Received: 10 September 2022 | Revised: 15 January 2023 | Accepted: 18 January 2023

DOI: 10.1002/pmrj.12953

ORIGINAL ARTICLE

PM&R

Effectiveness of spinal manipulation in addition to pharmacological treatment in fibromyalgia: A blinded randomized trial

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Abstract

Background: It has been suggested that spinal manipulation may alter sensorimotor integration in the central nervous system and therefore may be used to treat central sensitization syndromes.

Objective: To investigate the effectiveness of spinal manipulation in addition to pharmacological treatment in patients with fibromyalgia.

Design: A single-center, randomized, and placebo-controlled trial with three parallel arms

Setting: Outpatient clinics at a tertiary health care facility.

Participants: Female patients aged 18-55 years receiving pharmacological treatment.

Interventions: Spinal manipulation, sham manipulation, and control groups. Patients in the spinal manipulation group received high-velocity low-amplitude manipulation treatment twice a week for 3 weeks. Patients in the sham group received an application that was very similar to the active treatment but was not expected to have any real therapeutic effect. Patients in the control group continued to receive pharmacological therapy.

Main Outcome Measures: The primary outcome, pain score (visual analog scale), and secondary outcomes, pressure pain threshold (PPT), Revised Fibromyalgia Impact Questionnaire (FIQR), Widespread Pain Index (WPI), and Fibromyalgia Severity Score (FSS) were measured before, 1 month, and 3 months after randomization.

Results: Sixty patients with a mean age of 41.7 years (SD = 8.0) were enrolled in the study. A mixed-design repeated analysis of covariance was used to test the data. At 1 month after randomization, pain scores did not differ between groups. At 3 months after randomization, the spinal manipulation group had a significantly lower pain score (adjusted mean = 4.3 cm, SE: 0.4) than the control group (adjusted mean = 6.8 cm, SE: 0.4) and the sham manipulation group (adjusted mean = 5.7 cm, SE: 0.4). PPT did not differ between groups at any time point. FIQR, WPI, and FSS showed some improvement 1 or 3 months after randomization in favor of the spinal manipulation group.

Conclusions: Spinal manipulation used in addition to pharmacological treatment in young/middle-aged female patients with fibromyalgia could be an effective treatment for pain, disease severity, and functionality.

INTRODUCTION

Fibromyalgia (FM) is characterized by chronic, widespread pain, decreased pain threshold, fatigue, sleep

ClinicalTrials: NCT04673058

[Correction added on 18 March 2023, after first online publication: Supplemental appendices were omitted in error and are now included.]

disturbances, cognitive dysfunction, and other somatic symptoms.[1,2] The disease often leads to disability and significant impairment of quality of life. A combination of pharmacological and nonpharmacological treatments is recommended.[3] These include exercise, cognitive behavioral therapy, physical therapies, relaxation techniques, patient education, analgesics, antiepileptics, and antidepressants.

Although the cause of FM is not well understood, characteristic findings such as hyperalgesia and allodynia suggest problems with pain and sensory processing in the central nervous system.[4] More specifically, it is known that maladaptive plastic changes in the central nervous system (central sensitization) occur in FM.[4] Studies investigating the mechanism of action of spinal manipulation for pain point to peripheral mechanisms (eg, reduction in the release of pronociceptive and proinflammatory neurotransmitters, reduction in the production of oxygen free radicals, etc.), spinal cord mechanisms (eg, modulation of central sensitization, reduction of temporal summation, suppression of wide dynamic range neurons with proprioceptive afferents, etc.), and supraspinal mechanisms (eg, descending inhibitory system, endogenous analgesics, etc.).[5] In this context, it has been suggested that spinal manipulation may be useful for FM by normalizing maladaptive changes particularly through spinal and supraspinal effects.[6,7] However, spinal manipulation was not recommended in the 2016 European Alliance of Associations for Rheumatology (EULAR) treatment recommendations because the low quality of the (open-label, quasiexperimental) studies conducted to date.[3] It was recommended that future studies should investigate whether the combined use of pharmacological and nonpharmacological treatments is more effective than single-modality management.[3] However, studies conducted after the publication of the EULAR recommendations did not achieve a high level of evidence for the effectiveness of spinal manipulation in FM. Reasons for this were the lack of a detailed description of the manual therapy methods used, the conduct of studies that mainly involved soft tissue techniques, and the failure to follow the Consolidated Standards of Reporting Trials (CONSORT).[8]

The choice of control group in clinical trials of manual therapy is still controversial.[9] It is possible that studies using only a "nonintervention group" as a control are biased in favor of the intervention arm. Therefore, it is recommended that a placebo control be used, especially in studies with a "self-reported" outcome.[10] However, because of the increasing knowledge of manual therapy in society, patients in the sham treatment group may recognize that they are receiving a sham treatment. This could lead patients to have biased impressions of their outcome because of the reduced credibility of the treatment.[11] The use of a sham treatment as a placebo in manual therapy therefore requires some special adjustments in the way the sham treatment is administered to obtain a sham control that is as similar as possible to the active therapy.

This study was planned to test the true therapeutic and nonspecific effects of spinal manipulation on FM, using a unique sham treatment. We hypothesized that spinal manipulation is an effective additional treatment for pain intensity and this effect has a true therapeutic component superior to placebo. We also planned to evaluate the effectiveness of spinal manipulation on tenderness, functionality, extent of pain, and severity of disease in FM as secondary outcomes without a priori hypothesis.

METHOD

Study design

A single-center, randomized, triple-blind, and placebo-controlled parallel-group design was used to ensure internal validity. In addition, a nonintervention (control) group was added to allow a pragmatic comparison of spinal manipulation plus pharmacological treatment with pharmacological treatment alone.

Patients

Patients diagnosed with FM and receiving pharmacological treatment were recruited. The study was conducted with female patients aged between 18 and 55 years to limit age-related musculoskeletal problems and gender differences in pain perception and pain threshold as confounding variables. The purpose and method of the study were explained to eligible patients, and written informed consent was obtained from those who agreed to participate. Patients were included in the study if they had an FM diagnosis according to the 2016 American College of Rheumatology (ACR) FM diagnostic criteria,[12] had been pharmacologically treated for FM for at least 2 weeks, and had a pain score > 4, which was assessed using a visual analog scale (VAS). Patients were excluded if they had a structural musculoskeletal problem (eg, acute disc herniation, acute spondylolisthesis/lysis, fractures and dislocations, advanced degenerative changes, etc.); were pregnant or breastfeeding; had an inflammatory or infectious disease, malignant tumor, neuromuscular disease, history of spinal surgery, or unstable psychiatric condition; had previously received a treatment administered by a manual therapist who trained at a manual medical school or by a chiropractor or an osteopath; or had enough information about such treatment to distinguish between sham and active therapy (eg, researched extensively on the internet, watched videos, etc.). The study was conducted at Bezmialem Vakif University Hospital, Department of Physical Medicine and Rehabilitation. All

eligible patients were recruited between January 26, 2021, and August 23, 2021. Follow-up occurred at two time points: 1 month (1 week after the last intervention) and 3 months after randomization. An approval (Number: E-71306642-050.05.04-2375) was obtained from the Clinical Research Ethics Committee. The study was registered on the ClinicalTrials website on 12/07/2020 under the ID of NCT04673058.

Randomization

The allocation sequence was generated by a statistician with an allocation ratio of 1:1:1 and a random block size of six. Patients enrolled in the study were referred to an outcome assessor for their baseline assessment. Thereafter, the outcome assessor wrote the name and ID number for each patient on a sealed sequentially numbered opaque envelope and referred the patient to the therapists. The therapists opened the envelopes and assigned patients to the spinal manipulation, sham manipulation, or control group. Patients in the spinal manipulation and sham manipulation groups received an appointment for their first session within 1 week of randomization.

Blinding

Patients in the intervention groups, the outcome assessor, and care provider physicians were blinded to allocation. Data were presented to the statistician with masked allocation information. In addition, the blinded data interpretation method was used to avoid any possible bias in the interpretation of the study results.[13] The results of the analysis performed by the blinded statistician were presented to the writing committee by labeling the group names with the letters A, B, and C. This required the evaluation of several possibilities, with each letter representing a different group in each possibility. Details of this meeting and the signed document are provided in Appendix S1. The randomization code was broken only after the committee had interpreted and signed off on these results for all alternative possibilities. According to the broken code, it was revealed that the letter A represented the control group, the letter B represented the spinal manipulation group, and the letter C represented the sham treatment group. Among the interpreted possibilities, the one that corresponded to the real situation was then used for the data interpretation of the study.

Interventions

In the spinal manipulation group, therapists examined patients in each session using manual methods and identified somatic dysfunctions of the spine in each region (cervical spine, thoracic spine, and lumbar spine). An appropriate provocation test was performed to determine the direction of the thrust to be applied. The direction that is pain free during the test was chosen as the thrust vector for therapy. The patient was then placed in a locking position in which the joints proximal and distal to the affected segment were immobilized. A high-velocity low-amplitude (HVLA) thrust was then given and the stimulation was delivered to the affected segment. The therapy sessions were standardized in terms of the techniques that therapists were allowed to use. Detailed information on the allowed techniques can be found in Appendix S2. The therapists were an International Federation for Manual/Musculoskeletal Medicine-certified physician who is a specialist in physical medicine and rehabilitation and a physiotherapist with a master's degree in chiropractic, both of whom had at least 4 years of experience in the field of manual therapy. In the sham treatment, the patient received an application that was very similar to the active treatment but was not expected to have any real therapeutic effect. To do this, the therapist first identified the regions where she/he found somatic dysfunction and kept the applications away from these areas. For each application, the patient was positioned as in the active treatment, but after being placed in the locking position, she was released back slightly to an unlocked position, and a smaller force than usual was given. In this way, it was aimed to avoid an effective stimulus that reaches the elastic zone of joint movement.[14] At the same time a sham intervention was obtained, with a stronger resemblance compared to applications such as light touch or massage. Each treatment session was conducted in 20-minute sessions consisting of 10 minutes of manual examination and 10 minutes of spinal manipulation. Treatments were performed twice a week for 3 weeks. To avoid performance bias, treatment sessions were alternated between the two therapists. During the study, pharmacological treatments for all patients were managed by blinded care provider physicians according to current treatment guidelines, regardless of interventions and testing.

Outcome measures

Outcome measures were selected in accordance with the Outcome Measures in Rheumatology Clinical Trials core set.[15] Patients came for follow-up visits in the morning or afternoon on the day of the appointment. Outcomes were assessed by the same investigator in all patients at baseline and at all follow-up visits. The primary outcome measure of the study was pain intensity (VAS). Patients were asked to rank their pain between 0 (no pain) and 10 (unbearable pain) at each

visit. Secondary outcomes were pressure pain threshold (PPT), the revised Fibromyalgia Impact Questionnaire (FIQR), the Widespread Pain Index (WPI), and the Fibromyalgia Severity Scale (FSS). PPT was measured to assess tenderness. The PPTs of 18 points specified in the 1990 ACR FM classification criteria were assessed using the Lafayette Manual Muscle Tester Model 01165 (Lafayette Instrument Company, Lafayette, IN, USA).[2] This instrument is a dynamometer. Hand-held dynamometers with wider tips than standard algometers ($1cm^2$) have also been shown to be valid and reliable in PPT measurement when circumference, rather than area, is used as the correction coefficient.[16] The Lafayette hand-held dynamometer uses a tip with a circumference of 5.65 cm. The device was placed on the skin at a 90° angle, and a force was applied for 4 seconds resulting in an increase of 1 kg per second. The value at which the patient first felt pain was divided by 5.65, and the pressure was recorded as the pain threshold. The arithmetic mean of the data obtained at 18 points is recorded as the Tender Point Pain Threshold Score.[2,17] Functional limitation was assessed with the FIQR.[18] The FIQR is scored between 0 and 100. Increasing scores indicate a poor outcome. The WPI quantifies the extent of bodily pain on a scale of 0–-19 by asking patients whether they experienced pain in 19 different body regions in the past week, with each painful region scored as 1 point.[1] FM severity was assessed with the FSS which is the sum of the WPI and symptom severity scale (SSS) scores.[12] The SSS can range from 0 to 12. Increasing scores indicate a poor outcome. Treatment credibility was assessed at the first month after randomization. Patients were asked to choose the type of treatment they had received, regardless of the results of the treatment. In addition to the primary and secondary outcome measures at each time point, adverse effects and changes in pharmacological treatment were also recorded.

Sample size

G*Power® (Version 3.1.9.6) program, "Repeated measures, within-between interaction" test from the family of F-tests was used to calculate the sample size. To detect a difference with a medium effect size according to Cohen's partial eta squared (η_p^2) cutoff value (0.06)[19] by a mixed analysis of variance with a power of 90% and a significance level of 0.05%, the total number of samples required was calculated as 45. Considering a 25% loss of follow-up, the number of patients for each group was set at 20.

Statistical analysis

A mixed-design repeated analysis of covariance (ANCOVA) with baseline value as a covariate was used for the primary and secondary outcomes. Subgroup analyses were conducted with a mixed- or one-way repeated-measures ANCOVA to assess the effects of disease duration and pharmacological treatments used in relation to pain score, which was the primary outcome. The data set was planned to be divided into two groups to allow comparison by duration of the disease. As the data were not normally distributed, the median of 12 months was chosen as the threshold. Two groups were formed: those with a duration of illness of 12 months or more and those with a shorter duration. This second independent variable was included in the ANCOVA. All randomized patients were included in the analysis according to the intention-to-treat principle. Missing data were imputed by assigning the mean of a variable that contains missing values. In addition, a per-protocol analysis was performed for the sensitivity analysis, which included only those patients who had completed the originally assigned treatment. On November 3, 2021, the writing committee met, and the coded statistical results were received from the statistician. The code was broken only after the blinded data had been interpreted and signed off (see Appendix S1).

RESULTS

Of the 97 eligible patients, 60 were enrolled in the study. Only one patient dropped out because she was diagnosed with ankylosing spondylitis during the study. The flow chart of the study is shown in Figure 1. Each patient received at least one application in each region during each session. The mean age of the patients was 41.7 years (SD = 8.0). The duration of symptoms ranged from 1 month to 10 years (*Mdn* = 12). The majority of the patients were married. Pregabalin was the most commonly used pharmacological treatment in all groups. The demographic characteristics and baseline findings of the groups are shown in Table 1. None of the patients reported any adverse effects.

Analysis of variance revealed a significant interaction between group and time for pain intensity ($F\ [4112] = 4.901$, $\eta_p^2 = 0.149$, $p = .001$). Follow-up of this interaction showed that the spinal manipulation group had a statistically significant improvement at the third month after randomization compared with the control group (mean difference of 2.5 cm, 95% confidence interval [CI]: 1.1 to 3.8) and compared with the sham manipulation group (mean difference of 1.3 cm, 95% CI: 0.0 to 2.6). Although the spinal manipulation and sham manipulation groups showed significant improvement compared with their baseline values at the first month after randomization, they did not differ significantly from the control group at this time point (Figure 2).

PPT showed significant effects only in the time main factor ($F\ [1.59, 89.4] = 8.839$, $\eta_p^2 = 0.136$, $p = .001$),

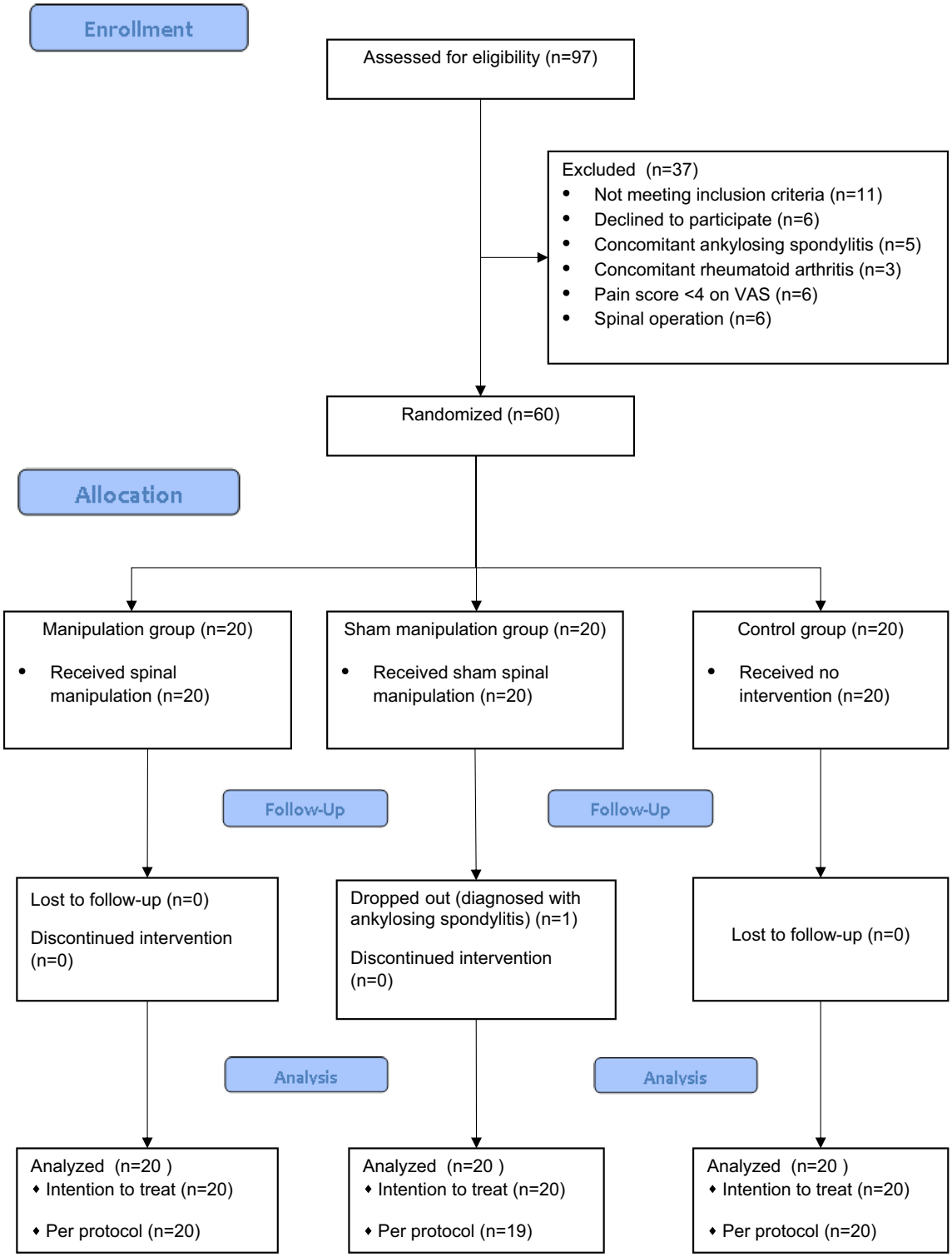

FIGURE 1 Flow chart of study. VAS, visual analog scale

indicating a worsening for the whole sample but not differing at group level over time (Figure 3). An almost significant interaction was found for the FIQR ($p = .064$), which was found to be significant in the sensitivity analysis (per protocol analysis): F (3.51, 96.7) = 2.618, $\eta_p^2 = .0087$, $p = .046$. Follow-up of this interaction showed that the spinal manipulation group had better FIQR scores than the control group at the third month after randomization. A significant interaction was found for WPI (F [4112] = 3.081, $\eta_p^2 = 0.099$, $p = .019$), and

TABLE 1 Demographic characteristics and baseline findings of patients

	Manipulation group (n = 20)	Sham manipulation group (n = 20)	Control group (n = 20)
Age, years, mean (SD)	42.4 (8.8)	41.8 (8.4)	40.8 (7.1)
Education, years median (range)	5 (5-16)	5 (5-16)	8 (5-16)
Duration of symptoms, months, median (IQR)	12.0 (33.0)	7.0 (30.5)	7.0 (9.5)
Marital status, n (%)			
Married	17 (85)	17 (85)	20 (100)
Single	3 (15)	3 (15)	0 (0)
Pregabalin users, n (%)	17 (85)	14 (70)	16 (80)
Duloxetine users, n (%)	8 (40)	11 (55)	11 (55)
Amitriptyline users, n (%)	1 (5)	2 (10)	1 (5)
Other medication users, n (%)	0 (0)	0 (0)	1 (5)[a]
VAS score, mean (SD)	6.57 (1.31)	6.80 (1.57)	5.88 (1.50)
WPI, mean (SD)	11.8 (2.81)	11.0 (3.06)	9.75 (2.59)
PPT, kg/cm, mean (SD)	1.07 (0.33)	1.03 (0.23)	1.15 (0.37)
FIQR, mean (SD)	50.3 (7.86)	49.7 (13.6)	42.3 (11.1)
FSS, mean (SD)	20.2 (3.47)	19.9 (3.88)	17.3 (3.49)

Abbreviations: FIQR, revised Fibromyalgia Impact Questionnaire; FSS, Fibromyalgia Severity Scale; IQR, interquartile range; PPT, pain pressure threshold; VAS, visual analog scale; WPI, Widespread Pain Index.
[a]Venlafaxine.

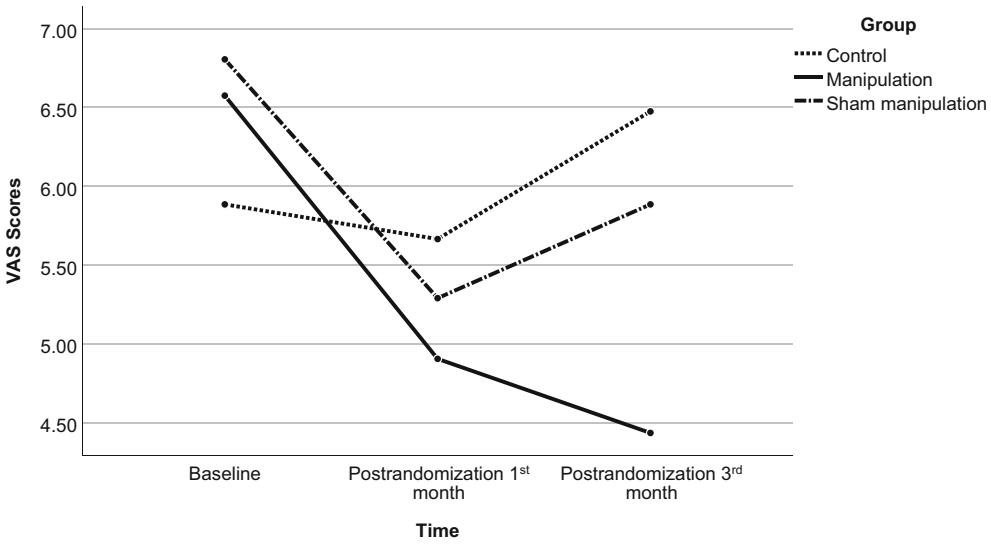

FIGURE 2 Comparison of pain scores at follow-up visits. The spinal manipulation group had a statistically significant improvement compared to the sham ($p = .045$) and control ($p < .01$) groups at the third month after randomization. No significant difference was found between groups at the first month after randomization. VAS, visual analog scale

FSS (F [4112] = 3.362, $\eta_p^2 = 0.107$, $p = .012$), indicating that the spinal manipulation group had a statistically significant improvement compared to both groups at the first month after randomization. At the third month after randomization, the only significant difference in WPI was between the spinal manipulation group and the control group. The spinal manipulation group had statistically better FSS scores than the control group at all follow-up visits. No other significant difference was found between the groups in the other pairwise comparisons. The primary and secondary outcome scores and the pairwise comparisons of the groups at the assessment time points are shown in Table 2 and Table 3.

Subgroup analyses

No significant interaction was found between group, time, and duration of disease (F [4104] = 1.098, $\eta_p^2 = 0.041$, $p = .362$). At baseline assessment, 12 patients were taking pregabalin only, 2 patients were taking duloxetine only, and 2 patients were taking both pregabalin and duloxetine in the spinal manipulation group. Four patients

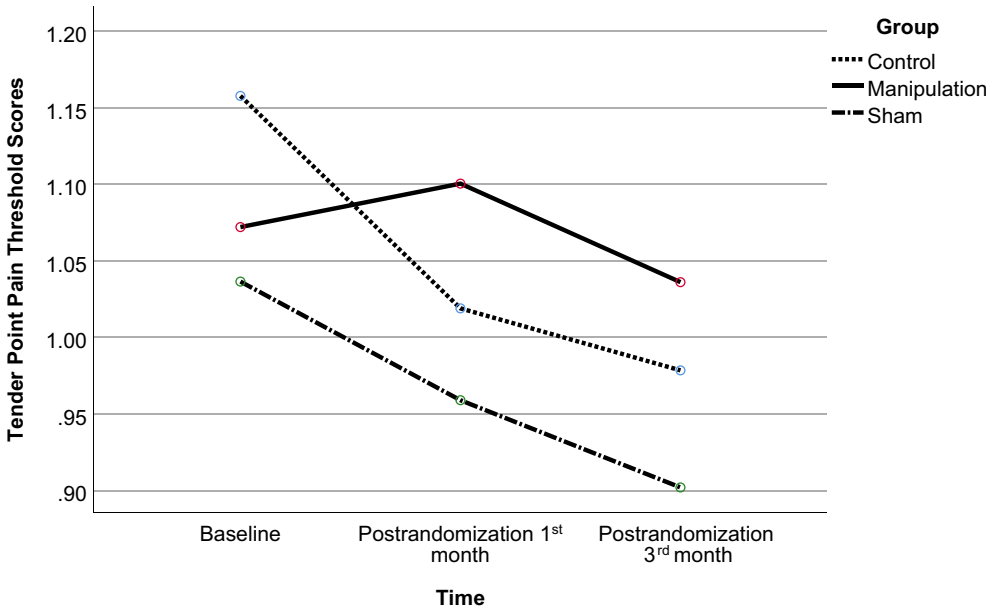

FIGURE 3 Comparison of tender point pain threshold scores at follow-up visits. No significant difference was found between groups at any time point

TABLE 2 The primary and secondary outcome scores and pairwise comparisons of the groups at the first month after randomization[a]

	Manipulation group	Sham manipulation group	Control group	Pairwise comparisons
Primary outcome				
VAS score, cm, mean (SE)	4.8 (0.4)	5.1 (0.4)	5.9 (0.4)	Manipulation vs sham, MD = 0.3, 95% CI: −1.0 to 1.6, $p > .99$
				Manipulation vs control, MD = 1.1, 95% CI: −0.3 to 2.5, $p = .156$
				Sham vs control, MD = 0.8, 95% CI: −0.6 to 2.2, $p = .442$
Secondary outcomes				
PPT, kg/cm, mean (SE)	1.1 (0.0)	1.0 (0.0)	1.0 (0.0)	Manipulation vs sham, MD = 0.1, 95% CI: −0.0 to 0.3, $p = .137$
				Manipulation vs control, MD = 0.1, 95% CI: −0.0 to 0.3, $p = .060$
				Sham vs control, MD = 0.0, 95% CI: −0.0 to 0.16, $p > .99$
FIQR, mean (SE)	36.7 (2.6)	39.6 (2.5)	40.9 (2.6)	Manipulation vs sham, MD=2.9, 95% CI: −5.8 to 11.6, $p > .99$
				Manipulation vs control, MD = 4.1, 95% CI: −5.0 to 13.3, $p = .796$
				Sham vs control, MD = 1.2, 95% CI: −7.7 to 10.1, $p > .99$
WPI, mean (SE)	7.1 (0.7)	9.7 (0.7)	10.4 (0.7)	Manipulation vs sham, MD = 2.6, 95% CI: 0.0 to 5.1, $p = .045$
				Manipulation vs control, MD = 3.3, 95% CI: 0.7 to 6.0, $p = .009$
				Sham vs control, MD = 0.7, 95% CI: −1.9 to 3.3, $p > .99$
FSS, mean (SE)	14.3 (1.1)	16.5 (1.1)	18.3 (1.1)	Manipulation vs sham, MD = 2.3, 95% CI: −1.5 to 6.0, $p = .424$
				Manipulation vs control, MD = 4.0, 95% CI: 0.1 to 8.0, $p = .043$
				Sham vs control, MD = 1.8, 95% CI: −2.1 to 5.7, $p = .803$

Abbreviations: CI, confidence interval; FIQR, revised Fibromyalgia Impact Questionnaire; FSS, Fibromyalgia Severity Scale; MD, mean difference; PPT, pain pressure threshold; VAS, visual analog scale; WPI, Widespread Pain Index.
[a]Values were adjusted according to the baseline covariate.

were switched between pregabalin and duloxetine during follow-up. Within the spinal manipulation group, there was no significant difference in pain intensity scores at any follow-up between patients who took pregabalin and those who did not, or between those who switched their medication and those who did not. Other subgroups were not available for statistical analysis owing to the small number of samples.

Treatment credibility

At the first month after randomization, two (10%) of the manipulation group and three (15%) of the sham manipulation group indicated that they thought the treatment applied to them was a sham treatment. There was no difference between groups in treatment credibility ($p > .99$).

TABLE 3 The primary and secondary outcome scores and pairwise comparisons of the groups at the third month after randomization[a]

	Manipulation group	Sham manipulation group	Control group	Pairwise comparisons
Primary outcome				
VAS score, cm, mean (SE)	4.3 (0.4)	5.7 (0.4)	6.8 (0.4)	Manipulation vs sham, MD = 1.3, 95% CI: 0.0 to 2.7, $p = .045$
				Manipulation vs control, MD = 2.5, 95% CI: 1.2 to 3.8, $p < .001$
				Sham vs control, MD = 1.1, 95% CI: −0.2 to 2.5, $p = .123$
Secondary outcomes				
PPT, kg/cm, mean (SE)	1.0 (0.0)	0.9 (0.0)	0.9 (0.0)	Manipulation vs sham, MD = 0.1, 95% CI: −0.0 to 0.3, $p = .213$
				Manipulation vs control, MD = 0.1, 95% CI: −0.0 to 0.3, $p = .203$
				Sham vs control, MD = 0.0, 95% CI: −0.0 to 0.2, $p > .99$
FIQR, mean (SE)	32.2 (3.0)	39.3 (2.9)	44.1 (3.0)	Manipulation vs sham, MD = 7.0, 95% CI: −3.2 to 17.2, $p = .286$
				Manipulation vs control, MD = 11.8, 95% CI: 1.2 to 22.5, $p = .025$
				Sham vs control, MD = 4.8, 95% CI: −5.7 to 15.3, $p = .779$
WPI, mean (SE)	7.8 (0.7)	10.0 (0.7)	10.9 (0.8)	Manipulation vs sham, MD = 2.2, 95% CI: −0.4 to 4.8, $p = .122$
				Manipulation vs control, MD = 3.0, 95% CI: 0.4 to 5.7, $p = .020$
				Sham vs control, MD = 0.9, 95% CI: −1.7 to 3.5, $p > .99$
FSS, mean (SE)	14.0 (1.1)	17.5 (1.1)	19.5 (1.1)	Manipulation vs sham, MD = 3.5, 95% CI: −0.3 to 7.3, $p = .086$
				Manipulation vs control, MD = 5.6, 95% CI: 1.5 to 10.0, $p = .004$
				Sham vs control, MD = 2.0, 95% CI: −1.9 to 6.0, $p = .609$

Abbreviations: CI, confidence interval; FIQR, revised Fibromyalgia Impact Questionnaire; FSS, Fibromyalgia Severity Scale; MD, mean difference; PPT, pain pressure threshold; VAS, visual analog scale; WPI, Widespread Pain Index.
[a]Values were adjusted according to the baseline covariate.

DISCUSSION

This study compared the effects of a specific manual technique (HVLA thrust) applied to the spine 2 days per week for 3 weeks with the effects of sham manipulation and no additional intervention in patients receiving pharmacologic treatment. The results of our study showed that spinal manipulation was superior to both the sham treatment and control groups in terms of FM pain intensity at the third month after randomization, but this was not the case at the first month after randomization. Our study stands out in terms of evaluating the nonspecific effects of spinal manipulation, particularly through the unique method of sham manipulation.

Although the placebo response is an integral part of treatment in manual therapy, demonstrating a true therapeutic effect that cannot be achieved with only nonspecific effects is essential for the cost-effectiveness and ethical applicability of treatment.[20] In our study, the absence of any statistically significant differences between the sham and control groups and the superiority of manipulation over sham treatment at the third month after randomization support the existence of a "true" treatment effect of spinal manipulation for FM pain in our population. Furthermore, pragmatic comparisons are essential in presenting real-world evidence.[21] A previous study found that the minimum clinically important difference (MCID) in FM pain was an improvement of 2 units (or 30%-35%) on the 11-point numerical scale.[22] In our study, the superiority of the spinal manipulation group over the control group with an amount greater than the MCID at the third month after randomization suggests that the overall effect of spinal manipulation on FM pain is clinically important.

The changes we observed in WPI scores at the first month after randomization also support the existence of a true therapeutic effect. Although the manipulation group did not show superiority over the sham treatment in WPI at the third month after randomization, the absence of a significant difference between the sham treatment and the control group suggests that the superiority of the spinal manipulation group over the control group at this time point cannot be attributed to placebo alone. Our findings in favor of spinal manipulation in the FIQR at 3 months after randomization and in the FSS at both 1 and 3 months after randomization also cannot be attributed to placebo alone. It seems difficult to explain these effects, which were observed in different sizes and at different time points. There is a need for future research to determine whether our findings are reliable and, if so, for mechanism research to understand the reasons.

We found no statistically significant improvement in PPT in any of the three groups during the 3-month follow-up. On the contrary, we observed a worsening

for the whole sample in PPT. Moustafa et al., in their study comparing multimodal treatment given once a week for 12 weeks and 20 sessions of C1-C2 mobilization and manipulation in addition to this treatment, found no significant difference in PPT immediately after treatment. At the 1-year follow-up of the same study, however, PPT improved more in the group receiving manual therapy.[23] Castro-Sánchez et al. found that 20 weeks of myofascial therapy and craniosacral therapy significantly reduced the number of painful tender points.[24] As a result, more intensive and prolonged intervention protocols may be required for manual therapy to be effective in improving tenderness.

It is difficult to standardize the intervention in studies that use manual therapy as a whole rather than a particular technique.[17,25] In these protocols, the boundaries of this treatment are as broad as the entire body of knowledge of manual therapy and include various combined soft tissue and manipulative techniques. It is not possible to generalize the results of such treatment, which cannot be standardized. Our study, on the other hand, provides information on a single technique (eg, HVLA) applied within well-defined standards. Castro-Sánchez et al. and Moustafa et al. found improvements in FM outcomes in their studies with well-standardized intervention programs.[23,24] However, there is no placebo control in these studies. When evaluating hands-on therapies, nonspecific effects and their magnitude should not be ignored. A reasonable placebo control is also necessary to ensure patient blinding and avoid bias. In our study, we not only used a placebo control but also aimed for a more substantial similarity to manipulation therapy, in contrast to previous studies. The fact that there was no significant difference between our intervention groups in terms of treatment credibility indicates that this similarity was achieved. In this regard, it can be said that our sham manipulation protocol has more similarity with the active treatment compared to the applications used in the literature such as light massage, touch, or physical agents (eg, ultrasound, heat, etc.). Furthermore, this result is important to test how successful the blinding of patients was.

Limitations of the study

Although the placebo design of our study was appropriate to test internal validity, it was not adequate for external validity. This hypothesis needs to be tested in further studies that focus on external validity (eg, multicenter, including broader age groups and male gender).[21]

Another limitation of our study was that the patients in the control group and the therapists were not blinded. Although every effort was made to avoid bias, these individuals who applied and those who did not receive the treatment could not be blinded because of the nature of spinal manipulation. The worse results of the control group could be because the spinal manipulation and sham groups simply received more treatment than the control group.

CONCLUSIONS

Spinal manipulation used in addition to pharmacological treatment in young/middle-aged female patients with FM could be an effective treatment for pain, disease severity, and functionality. Because this study is our first well-designed initiative to test the effectiveness of spinal manipulation, it was designed to take the least amount of time and be as cost effective as possible. Following these results, further studies should test the effectiveness of spinal manipulation in more intensive and prolonged treatment regimens. Older age groups and male patients should also be investigated.

DISCLOSURES

None.

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SUPPORTING INFORMATION

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How to cite this article: Ince B, Kara M, Erdem I, Yurdakul OV, Erden T, Aydın T. Effectiveness of spinal manipulation in addition to pharmacological treatment in fibromyalgia: A blinded randomized trial. *PM&R*. 2023;15(3):342-351. doi:10.1002/pmrj.12953