PPT testing location approached the defined threshold [49]. Dorron et al. hypothesized that the immediate analgesia following SMT may further influence clinical outcomes by providing an opportunity to facilitate rehabilitative exercise in patient populations with spinal pain [69]. However, at 3 weeks postintervention, both the SMT and sham SMT groups failed to achieve at least a 15% increase in PPT at the remote location, while the sham SMT group did not meet the established clinical threshold at the local (12.5%) and regional (9.4%) locations. Also, immediately postfirst intervention, both intervention groups did not realize the 15% clinically relevant threshold at any of the three PPT testing locations (local, regional, and remote).

Clinical outcomes

Similarly, our results did not show group-related differences, but a main effect for time in measures of clinical pain and disability over the three weeks of the study. Despite some past clinical trials [7,8] reporting that SMT appears efficacious for managing low back disorders, our results were similar to a previous clinical trial [29]. Bialosky et al. [29] did not observe group-related differences over a 2-week study examining the effects of SMT on clinical pain and disability. However, a significant main effect for time was observed for reduced pain and disability [29]. They cautioned that the design of their trial may have been underpowered to detect clinical treatment effects since their number of subjects were limited across four arms (total n = 110 or ~ 27 per group). Based upon our *post-hoc* analyses, we obtained an observed power value < 80% for clinical

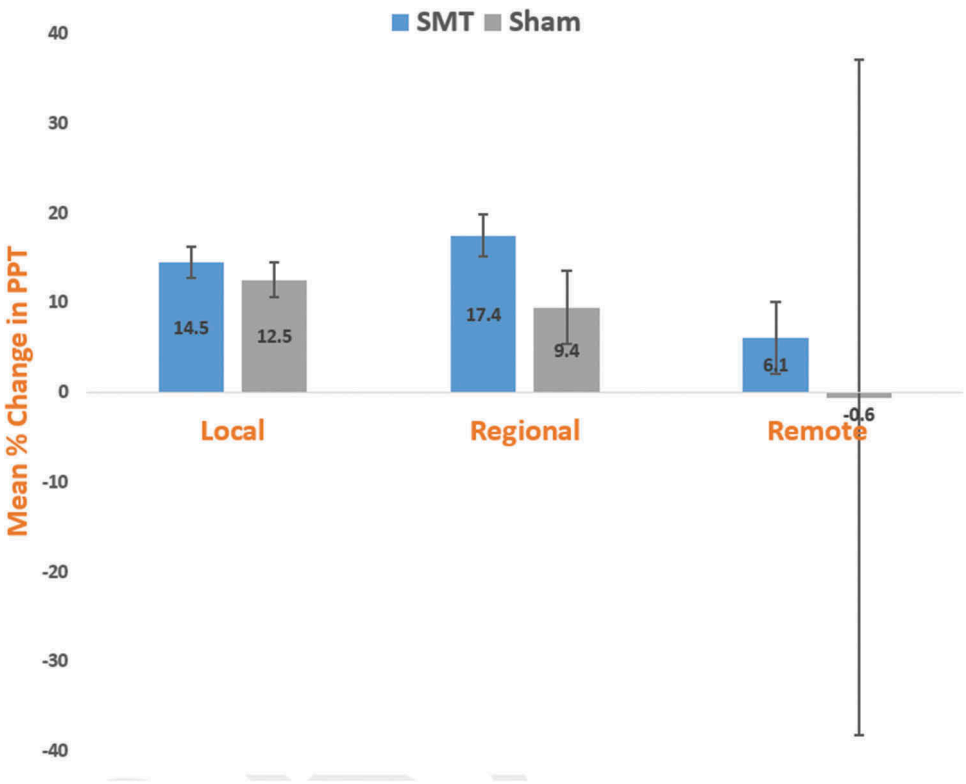

Figure 3. Mean percentage change in PPT from prefirst intervention to 3 weeks postfirst intervention for chronic non-specific low back pain subjects at local, regional, and remote testing locations. For *within-group* comparisons, negative values indicate reduced PPT (hyperalgesia), while positive values indicate increased PPT (hypoalgesia). A 15% change in PPT may be considered clinically relevant [49]. SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = lumbar paraspinal musculature. Regional = tibialis anterior muscle. Remote = elbow lateral epicondyle. Error bars = standard error.

outcomes (NPRS and ODI) between-subjects effects, thus we acknowledge the possibility of a type II error. With alpha set at .05, we estimated *post-hoc* power using G*Power [70] along with effect sizes using Cohen *d* [71] (Table 3). Our results signified small, but potentially meaningful changes in patient-rated outcomes. A reduction of 13.29 points (or 1.329 points on an 11-point NPRS scale) in the NPRS score within the SMT group met the MCID of 1.25 [33] points for low back pain patients (Figure 4). However, a reduction of 9.33 points (or 0.933 points on an 11-point NPRS scale) in the NPRS score within the sham SMT group indicated a score below the stated MCID threshold. Alternatively, the SMT group demonstrated a 31.9% reduction in the NPRS score, thereby meeting the MCID of 27.9% reduction [34] (raw change/baseline × 100) for CLBP patients. Again, the sham SMT group failed to achieve the defined MCID with a reduction of 25.3% in the NPRS score. There were 6 (46.2%) subjects in the SMT group and 7 (46.7%) in the sham SMT group that had a pain reduction greater than the MCID.

Limitations

Pressure may be considered a non-specific stimuli that elicits a response from mechanoreceptors and nociceptors in surrounding tissues [72]. Pressure pain threshold (PPT) may be used as an *indirect* measure of peripheral and central sensitization for musculoskeletal disorders [13]. In addition, a slow, gradual application of pressure until a pain threshold is reached might reflect a different neural pathway than rapidly applied stimuli [72]. This investigation only examined the effect of SMT in response to mechanical stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT.

In addition, the mean age of our sample at 23.86 (± 5.74) years may not be representative of the CNSLBP population. Previous scientific literature has reported the mean ages of CNSLBP patients seeking SMT ranging from 31.68 (± 11.85) [29] to 'middle-aged' [9]. Thus, our study sample may have been younger than reported in previous studies examining the effects of SMT, perhaps limiting the generalizability of our results. However, epidemiological data indicates that between 1992 and 2006, the prevalence of chronic low back pain increased by 201% in the 21 to 34 year age group, while the peak incidence rate for low back pain in the United States occurs between 25 and 29 years of age [73,74]. In addition, our baseline pain (NPRS) and low back-related disability (ODI) values across both study groups were similar to a previous study [29] investigating the effects of SMT on pain sensitivity.

This study may have been more clinically meaningful if we had monitored our subjects at some further time interval (6 months or 1 year). Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, long-term follow-up may have provided us with a more consequential measure of the effect of SMT on CNSLBP, thereby contributing to the development of more comprehensive evidence-based practice guidelines for managing low back disorders.

Conclusions

Following a 3-week course of SMT or sham SMT in CNSLBP patients, we found hypoalgesia at local and regional sites along with improved pain and low back-related disability. However, there was no difference between the two interventions in terms of PPT or clinical outcomes (NPRS and ODI) indicating that the *method* of

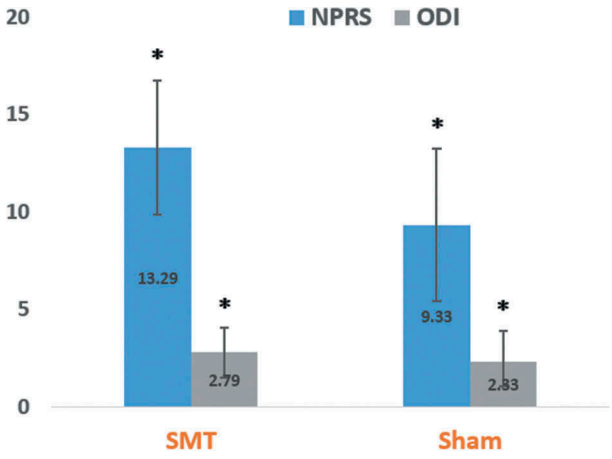

Figure 4. 3-week mean change in low back-related pain intensity and disability. Bars signify change in scores (prefirst intervention to 3 weeks postintervention) with positive numbers on the *y*-axis signifying declining pain and disability following intervention. We observed a significant main effect of time for pain and disability, but neither clinical outcome was dependent upon group assignment. NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). ODI = Oswestry disability index (0–100% with smaller numbers representing less disability). SMT = spinal manipulative therapy. Error bars = standard error. *significant *within*-group differences ($p < .05$).

Table 3. Effect size (Cohen *d*) of within-group and between-group changes in pain, disability, and PPT.

	Numeric Pain Rating Scale	Oswestry Disability Index	PPT (Local)	PPT (Regional)	PPT (Remote)
Time (within-group comparison)	0.83	0.48	0.44	0.47	0.29
SMT vs. Sham (between-group comparison)	0.11	0.04	0.03	0.11	0.09

PPT = pressure pain threshold. Local = lumbar paraspinal musculature. Regional = tibialis anterior muscle. Remote = elbow lateral epicondyle.

SMT force application may not signify a fundamental influence on biological outcomes.

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Appendix 1
Contraindications for Spinal Manipulative Therapy Used in our Study

Exclusion criteria include the occurrence of any of the following conditions or findings as determined by examination:

- previous low back surgery;
- severe structural spinal deformity;
- neurological compromise/spinal cord compression;
- severe spinal instability;
- severe osteoporosis/osteopenia;
- head trauma (recent);
- spinal infection (recent);
- known neurological, neuromuscular, systemic or orthopedic problems that might prevent them from participating in manual therapy interventions;
- pregnancy;
- obesity;
- pain or paresthesia below the knees;
- systemic illness known to affect sensation, i.e. diabetes;
- acute and/or chronic pain condition unrelated to low back pain; and
- spinal manipulation within the past 4 weeks.

Appendix 2

Spinal manipulative therapy and sham spinal manipulative therapy [29].