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The Effects of Osteopathic Manipulative Treatment on Pain and Disability in Patients with Chronic Neck Pain: A Single-Blinded Randomized Controlled Trial

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Abstract

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Background: Neck pain (NP) affects as much as 70% of individuals at some point in their lives. Systematic reviews indicate that manual treatments can be moderately effective in the management of chronic, nonspecific NP. However, there is a paucity of studies specifically evaluating the efficacy of osteopathic manipulative treatment (OMT).

Objective: To evaluate the efficacy of OMT in reducing pain and disability in patients with chronic NP.

Design: Single-blinded, cross-over, randomized controlled trial.

Setting: University-based, osteopathic manipulative medicine outpatient clinic.

Participants: 97 participants, 21–65 years old, with chronic, nonspecific NP.

Interventions: Participants were randomized to two trial arms: immediate OMT intervention or waiting period first. The intervention consisted of 3–4 OMT sessions over 4–6 weeks, after which the participants switched groups.

Main outcome measures: Primary outcome measures were pain intensity (average and current) on the numerical rating scale and Neck Disability Index. Secondary outcomes included PROMIS-29 health domains and Fear Avoidance Beliefs Questionnaire. Outcomes obtained prior to the cross-over allocation were evaluated using general linear models and after adjusting for baseline values.

Results: 38 and 37 participants were available for the analysis in the OMT and waiting period groups, respectively. The results showed significantly better primary outcomes in the immediate OMT group for reductions in average pain (−1.02, 95%CI:(−1.72, −0.32), p=0.005), current pain (−1.02, 95%CI:(−1.75, −0.30), p=0.006), disability (−5.30%, 95%CI:(−9.2%, −1.3%), p=0.010) and improved secondary outcomes (PROMIS) related to sleep (−3.25, 95%CI: (−6.95, −1.54), p=0.003), fatigue (−3.26, 95%CI:(−6.04, −0.48), p=0.022), and depression (−2.59, 95%CI:(−4.73, −0.45), p=0.018). The effect sizes were in the clinically meaningful range between 0.5 and 1 standard deviation. No study-related serious adverse events were reported.

Conclusions: OMT is relatively safe and effective in reducing pain and disability along with improving sleep, fatigue, and depression in patients with chronic NP immediately following treatment delivered over approximately 4–6 weeks.

Trial registration: ClinicalTrials.gov NCT# 02261259

Keywords

Cervical spine; Neck pain; Osteopathic manipulative medicine; Disability

Introduction

Neck pain (NP) is one of the three most frequently reported musculoskeletal complaints [1,2]. It affects as much as 70% of individuals at some point in their lives [3,4], is the fourth leading cause of years lived with disability [5], and this outlook has not changed significantly in recent decades [6]. Most people with NP do not recover completely and may experience recurrence of the symptoms 1–5 years later [7–10]. Forty-four percent of patients with chronic NP consult their general practitioners annually, one third of these patients are referred to paramedical

or medical specialists, and a majority of them receive some form of conservative treatment, which may include medication, physical therapy, and other interventions (e.g., manual treatment, postural therapy, acupuncture, etc.) [11]. Consequently, NP results in a significant socioeconomic burden, predominantly due to lost wages and work absenteeism, but also due to healthcare costs [12].

Most NP cases do not involve specific structural pathologies and are often referred to as “nonspecific,” “soft tissue,” or “mechanical” NP [13]. Causes and prognostic factors are numerous, complex, and include psychosocial determinants [4,7,14]. Thus, a syndromic diagnosis has been recommended to manage the majority of NP and searching for specific tissue pathology can become counterproductive [15]. Informed by scientific evidence, various clinical guidelines endorse conservative, symptomatic management of nonspecific NP [16–19]. Among these guidelines, physical exercise and some form of manual treatment are the most frequently recommended interventions [20].

Recent meta-analyses and systematic reviews of randomized clinical trials (RCTs) indicate that manual treatment, such as mobilization (involving non-thrust techniques), manipulation (involving thrust techniques), and massage are effective interventions for the management of NP [21–23]. However, these reviews did not consider osteopathic manipulative treatment (OMT) as a distinctive modality. OMT employs a wide variety of manual techniques to diagnose and treat musculoskeletal dysfunction, including mobilization and manipulation [24–26], though these techniques can also be used by other health professionals.

To date, there are only three published RCTs on the efficacy of OMT in the management of chronic NP: two from Germany [27,28], and one from Brazil [29]. Schwerla et al. showed the superiority of OMT over sham ultrasound on several measures of pain and function [27]. Similarly, Rotter et al. demonstrated significant improvements in pain and disability among musicians with chronic NP who received OMT in comparison to those who received no intervention [28]. Finally, Groisman et al. evaluated OMT in addition to exercise, which resulted in better outcomes than exercise alone [29]. The purpose of the current RCT was to add to the sparse data on the efficacy of OMT for chronic NP. We hypothesized that OMT intervention will result in a significant reduction in pain and disability when compared with the waiting period control group.

Methods

Trial design.

The RCT reported here was primarily designed to validate several tests for head-neck motor control as objective measures of pain interference [30]. To maximize the number of data points for the validation of these tests, while allowing all participants to receive real treatment, a cross-over design was adopted (Figure 1). In this paper, we present a part of the study that involves patient-reported outcomes of OMT intervention.

Adults with chronic NP were randomized to two trial arms: Sequence (AB) - immediate OMT (A-active intervention) followed by a waiting period (B-inactive control), or Sequence (BA) - a waiting period (B-inactive control) followed by OMT (A-active intervention), with

1:1 allocation ratio. Subjects starting in the immediate treatment group received 3–4 OMT sessions (approximately once a week, allowing a minimum of 3 and a maximum of 14 days between the OMT sessions). Subjects starting in the waiting period group did not receive any treatment. After 4–6 weeks from baseline, patients switched group assignments (Figure 1). Questionnaires with patient-reported outcomes were administered to all participants at baseline (T_0), at a cross-over time point (T_1), and at the end of the study (T_2). Participants remained in the study between 9 and 16 weeks, including the orientation session and the final follow-up on adverse events (AEs).

The study was registered with ClinicalTrials.gov (NCT# 02261259) and approved by the Michigan State University's Biomedical and Health Institutional Review Board prior to enrollment. A Data and Safety Monitoring Board (DSMB) consisted of two individuals who were not associated with the study institution and one individual from a different college at the study institution. Both data and safety monitoring plan and DSMB were approved by the National Center for Complementary and Integrative Health (NCCIH). Additionally, a third-party monitor (Westat Corp., Rockville, MD, USA) conducted pre- enrollment and subsequent annual site visits.

Participants.

Eligible participants were adults with chronic, nonspecific NP who met the inclusion/exclusion criteria listed in Table 1. "Chronic" was defined as pain lasting for a minimum of 3 months or longer [31]. The "nonspecific" definition was taken from The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders [13], which excludes any NP that is associated with serious local pathology or systemic disease (see exclusion criteria in Table 1). The eligibility of participants was verified with a two-step process. First, an online screening questionnaire addressed most of the inclusion/exclusion criteria (paper version was provided to those who did not have access to internet). Second, upon passing the online screening, participants were invited to the lab, signed an informed consent form, and were examined by a PM&R board-certified physician (LLP) who ruled out "red flags" and verified the eligibility criteria.

Study participants were recruited from the general population in the Greater Lansing and surrounding areas between June 2014 and July 2018. Recruitment strategies included personal communication, direct mail (using numerous databases), emails and advertisements (e.g., newspaper, radio, handouts, flyers, websites, and social media - such as, but not limited to, Facebook or Twitter). The advertisement flyers were also placed in several area clinics specializing in pain management or musculoskeletal disorders. The participants were compensated with a $100 gift card upon the completion of the study.

Interventions.

All treatments were delivered by one of five osteopathic physicians (LAD, JJR, TJF, MAZ, and LLP) specializing in OMT. The physicians initially evaluated patients for somatic dysfunction, which could be related to NP, in the thoracic spine, rib cage, cervical spine and cranium as implemented by Licciardone et al. [26]. Then, the physician addressed the diagnosed dysfunction with treatment, using a high-velocity, low-amplitude (HVLA) thrust

technique to the cervical spine region and any (or none) combination of the following 4 techniques: (i) soft tissue, (ii) muscle energy, (iii) myofascial, (iv) articulatory. These techniques are defined as follows [32]: (i) soft tissue – techniques that involve lateral stretching, deep pressure, and/or separation of muscle origin and insertion; (ii) muscle energy – a method in which the patient's muscle are contracted from a specific position, in a specific direction, and against physician's counterforce; (iii) myofascial – techniques utilizing continual palpatory feedback to alleviate restriction of the musculature and fascia; (iv) articulatory – a method in which a low velocity/moderate to high amplitude force is applied to a dysfunctional joint. All participants were positioned to attempt HVLA maneuver by the treating physician. Individuals that could not tolerate this maneuver did not receive HVLA in that session, resulting in an "HVLA attempted-not performed" entry in the treatment log. The clinician re-evaluated the degree of somatic dysfunction during the treatment session and repeated or changed the technique. Treatment sessions were up to approximately 30 minutes in duration.

The OMT techniques utilized by treating physicians may vary for many reasons, including the degree of restriction, acuteness of symptoms, provider preference, or patient tolerance/cooperation. However, no specific manual treatment technique demonstrates superior clinical outcomes (i.e., manipulation vs. mobilization) and, thus, there is no optimal technique that can be recommended for treating NP [33,34]. Therefore, the selection of an appropriate treatment protocol for our study was made based on the most commonly used manual techniques used by osteopathic physicians in the United States [24–26]. This protocol fit a more pragmatic research design, in which the efficacy of OMT was evaluated under "usual treatment" conditions [35]. At the same time, implementing cervical HVLA as the primary treatment modality and limiting physician's choices to four optional techniques made the treatment semi-standardized. The waiting period group served as an inactive control. Any non-study related manipulation (chiropractic or osteopathic), physical therapy, massage, acupuncture, and spinal injections were prohibited for both groups throughout the duration of the study. Medication usage was not limited.

Outcomes.

The primary clinical outcome measures were pain intensity and disability. Participants rated their current pain and the average pain over the last 7 days on a 11-point numeric rating scale (NRS) anchored with "no pain" at 0 and "worst pain imaginable" at 10. Disability was measured as a percentage using the Neck Disability Index (NDI) [36]. The secondary clinical outcomes included PROMIS-29 v1.0 health domains (pain interference, satisfaction with participation in social roles, sleep disturbance, fatigue, depressive symptoms, anxiety, and physical function) [37] and the Fear Avoidance Beliefs Questionnaire (FABQ) physical activity and work subscales [38]. The questionnaires, along with additional items aimed at rechecking exclusion criteria, were administered online at each time point using REDCap [39] and in-person interviews. All source data collected in paper format were transcribed into the REDCap database using a double data entry method.

Any unfavorable and unintended signs, symptoms, or disease occurring during the study were considered potential AEs, even if they were not related to the study [40]. Study

personnel queried participants about such signs and symptoms immediately after each visit, followed-up within 3 days and weekly via email, telephone, and in-person contacts until resolution. Participants rated the severity of their adverse signs or symptoms on a 11-point NRS. Because the variability of AE severity was not known a priori and such symptoms are not limited to the cervical region, we selected 2 NRS points as a threshold for classifying a symptom as an AE based on the minimal clinically important difference (MCID) recommended for general musculoskeletal pain [41,42]. In other words, an increase in any adverse symptom severity during the study by more than 2 points from the previous assessment rendered the symptom an AE. The principal investigator (JC) graded their relatedness to this project (0 is not related and 4 is definitely related), expectancy (expected or unexpected) and severity (1 is mild and 4 is life-threatening) using the Common Terminology Criteria for Adverse Events (CTCAE v4.03) [40].

Sample size.

This study was powered for medium effect size of 0.7 (Cohen's d) between patients with NP and healthy individuals in head/neck motor control tests. To detect these differences with power of 0.80 or greater in two-sided tests at 0.05 significance level, a sample of 34 subjects in each group was required. Therefore, adding a small margin for participant attrition, the targeted accrual of completed cases was set at 36 per group. This target was exceeded with 44 participants randomized to the OMT-first Sequence (AB) and 43 to the waiting period-first Sequence (BA) (Figure 1 and 2).

Because carryover effects were present in the primary outcome measures (see results), statistical analyses were performed using data from the first stage of the study (T_1); timepoint prior to the cross-over allocation (i.e., comparison between immediate OMT vs. waiting period groups). Given the available sample size at T_1 of 38 participants in the OMT group and 37 participants in the waiting period group, the effect size of Cohen's d=0.66 was detectable in unadjusted analyses as statistically significant with power of 0.80 or greater in two-sided tests at 0.05 level of significance. In the analyses with adjustment for baseline, because of correlation of approximately 0.6 between T_0 (baseline) and T_1 measures, the error variance was reduced, and the detectable effect size was d=0.53.

Randomization and Blinding.

A randomization module in REDCap was used to assign subject's group. The allocation table was generated by a computer and locked once the project had started. REDCap revealed group assignment for each subject at the time of enrollment. Therefore, there was no way to predict any participant's allocation before enrollment or change it afterwards.

The PI, statistician, and treating team physicians were all blinded to group assignment (i.e., OMT or waiting period). An approximately 2-month lead-up period between the study commencement and enrollment of the first participant prevented the physicians from knowing whether a participant is receiving treatment immediately after enrollment or after the waiting period (Figure 1). Only the study coordinator and research assistants involved in coordinating clinical treatment had knowledge of group assignment. Study participants were

instructed not to discuss their group assignment with the treating physicians and other study personnel.

Statistical methods.

A modified intent-to-treat analysis was used, which included all participants who were randomized but also completed at least one post-baseline assessment. Participants' characteristics and outcome measures at baseline were summarized with descriptive statistics. Carryover effects were evaluated by comparing summed outcomes for two time periods (T_0 to T_1 and T_1 to T_2) between two allocation sequences (AB and BA) (Figure 1). Because tests of carryover effects are typically not powered [43], we estimated the effect sizes (Cohen's d) and applied a commonly used cut-off of d=0.33 for clinical importance of the differences in patient-reported outcome data[44]. The characteristics of dropouts were compared between experimental groups using t- or chi-square tests as appropriate.

The unadjusted estimates of treatment effects on the outcomes were obtained from the t-tests comparing the two experimental groups at T_1. The adjusted estimates of treatment effects were obtained from general linear models relating outcomes at T_1 to experimental group and baseline value of the outcome. The least square (LS) means were output from these models, and differences between them by experimental group were tested. The adjusted effect sizes were estimated as differences between LS means divided by the square root of the mean squared error. Improvement in outcomes were considered to be clinically meaningful if the effect sizes for experimental group differences were between 0.5 and 1 standard deviation (SD) [44,45]. All analyses were performed using SAS 9.4 statistical software (SAS 9.4 Copyright © 2013, SAS Institute Inc., Cary, NC, USA).

Results

The recruitment and enrollment for this study began in June 2014 and was completed in August 2017 when the targeted accrual of 36 participants per trial arm was exceeded. Out of 963 screened volunteers, 97 met the eligibility criteria, agreed to participate, and were randomized (Figure 2). On average, participants in this study were just over 40 years old, suffered from NP for more than 8 years, had average pain rating over 5 on a 0–10 scale, and the majority were females (Table 2).

Participants received a total of 298 OMT sessions. HVLA to the cervical region was performed, or at least attempted, in 96.6% of sessions (n=288/298), with cavitation occurring 60.4% (n=174/288) of time. There were 3 sessions where somatic dysfunction was not identified in the cervical region, thus HVLA was not attempted, and 7 sessions where HVLA was not attempted as per protocol or not documented as such (i.e., protocol deviations occurred). In addition to HVLA, patients also received muscle energy (88.3%), myofascial (55.4%), articulatory (45.3%), and soft tissue (5.4%) treatment techniques.

There were carryover effects present in the primary outcomes (persistence of improvements in outcomes following the OMT intervention) for average pain ($t(73)=-1.41$, $p=.16$, $d=0.33$), current pain ($t(73)=-2.16$, $p=0.03$, $d=0.52$), and NDI ($t(73)=-1.84$, $p=0.07$, $d=0.48$) (Figure 3), as well as in the secondary outcomes of PROMIS depression ($t(73)=-1.63$, $p=0.11$,

d=0.37) and PROMIS sleep disturbance (t(73)=−2.84, p<0.01, d=0.66). Therefore, further analyses were limited to the T_1 time point corresponding to the first stage of the study prior to the cross-over allocation. Due to the scheduling of laboratory and clinical visits, this time period (T_0 (baseline) to T_1) was significantly longer for the participants in the OMT group than in the waiting group (mean (SD) 5.2(0.8) vs. 4.4(0.8) weeks, respectively; (t(73)=−3.99, p<0.01). Six participants dropped out from each group during this time, however, their characteristics did not differ (Table 3). Consequently, 38 participants in the OMT group and 37 participants in the waiting period group were available for comparison (Figure 2).

The results of comparisons between groups were similar for the adjusted and unadjusted analyses, with both analyses indicating significantly better outcomes in the OMT group for average pain, current pain, NDI, PROMIS sleep disturbance and depression (Table 4). The better outcome in the OMT group for PROMIS fatigue was significant in the adjusted but not in unadjusted analysis. The adjusted, between-group differences were as follows: average pain −1.02 (95% CI:(−1.72, −0.32), p=0.005), current pain −1.02 (95% CI:(−1.75, −0.30), p=0.006), disability −5.30% (95% CI:(−9.2%, −1.3%), p=0.010), sleep disturbance −3.25 (95% CI: (−6.95, −1.54), p=0.003), fatigue −3.26 (95% CI:(−6.04, −0.48), p=0.022), and depression −2.59 (95% CI:(−4.73, −0.45), p=0.018). The effect sizes for experimental group differences were in the clinically significant range between 0.5 and 1 SD [44,45] (Table 4).

There was a total of 187 AEs reported during this study and none of them were rated as serious (Severity Grade 4 or greater). Of these, only 37 AEs, reported by 27 participants (some participants reported more than one AE after a single OMT session), could be attributed to any of the 298 delivered OMT sessions, as these AEs were classified as being at least “possibly related” (relatedness Grade 2 or greater) and these AEs were expected. The other AEs were classified as either not related to the study (relatedness Grade 0 or 1) or were associated with the motor control testing sessions. One AE, involving an increase in rib pain following an OMT session, was rated as Severe (Grade 3). The remaining AEs were mild or moderate (Grade 1 or 2) increase in NP (n=16), muscle soreness (n=15), headache (n=2), and other (n=3). Almost all OMT-related AEs resolved completely; one with minor sequela and one unknown (lost to follow-up).

Discussion

The results from the current study indicate that OMT intervention is effective in reducing pain and disability in patients with chronic NP, as compared to no intervention. The participants in the OMT group also showed significant improvements in sleep, fatigue, and depression scores. It is possible that improvements in sleep disturbance and fatigue came from the reduction in average pain. Improvements in depression profiles were not hypothesized because the theorized mechanisms of manual treatment do not typically include modifications of psychosocial factors [46–48]. However, there is a well-established link between chronic pain and depressive disorders, which share similar neurophysiological pathways [49,50]. In fact, in a large cross-sectional study, Juan et al. demonstrated a positive correlation between NP intensity and depression, which was mediated by sleep quality [51]. Sleep disturbance, pain, anxiety, depression, and fatigue (lack of energy), known as the

SPADE cluster, often co-occur in the general population and are difficult to manage in a primary clinical practice [52]. Concomitant improvements in pain, disability, depression, and sleep disturbance in the group receiving OMT intervention demonstrate its efficacy in addressing SPADE symptoms and point to the consistency in the results from the current study.

The significant group differences in the primary outcomes in our study ranged from 0.9 to 1.3 points for NRS pain scores and from 5.3% to 7.2% for NDI, depending on whether the adjusted or unadjusted means were considered. It is debated how much improvement in pain and disability can be considered clinically significant or important. Typically, the MCID is calculated as the smallest difference that patients perceive to be beneficial. It is frequently quoted as 1.3 points on NRS for mechanical NP, based on one study [53]. However, due to methodological differences [54], the reported MCID values for NDI are inconsistent across studies and range widely between 6 and 38% [55–57]. For that reason, Norman et al. proposed, and others supported, the 0.5 SD as a conservative estimate of an effect size that is likely to be clinically meaningful [44,45]. By this measure, all statistically significant improvements in the outcomes observed in this study are clinically meaningful, as they ranged between 0.5 and 0.7 SD compared with controls.

There are only three published RCTs on the efficacy of OMT for chronic NP, by which our results can be directly compared. Schwerla et al.[27] showed slightly larger differences in average and current pain (1.8 and 1.2, respectively) between the OMT and sham ultrasound groups. Similarly, slightly larger differences than in our study were reported for NDI between musicians who did and did not receive OMT (8.4%) [28]. However, the participants in these two studies received 5 OMT sessions in comparison to 3–4 sessions in the current study. A dose-response effect could account for the differences in outcomes. The results from the study by Groisman et al. [29], in which the individuals with chronic NP received OMT once a week for 4 weeks in addition to general exercise, were closer to our results (OMT+ exercise versus exercise alone group differences were 1.4 NRS for average pain and 7.6% for NDI). Unfortunately, the dose-response to manual treatment for NP is unknown, but such data on chronic low back pain suggests an optimum of 12 sessions of spinal manipulation [58] or 6 sessions of OMT to achieve similar improvement [59]. Thus, it is possible that an increase in the dose of OMT beyond 3–4 sessions would have been more effective in the current study.

There are many RCTs of the effects of other manual treatment techniques, broadly termed spinal manipulation and mobilization, on pain and disability in NP patients. Collectively, as described in a Cochrane systematic review of spinal manipulation and mobilization for NP, these techniques result in similar positive outcomes with small to medium effect sizes [23], which are on a par with the results of the current study demonstrating medium effect sizes (between 0.5 and 0.7). Given the complex biopsychosocial character of chronic pain [60], it should be reasonable to expect that a unimodal intervention may not address all the factors contributing to its persistence, thus producing modest outcomes [61]. Indeed, the multimodal programs that combine manual treatment with exercise and physical therapy appear to be superior to unimodal interventions for chronic NP [22,31].

Increase in pain, soreness, and headache are common AEs experienced by patients after manual treatment for NP, including OMT [62–64]. However, AEs are generally underreported in RCTs [65] and there are no standard selection criteria for reporting AEs [66]. For example, none of the previous three RCTs on OMT for chronic NP addressed AEs in a systematic manner. Groisman et al. stated only that “no adverse events were reported” without describing how they were monitored [29]. Similarly, Schwerla et al. stated that “no serious adverse events were recorded” and mentioned that in a few cases patients reported tiredness and symptoms in the area other than cervical spine [27]. Finally, among 28 patients who received 5 treatments, Rotter et al. identified two AEs (tiredness and dizziness) through interviews and participant reports to the study center [28]. It is, therefore, difficult to compare these numbers with the current study, in which we logged all unfavorable signs and symptoms after each visit and through weekly contacts, and then classified them systematically using the definitions and terminology endorsed by the National Institutes of Health [40]. Despite this diligence, the incidence of 37 AEs related to the 298 OMT sessions (12%) in the current study appears to be much lower in comparison with the 22% incidence after other manual treatment sessions in RCTs that reported AEs with the appropriate detail [67]. Had we counted all symptoms as AEs without the 2-point symptom intensity threshold, the incidence of AEs would have been higher. This discrepancy underscores the need for the standardized selection criteria in reporting AEs. Nevertheless, considering that all 37 AEs in this study were expected and no serious AEs occurred, it could be concluded that OMT is relatively safe as are other manual treatment modalities.

The lack of long-term follow-up is a major limitation of the current study, although the persistence of improvements in the primary clinical outcomes can be judged from the significant carryover effects that were sustained for at least 4 weeks in the second part of this cross-over experimental design. Participants were recruited based on self-reported NP and were not necessarily seeking care for their symptoms, which may not generalize to patients actively seeking care who might have shown bigger treatment effects. Due to the schedule of clinical visits, participants were randomized, and their group allocation was disclosed to them prior to the baseline assessment. This sequence makes the attrition rate larger (23%) by counting 10 participants who dropped out between the randomization and baseline assessment. Ideally, randomization should have been done after the baseline assessment, which would have given us a 14% attrition rate corresponding to the time period between T_0 and T_1. These attrition rates are in line with the 5 to 25% range typically seen in cluster randomized cross-over trials [68]. In addition, the number and characteristics of dropouts did not differ between the study groups.

Also due to the scheduling logistics, outcomes in the OMT group at T_1 (cross-over point) were assessed approximately 5 days later than in the waiting period group. However, this difference is unlikely to influence the outcomes, as the participants in this study suffered chronic NP, on average, for longer than 8 years. Furthermore, because this was a validation study for the head-neck motor control tests, it did not include an active treatment control group and was based on a single clinical center. Finally, due to carry-over effects, the analyses were conducted only up to the cross-over time point. Notwithstanding the above limitations, to date, this is only the fourth RCT on the efficacy of OMT for chronic NP. As such, it provides new data on this topic and will help in the design of future longitudinal or

multi-center studies. Because physicians in the current study were relatively free to choose techniques and areas of the body to treat based on their clinical examination, the results should have broader generalizability to other osteopathic practices.

Conclusions

Our study demonstrated that OMT intervention is effective in reducing pain and disability along with improving sleep, fatigue, and depression in patients with chronic NP immediately following treatment delivered over approximately 4–6 weeks. OMT applied to the cervical region is relatively safe. Given that OMT is cost-effective [69], it could be recommended as an effective option in the management of chronic NP.

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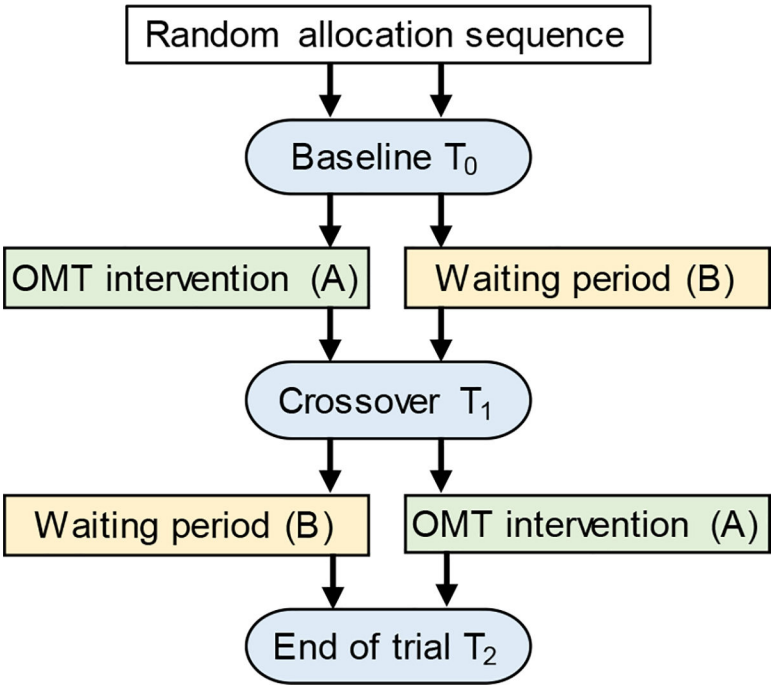

Figure 1.

Schematic of the randomized, cross-over, controlled trial design. Subjects in the AB arm received treatment (A – OMT intervention) followed by no treatment (B - waiting period); whereas subjects in the BA arm received no treatment (B - waiting period) followed by treatment (A – OMT intervention). Patient-reported outcomes were collected at baseline (T_0), cross-over point (T_1), and end of the trial (T_2). These three time points were spaced approximately 4–6 weeks.

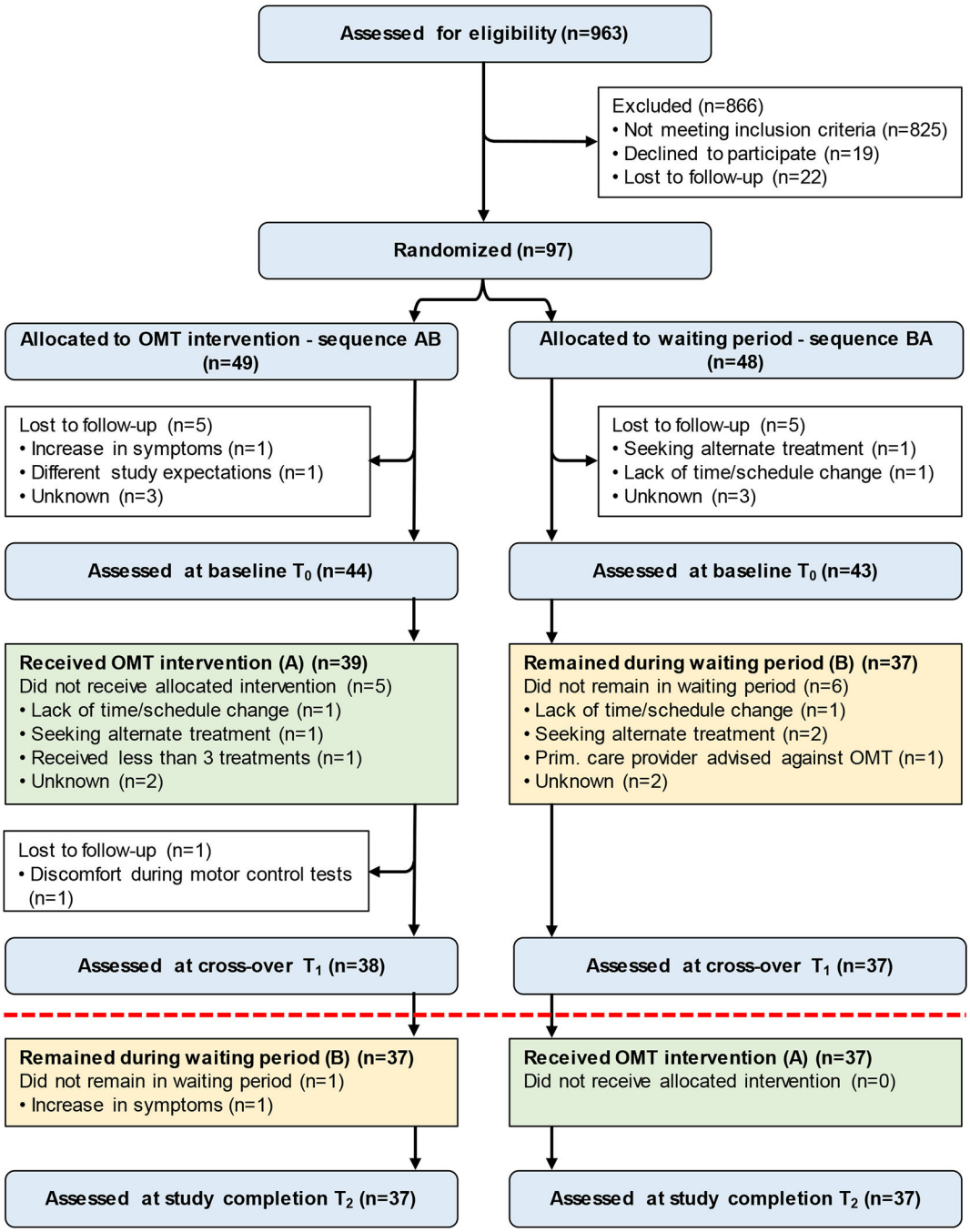

Figure 2.

CONSORT flow diagram of participants. Because of the carryover effects in the primary outcomes, the comparison between study groups was carried out prior to the cross-over allocation at T_1 (indicated with a red dashed line) with 38 participants in the immediate OMT intervention group and 37 participants in the waiting period group.

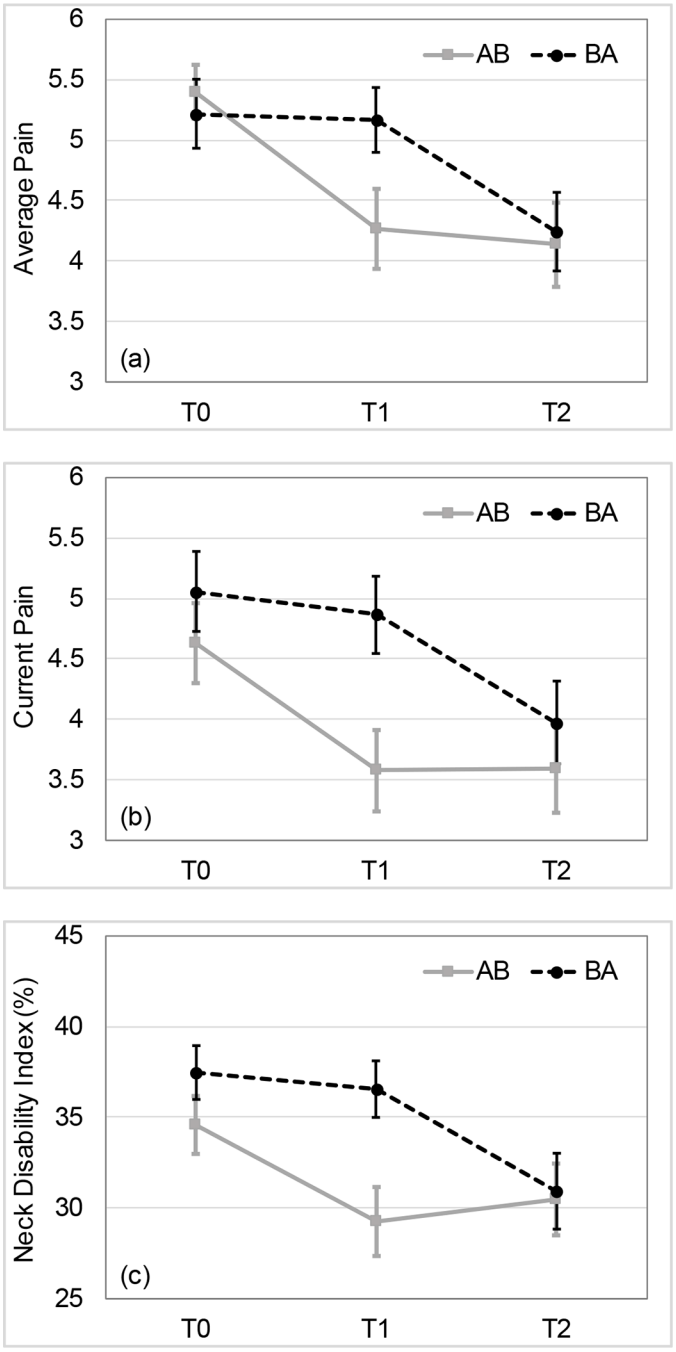

Figure 3.

Carryover effects in the primary outcome measures by trial arm. Both unadjusted and adjusted analyses revealed the significant group differences ($P<0.05$) at T_1 time point for average pain (a), current pain (b), and Neck Disability Index (NDI) (c). The allocation sequences indicate OMT intervention as A and waiting period as B. Error bars indicate standard errors. T_0 - baseline, T_1 - cross-over time point, T_2 - study completion.

Table 1.

Inclusion and exclusion criteria.

Inclusion Criteria
• Age 21–65 years
• Independently ambulatory
• Able to speak and read English
• Able to understand study procedures and to comply with them for the entire length of the study.
• Willing to be randomized to either immediate treatment-first or waiting period-first trial arms.
• Musculoskeletal pain - primarily in the cervical region lasting longer than 3 months
• Pain rating equal to or greater than 3/10 as indicated on the Numeric Rating Scale for Pain
• Neck Disability Index equal to or greater than 30%
Exclusion Criteria
• Inability or unwillingness of individual to give written informed consent.
• Physical therapy or any other form of manual medicine (e.g., Osteopathic Manipulative Medicine, Chiropractic Manipulation, etc.), acupuncture or spinal injections within one month prior to study enrollment
• Workers' compensation benefits in the past 3 months or ongoing medical legal issues
• Possibly pregnant
• Extreme obesity (BMI>36)
• Currently using electrical implants (e.g., cardiac pacemakers, drug delivery pumps, etc.)
History of:
• Spinal surgery
• Spinal fracture
• Spinal infection (e.g., osteomyelitis)
• Cancer
Unresolved symptoms from:
• Head trauma
• Inner ear infection with associated balance and coordination problems
• Orthostatic hypotension
• Uncontrolled hypertension
• Vestibular disorder (e.g. vertigo)
Current diagnosis of:
• Significant spinal deformity (e.g., scoliosis > 20 degrees, torticollis)
• Ankylosing spondylitis
• Spondylolisthesis grades III or IV
• Rheumatoid arthritis
• Osteoporosis
• Angina or congestive heart failure symptoms
• Active bleeding or infection in the neck
• Blindness
• Seizures
• Neurologic disease (e.g., Parkinson's disease, multiple sclerosis, cerebral palsy, Alzheimer's disease, amyotrophic lateral sclerosis, stroke or transient ischemic attack in the past year, cervical dystonia)
Conditions recognized by a physician any time during the study:

- Significant or worsening signs of neurologic deficits (e.g., diminished sensation, altered reflexes, and motor deficits)
- Symptoms are not consistent with mechanical findings
- Other conditions impeding protocol implementation

Table 2.

Baseline characteristics of participants with chronic neck pain (NP) by trial arm.

Characteristic	Arm 1 (Sequence AB: OMT then waiting period) N=44 Mean (SD) or N (%)	Arm 2 (Sequence BA: waiting period then OMT) N=43 Mean (SD) or N (%)
Age (years)	40.70 (13.12)	43.40 (13.97)
Sex		
Female	33 (75%)	33 (77%)
Male	11 (25%)	10 (23%)
Race		
American Indian or Alaska Native	1 (2.3%)	1 (2.3%)
Asian	4 (9.1%)	1 (2.3%)
Black or African American	1 (2.3%)	3 (7%)
More than one race	2 (4.5%)	2 (4.7%)
White	36 (81.8%)	36 (83.7%)
Ethnicity		
Hispanic or Latino	7 (15.9%)	2 (4.7%)
Not Hispanic or Latino	37 (84.1%)	39 (90.7%)
Unknown	0 (0%)	2 (4.7%)
Height (m)	1.69 (0.07)	1.69 (0.08)
Weight (kg)	77.77 (14.93)	80.01 (15.51)
BMI (kg/m^2)	27.31 (4.71)	28.17 (5.47)
Duration of NP (years)	8.29 (8.73)	10.13 (8.92)
Average pain	5.52 (1.36)	5.28 (1.74)
Current pain	4.86 (2.00)	5.14 (2.02)
NDI (%)	35.8 (9.9)	37.4 (8.9)
FABQ work	13.84 (8.32)	14.67 (8.83)
FABQ physical activity	12.02 (5.80)	12.44 (4.17)
PROMIS Profile pain interference	58.29 (7.52)	59.73 (5.60)
PROMIS Profile satisfaction with participation in social roles	45.34 (9.47)	44.34 (5.93)
PROMIS Profile sleep disturbance	56.46 (6.90)	57.00 (7.05)
PROMIS Profile fatigue	59.01 (7.31)	56.48 (7.80)
PROMIS Profile depression	50.13 (9.37)	51.77 (9.16)
PROMIS Profile anxiety	52.88 (9.54)	54.46 (8.54)
PROMIS Profile physical function	46.10 (6.61)	45.01 (6.60)

OMT=osteopathic manipulative treatment; SD=standard deviation; BMI=Body Mass Index; NDI=Neck Disability Index; FABQ=Fear Avoidance Beliefs Questionnaire; PROMIS= Patient-Reported Outcomes Measurement Information System.

Table 3.

Characteristics of dropouts from baseline (T_0) to crossover point (T_1) by study group.

Characteristic	OMT Group Dropouts N=6 Mean (SD) or N (%)	Waiting Period Group Dropouts N=6 Mean (SD) or N (%)	P-value
Age (years)	38.33 (14.09)	44.67 (15.36)	0.47 *
Sex			0.99 †
Female	5 (83%)	6 (100%)	
Male	1 (17%)	0 (0%)	
Duration of NP (years)	6.22 (5.84)	10.25 (6.87)	0.30 *
Average pain	6.33 (1.03)	5.67 (1.97)	0.48 *
Current pain	6.33 (1.03)	5.67 (2.16)	0.51 *
NDI (%)	43.3 (8.1)	36.8 (8.6)	0.27 *

OMT=osteopathic manipulative treatment; SD=standard deviation; NP=neck pain; NDI=Neck Disability Index.

* t-tests were used.

† Chi-square test was used.

Table 4.

Post-intervention outcomes by study group.

	Unadjusted Analyses *				Adjusted Analyses †			
Outcome	**OMT Group Mean (SE)**	**Waiting Period Group Mean (SE)**	**Between-Group Difference (95% CI) ‡**	**P-value, Effect Size (d)**	**OMT Groupy LS Mean (SE)**	**Waiting Period Group LS Mean (SE)**	**Between-Group Difference (95% CI) ‡**	**P-value, Effect Size (d)**
Average pain	4.26 (0.33)	5.16 (0.27)	**−0.90 (−1.75, −0.05)**	**0.039, d=0.49**	4.20 (0.25)	5.22 (0.25)	**−1.02 (−1.72, −0.32)**	**0.005, d=0.67**
Current pain	3.58 (0.34)	4.86 (0.32)	**−1.28 (−2.21, −0.36)**	**0.007, d=0.64**	3.71 (0.25)	4.73 (0.26)	**−1.02 (−1.75, −0.30)**	**0.006, d=0.65**
NDI (%)	29.30 (1.9)	36.50 (1.6)	**−7.20 (−12.2, −2.3)**	**0.005, d=0.68**	30.2 (1.4)	35.5 (1.4)	**−5.30 (−9.2, −1.3)**	**0.010, d=0.62**
FABQ work	12.92 (1.53)	13.92 (1.30)	−1.00 (−5.01, 3.01)	0.621, d=0.11	13.31 (1.17)	13.52 (0.18)	−0.21 (−3.53, 3.11)	0.896, d=0.03
FABQ physical activity	11.39 (0.88)	12.30 (0.82)	−0.91 (−3/30, 1.50)	0.456, d=0.17	11.50 (0.52)	11.74 (0.52)	−0.24 (−2.59, 1.49)	0.593, d=0.13
PROMIS Profile pain interference	56.28 (1.34)	57.75 (0.76)	−1.47 (−4.56, 1.63)	0.349, d=0.22	57.04 (0.84)	56.97 (0.85)	0.07 (−2.32, 2.47)	0.950, d=0.02
PROMIS Profile satisfaction with participation in social roles	45.97 (1.36)	46.36 (1.02)	−0.39 (−3.80, 3.02)	0.820, d=0.05	45.58 (1.00)	46.76 (1.01)	−1.18 (−4.02, 1.65)	0.408, d=0.19
PROMIS Profile sleep disturbance	51.97 (0.89)	56.51 (1.34)	**−4.54 (−7.73, −1.35)**	**0.006, d=0.66**	53.11 (0.95)	56.36 (0.96)	**−3.25 (−6.95, −1.54)**	**0.003, d=0.72**
PROMIS Profile fatigue	54.77 (1.02)	56.65 (1.41)	−1.88 (−5.34, 1.58)	0.283, d=0.25	54.09 (0.97)	57.35 (0.99)	**−3.26 (−6.04, −0.48)**	**0.022, d=0.55**
PROMIS Profile depression	46.60 (1.18)	50.66 (1.46)	**−4.06 (−7.78, −0.34)**	**0.033, d=0.50**	47.33 (0.75)	49.92 (0.76)	**−2.59 (−4.73, −0.45)**	**0.018, d=0.56**
PROMIS Profile anxiety	48.52 (1.23)	51.28 (1.48)	−2.76 (−6.64, 1.11)	0.159, d=0.33	49.23 (0.99)	50.54 (1.00)	−1.31 (−4.13, 1.51)	0.358, d=0.22
PROMIS Profile physical function	46.13 (1.19)	44.00 (1.05)	2.13 (−1.04, 5.30)	0.184, d=0.31	45.75 (0.78)	44.40 (0.79)	1.35 (−0.87, 3.57)	0.228, d=0.28

OMT=osteopathic manipulative treatment; SE=standard error; CI=confidence interval; LS=least square; NDI=Neck Disability Index; FABQ=Fear Avoidance Beliefs Questionnaire; PROMIS= Patient-Reported Outcomes Measurement Information System.

* The unadjusted estimates of treatment effects on the outcomes were obtained from the t-tests comparing the two experimental groups.

† The adjusted estimates of treatment effects were obtained from general linear models relating outcomes at T_1 to experimental group and baseline value of the outcome.

‡ Significant ($p<0.05$) differences are bolded.