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Clinical Study

Dose response and efficacy of spinal manipulation for chronic cervicogenic headache: a pilot randomized controlled trial

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Abstract

BACKGROUND CONTEXT: Systematic reviews of randomized controlled trials suggest that spinal manipulative therapy (SMT) is efficacious for care of cervicogenic headache (CGH). The effect of SMT dose on outcomes has not been studied.

PURPOSE: To compare the efficacy of two doses of SMT and two doses of light massage (LM) for CGH.

PATIENT SAMPLE: Eighty patients with chronic CGH.

MAIN OUTCOME MEASURES: Modified Von Korff pain and disability scales for CGH and neck pain (minimum clinically important difference=10 on 100-point scale), number of headaches in the last 4 weeks, and medication use. Data were collected every 4 weeks for 24 weeks. The primary outcome was the CGH pain scale.

METHODS: Participants were randomized to either 8 or 16 treatment sessions with either SMT or a minimal LM control. Patients were treated once or twice per week for 8 weeks. Adjusted mean differences (AMD) between groups were computed using generalized estimating equations for the longitudinal outcomes over all follow-up time points (profile) and using regression modeling for individual time points with baseline characteristics as covariates and with imputed missing data.

RESULTS: For the CGH pain scale, comparisons of 8 and 16 treatment sessions yielded small dose effects: $|AMD| \leq 5.6$. There was an advantage for SMT over the control: AMD=−8.1 (95% confidence interval=−13.3 to −2.8) for the profile, −10.3 (−18.5 to −2.1) at 12 weeks, and −9.8 (−18.7 to −1.0) at 24 weeks. For the higher dose patients, the advantage was greater: AMD=−11.9 (−19.3 to −4.6) for the profile, −14.2 (−25.8 to −2.6) at 12 weeks, and −14.4 (−26.9 to −2.0) at 24 weeks. Patients receiving SMT were also more likely to achieve a 50% improvement in pain scale: adjusted odds ratio=3.6 (1.6 to 8.1) for the profile, 3.1 (0.9 to 9.8) at 12 weeks, and 3.1 (0.9 to 10.3) at 24 weeks. Secondary outcomes showed similar trends favoring SMT. For SMT patients, the mean number of CGH was reduced by half.

CONCLUSIONS: Clinically important differences between SMT and a control intervention were observed favoring SMT. Dose effects tended to be small.

Keywords: Cervicogenic headache; Dose response; Spinal manipulation; Chiropractic; Neck pain; Randomized trial

Introduction

Primary headaches are one of the most common ailments, with a point prevalence in the general population of about 16% [1]. Epidemiological studies report that 5% of adults suffer from headaches on a daily basis [2]; approximately 7 million adults report suffering from headaches every other day [3]. Three types of headaches have been shown to account for the majority of these episodes: migraine, tension type, and cervicogenic [4]. The impact

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EVIDENCE & METHODS

Context
The efficacy of chiropractic spinal manipulation (CSMT) in the treatment of presumed cervicogenic headache remains controversial. The interpretation of all prior studies has been clouded by the heterogeneity of the headache patient population studied and the lack of a standardized spinal manipulation regimen.

Contribution
The authors have found in the patient population studied that CSMT administered to the cervical and upper thoracic spine resulted in a significantly greater improvement in pain scores when compared to a control group that received light massage. There was no significant difference in patient outcomes in patients who received eight or 16 CSMT treatments.

Implications
There are no dose-response studies on CSMT for cervicogenic headache, and an important implication of this study is that there were no better outcomes with more than eight treatment sessions. These results are similar to those reported for other dose response studies where CSMT has been used to treat complaints related to the lumbar spine. The benefits of CSMT in treating cervicogenic headache reported in this study are limited by the research methodology and the context of a pilot study. In particular, the results of this study cannot be confidently generalized to other populations of patients presenting with suspected cervicogenic headache.

—The Editors

on quality of life can be comparable to patients with heart disease [5]. In terms of the financial burden, it has been estimated that headaches account for 157 million days per year lost from work, costing society approximately $50 billion in absenteeism and medical benefits [6].

Cervicogenic headache (CGH) is associated with neck pain and dysfunction [7,8]. Point prevalence estimates range from 0.4% to 4.6% [9–11]. Substantial consumer utilization of complementary and alternative medicine for the care of headache and neck pain has been demonstrated; perceived ''helpfulness'' compared with conventional medicine for symptomatic relief was cited as the reason for the preference [12,13].

The efficacy of spinal manipulative therapy (SMT) for the relief of chronic CGH has been summarized in systematic reviews of randomized controlled trials. One review found insufficient evidence to reach a conclusion [14]. However, the majority of these reviews found evidence for efficacy of SMT in terms of headache intensity, frequency, or duration [15–19]. In particular, higher quality trials showed manipulation to be superior to deep massage [20], placebo [21], and no treatment [22].

To date, one small feasibility trial (n=24) by Haas et al. [23] has evaluated the dose response of SMT in combination with physical modalities for the care of CGH (3–12 treatments in 3 weeks). The authors found significant sustained reduction in headache pain from 4 to 12 weeks after randomization.

Although there is accumulating evidence of efficacy for spinal manipulation in the treatment of headache, treatment visits vary widely in randomized trials: up to twice per week for 3 to 8 weeks. This variability reflects a lack of consensus on the appropriate dose of manipulation that is needed to achieve maximal relief of symptoms. We therefore conducted a pilot study with sufficient power to compare a higher dose versus lower dose of SMT on CGH pain intensity. The study was also designed to test the hypothesis of no difference between SMT and a low-intensity manual therapy control (light massage [LM]).

Methods

Design

A prospective, randomized, controlled trial was conducted using a 2×2 balanced factorial design. The purpose of the study was to make a preliminary evaluation of 1) the effect of the number of treatment sessions (dose) provided by a chiropractor and 2) the relative efficacy of SMT for the care of CGH. The study was conducted in the Western States Chiropractic College Outpatient Clinic and three Portland area private chiropractic clinics between September 2004 and July 2007. A total of 80 participants (n=20 per group) were randomized. Patients were allocated to two levels of dose (8 or 16 treatment sessions). They were also randomized to two levels of intervention: SMT or a minimal LM control to isolate the effect of SMT above the effect of touching the patient therapeutically. Randomization was conducted using computer-generated design adaptive allocation [24] to balance seven potential confounding baseline variables: age, gender, migraine, CGH pain intensity, number of CGHs, relative confidence in SMT and LM, and difference in expected optimal number of sessions for treatment with SMT and LM. The variables are discussed in detail under assessment below. Before randomization, allocation was concealed from all study personnel and participants; data required by the computer program for allocation were collected immediately before randomization to ensure study group concealment. Participants and treating chiropractors were not blinded to intervention after randomization.

All participants received 16 office visits to a study chiropractor, two per week for 8 weeks. Patients were treated once or twice per week. Participants allocated to eight treatment sessions were also assigned to eight visits for a manual

examination once per week. These attention-control visits were used to control time and interaction with the chiropractor, as well as the effects of touching the patients. Palliative medication was permitted for ethical reasons and to facilitate accurate reporting. Care for headaches by a provider outside the study was prohibited during the treatment phase, except if the patient felt it was absolutely required.

Follow-up of study outcomes was conducted through mailed questionnaire at 12 and 24 weeks and through phone interview by a blinded research assistant at 4, 8, 16, and 20 weeks. The primary outcome, identified in advance, was self-reported CGH pain intensity. Study guarantees of the participants' rights and safety were approved by Western States Chiropractic College Institutional Review Board (FWA 851), and data were secured in the College's Center for Outcomes Studies.

Study protocol

Participants were recruited through advertisements in craigslist and local newspapers. The project manager conducted a preliminary eligibility screening by telephone. At the first baseline visit, participants gave informed consent, completed the first baseline questionnaire, received cervical X-rays to rule out contraindications to SMT, and were examined by the screening chiropractor at the college. Eligible persons attended a second baseline visit in the office of a study-treating chiropractor, chosen for patient convenience. Participants completed a second baseline questionnaire and received a brief confirmatory physical examination. Participants were then randomized by the project manager using the allocation computer program.

All intervention and attention-control visits lasted 10 minutes. The patient-provider interaction was evaluated by patient phone interview at 2 weeks to ensure adherence to protocol. Protocol standardization was maintained through office observation and quarterly training. It was further evaluated by a patient interview at 2 weeks. Participants were compensated for their inconvenience and time spent on study assessment ($20 per visit, $10 per returned mailed questionnaire, and $5 per phone interview).

Participants

Volunteers were eligible if they had a history of at least five CGHs per month for a minimum of 3 months, with CGH as defined by the International Headache Society (IHS) in 1998 (excluding the radiographic criterion) [7] and used in the trial by Nilsson [25]. The IHS criteria were 1) pain localized in the neck and occipital region, may project to forehead, orbital region, temples, vertex, or ears; 2) pain precipitated or aggravated by particular neck movements or posture; and 3) either resistance or limitation of passive neck motion, palpatory changes in neck musculature or altered response to stretching/contraction, or abnormal neck muscle tenderness. The newer IHS criteria [8] differ in that they include post hoc headache resolution unusable for study eligibility. To prevent a floor effect, participants were required to have a minimum score of 25 on the 100-point pain intensity scale described below.

Potential participants were excluded if they could not attend two visits per week for 8 weeks for health or logistical reasons. They were also excluded if they were taking prophylactic prescription medication for the treatment of headache or had manipulation/professional massage care for the neck or for headache in the 3 months before baseline. Participants were ineligible for contraindications to spinal manipulation [26] or complicating conditions that may be related to clinical outcomes: malignancy or history of active cancer in the last 5 years, spinal infection, vertebral tumors or fracture, cervical instability, blood dyscrasia, anticoagulant therapy (warfarin or heparin), thrombophlebitis, long-term corticosteroid use, history or symptoms indicating stroke risk, current use of prophylactic headache medication, severe head/neck trauma within the last 12 months, neck/intracranial surgery within the previous 5 years, radiating pain/neurological deficits to the upper extremities or cervical disc condition, arthritis of the cervical spine, severe osteoporosis (suspected from X-ray), referred neck pain of organic origin, or pregnancy (X-ray prohibited).

Persons were also ineligible for other types of headache with etiologies that may confound the effects of manipulation on the cervicogenic component. These headaches types [8] include cluster; metabolic/toxic; sinus; and headaches associated with temporomandibular disease, tumors, and glaucoma.

Patients were permitted to have concomitant migraine and tension-type headaches because of apparent strong concomitance with CGH. Most respondents to ads for our feasibility study reported other headache, usually migraine [23]; many CGH sufferers were shown to have migraine in a previous study [27]; and a common pathway had been proposed for the headache types [28,29]. In addition, we did not consider these headache types a major confounder because they had been shown to be responsive to SMT [19].

Assessment and intervention

A chiropractor/faculty member with 15-years experience screened volunteers for study eligibility through case history, standard orthopedic/neurological examination, heat sensitivity test, and 3-view cervical X-ray using the protocols of Vernon [30] and Souza [31] for CGH and those of Gatterman and Panzer [26] for the cervical region. Four chiropractors with over 20 years of experience served as the primary study therapists; an additional chiropractor in each clinic served as a backup therapist. These chiropractors provided all interactions with the participants during the 10-minute study visits.

The two SMT groups received high-velocity low amplitude spinal manipulation of the cervical and upper thoracic

(transitional region) spine at each visit as described by Peterson and Bergmann [32]. This form of manipulation is the most commonly used by chiropractors [33,34]. Modifications in manipulation recommended for older patients were permitted as required [35,36]. To relax the neck and upper back in preparation for spinal manipulation [37], the chiropractor administered a moist heat pack for 5 minutes and conducted an LM for 2 minutes (described below) as in previous headache trials [38,39]. These procedures are commonly used by chiropractors [33,34,40]. Patient progress was discussed during the 5 minutes with moist heat.

The two LM control groups received 5 minutes of moist heat (as above) followed by 5 minutes of LM. Light massage consisted of gentle effleurage (gliding) and gentle pétrissage (kneading) of the neck and shoulder muscles [32,41]. This allowed us to control contact with the patient with an intervention that was expected to have relatively small specific effects. This was because SMT had been shown superior to deep massage [20], and the LM application was much lighter and of much shorter duration than found in massage trials and in common practice [42,43].

Participants receiving only eight treatment sessions attended the attention-control examination visits. These included a 2-minute discussion of the patient's condition followed by a standardized manual examination (8 minutes): motion and static palpation of the cervical and upper thoracic regions, inclinometric evaluation of active cervical range of motion and associated pain, and algometric pain threshold evaluated over articular pillars/transverse processes [32].

Outcome measures and baseline variables

Cervicogenic headache and neck pain intensity and disability were evaluated using the Modified Von Korff (MVK) scales of Underwood et al. [44]. The primary outcome was the MVK pain scale for CGH. The MVK pain scale is the average of three 11-point numerical rating scales: CGH pain today, worst CGH pain in the last 4 weeks, and average CGH pain in the last 4 weeks. The MVK disability scale (secondary outcome) is the average of three 11-point scales evaluating interference with daily activities, social and recreational activities, and the ability to work outside or around the house. The two scales are scored from 0 to 100 with a lower score more favorable. A 10-point difference between groups was designated in advance as clinically important [19]. The scales have been shown to be reliable, valid, and responsive instruments for measuring pain and disability (including headache) and were chosen for their brevity, simplicity, acceptability to participants, and validity as a phone questionnaire [44]. Other secondary outcomes were quantified over the previous 4 weeks: number of CGH and number of other headaches, as well as prescription medication, over-the-counter medication, and supplement/botanical use for headache treatment/prevention. Professional care outside the study was also recorded.

Baseline variables included measures of outcomes, sociodemographics, and comorbidity. General health status was evaluated using Physical and Mental Component Summary Scales of the SF-12 (Health Status Questionnaire Version 2.0) [45]. Depression was assessed with a 3-item screen associated with the health status questionnaire [46]. Participants were classified as having ''other comorbidity,'' a predictor of pain outcomes [47,48], if they checked any from the following list: arthritis, asthma or allergies, gastrointestinal problems, gynecological problems, hypertension, or other chronic conditions. Treatment credibility was evaluated with 6-point Likert scales on participant confidence in the two interventions' success from Interstudy's Low Back Pain TyPE Specification instrument [49].

Statistical analysis

A full intention-to-treat analysis was conducted with each participant included in the original allocation group; missing data were imputed. The imputation was done as follows: If a missing datum was preceded and followed by present data, then the imputed value was by linear interpolation. If the missing datum was at the end of the present data, then the last present value was carried forward. A sensitivity analysis with missing data excluded was also conducted for the primary outcome, the MVK pain scale for CGH.

All analyses included dose, intervention, and their interaction as the independent variables. Group comparisons were adjusted for baseline covariates in all analyses to yield adjusted mean differences (AMD) between groups and adjusted mean outcomes. The covariates were the seven variables used to randomize participants: CGH pain scale, CGH number, age, gender, migraine, relative confidence in SMT and massage, and difference in expected optimal number of treatment sessions with SMT and LM. The baseline value of the outcome measure was added if not already included in the list.

The primary analysis consisted of linear models. Simultaneous regression, a refinement of repeated measures analysis of covariance, was used to model outcomes for the individual time points [50]. Longitudinal models with generalized estimating equations were used to model profile data over all follow-up time points; this analysis accounts for within-person correlations between time points [50]. The main effects of the intervention and dose factors compared all persons with SMT to all persons with LM and all persons with eight treatment sessions to all persons with 16 treatment sessions, respectively ($n=40$ per arm). Groups were also compared pairwise ($n=20$) to identify if one level of a factor might be dominating any between-group differences (eg, differences between SMT and LM might be considerably greater for 16 treatment sessions than for eight sessions).

In a secondary analysis, CGH and neck pain and CGH number were dichotomized to show the proportion of patients with a 50% improvement in outcomes. The analysis above was then repeated using multiple logistic

regression. Five patients were dropped from this secondary analysis for lack of any follow-up data.

The sample size was determined a priori to provide 80% power to detect a between-group effect of 10 of 100 points for the primary outcome (CGH pain scale) at the .05 level of significance, assuming 20 per group and a 10% loss to follow-up. This group difference (about 20% of baseline pain) has been taken to be clinically important in past studies [6,51] and in a Cochrane review [19] and generally associated with a moderate effect size (0.5) [19]. The study was not powered to detect an interaction effect between intervention and dose conditions. Statistical testing for all other variables was considered secondary analysis and tested at the .05 level of significance. All analyses were conducted with Stata 9.1 (StataCorp, College Station, TX).

Results

The study flowchart is presented in Fig. 1. Adherence to attendance of study visits was sufficiently uniform across groups. The figure shows that at least 75% of the patients in each group attended 12 of 16 visits. On average, participants complied with 86% of the required visits and 70% of the participants attended all study visits. Compliance with follow-up questionnaires was also uniform; 80% to 85% of patients returned the mailed 12-week questionnaire, and 85% to 95% returned the 24-week questionnaire. The seven dropouts were participants who refused to continue care past 2 weeks or provide follow-up data. Ten persons sought care from a provider outside the study during the treatment phase: broken down as six LM and four SMT patients and as six low-dose and four high-dose patients. Only four patients received

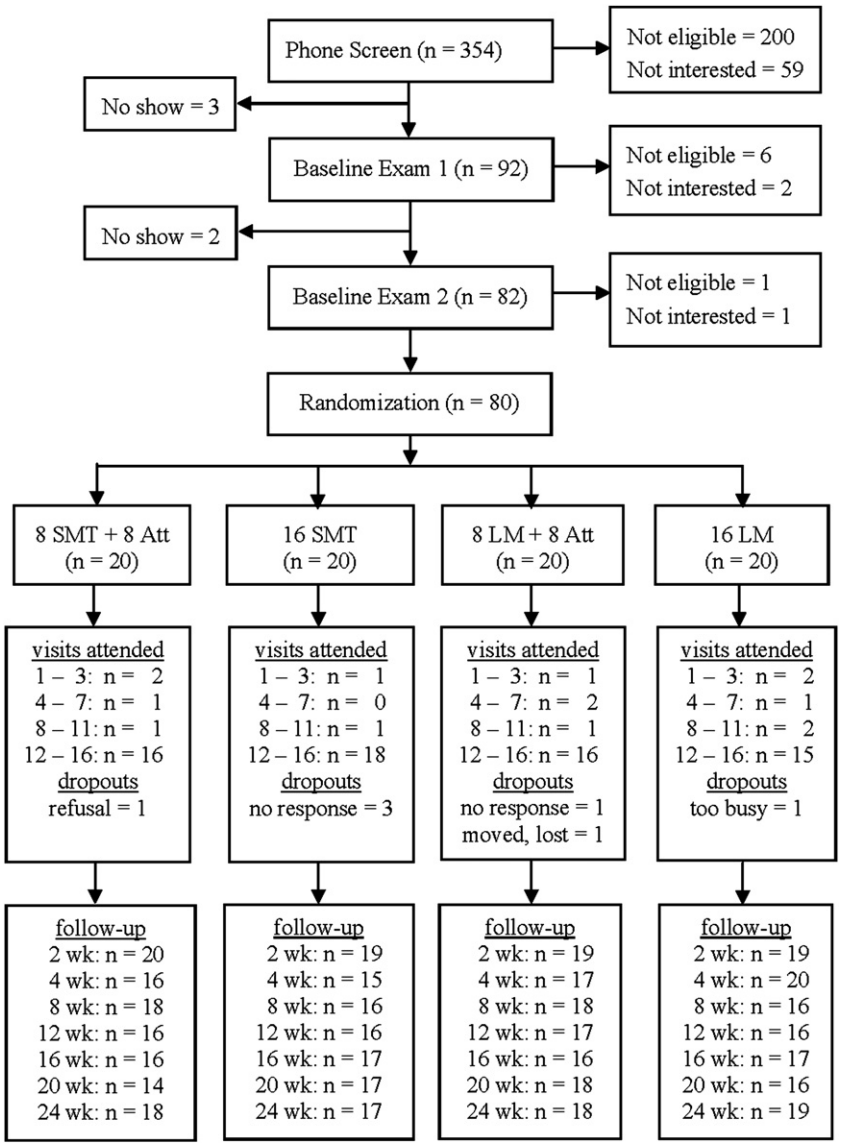

Fig. 1. Patient flow diagram. All patients were assigned 16 visits where they received spinal manipulative therapy (SMT), light massage (LM), or attention-control physical examination (att). Adherence to study visits and compliance with follow-up are identified.

SMT outside the study. Outside care visits were balanced across groups and uncorrelated with pain improvement between 4 and 24 weeks ($p>.05$).

Baseline

Table 1 shows the baseline characteristics for the four study groups. Participants tended to be young (mean=36), white, non-Hispanic (85%) women (80%). The overall mean CGH pain and functional disability scale values were 54.3 and 45.0, respectively. The sample averaged approximately four CGHs per week and less than one ''other'' headache per week. About 1 of 4 subjects reported suffering from migraine, 1 of 2 had low back pain, and 2 of 3 identified another comorbid condition. Participants took some form of oral medication about five times per week on average: mostly over-the-counter analgesics with little prescription drug use.

Participants were asked if they could discern their CGH from other headaches they experienced at baseline and each follow-up time point. Between 89% and 94% of the patients reported that they could distinguish CGH from other types, ''most of the time'' or ''always.'' Also, chi-square analysis showed no significant difference between groups in discernment at any time point ($p>.05$).

CGH pain and disability

Group means with standard deviations, as well as adjusted mean differences with 95% confidence intervals (CIs), for the main and interaction effects are presented in Table 2 for follow-up at 12 weeks, 24 weeks, and the full

Table 1
Baseline participant characteristics

	SMT 8 visits (n=20)	SMT 16 visits (n=20)	LM 8 visits (n=20)	LM 16 visits (n=20)	All (n=80)
Sociodemographic information					
Age (y)	38±10	35±12	37±13	34±10	36±11
Gender (female), %	16 (80)	16 (80)	15 (75)	17 (85)	64 (80)
Race (white non-Hispanic), %	20 (100)	18 (90)	12 (60)	18 (90)	68 (85)
Marital status (married), %	10 (50)	10 (50)	10 (50)	7 (35)	37 (46)
Education (college degree), %	9 (45)	8 (40)	6 (30)	5 (25)	28 (35)
Income (<$24,000/y), %	6 (30)	9 (45)	9 (45)	9 (45)	33 (41)
Expectations					
Confidence in SMT*	4.4±1.3	4.0±1.1	4.0±1.5	4.2±1.3	4.1±1.3
Confidence in LM*	4.1±1.1	4.0±1.3	4.0±1.1	4.2±1.3	4.1±1.2
Optimal visits for SMT (4–20)	12.4±4.8	13.4±5.1	11.6±5.3	13.4±4.7	12.7±5.0
Optimal visits for LM (4–20)	14.4±5.1	14.2±4.6	13.2±5.5	15.2±5.1	14.3±5.0
CGHs					
Pain intensity†	51.2±17.7	50.7±16.8	56.8±15.8	58.7±17.1	54.3±16.9
Pain unpleasantness†	53.0±21.1	55.5±19.6	58.5±16.3	58.0±18.5	56.3±18.7
Functional disability†	47.3±25.6	38.0±19.6	49.3±21.6	45.5±24.5	45.0±22.9
Number (last 4 wk)	14.8±8.4	16.0±7.8	15.8±8.7	16.2±7.0	15.7±7.9
Disability days (last 4 wk)	5.1±4.0	3.3±3.7	5.2±4.8	7.0±6.9	5.1±5.1
Other headaches					
Number (last 4 wk)	2.0±2.4	1.5±6.7	4.6±8.9	5.5±7.5	3.4±6.2
Disability days (last 4 wk)	0.9±1.9	0.8±1.4	1.3±2.3	2.9±6.9	1.5±3.8
Neck					
Pain intensity†	53.3±21.2	53.0±22.7	60.5±21.4	59.0±20.8	56.4±20.8
Functional disability†	46.3±21.7	36.2±22.6	48.5±23.6	41.6±22.8	43.2±22.8
Health status					
Physical health‡	47.0±8.8	47.4±9.2	43.7±9.5	44.7±9.9	45.7±9.3
Mental health‡	45.1±10.1	49.3±8.4	49.1±8.2	45.7±10.6	47.3±9.4
Migraine sufferer (self-report), %	6 (30)	6 (30)	5 (25)	5 (25)	22 (28)
Low back pain (%)	10 (50)	11 (55)	10 (50)	8 (40)	39 (49)
Depression screen (positive), %	8 (40)	8 (40)	6 (30)	7 (35)	29 (36)
Other comorbidity, %	15 (75)	13 (65)	13 (65)	12 (60)	53 (66)
Oral medication use (times in last 4 wk)					
Prescription	3.9±7.8	1.7±3.6	1.1±3.1	4.0±7.8	2.6±6.1
Over the counter	12.7±11.9	13.1±14.1	9.9±11.7	9.7±7.3	11.4±11.4
Supplements	3.9±12.5	1.8±67	6.7±13.7	9.0±11.8	5.4±11.6
Total	20.4±21.3	16.5±17.0	18.0±20.6	22.7±15.8	19.4±18.6

CGH, cervicogenic headache; LM, light massage; SMT, spinal manipulative therapy.

*Six-point Likert scale with 1 indicating lowest confidence and 6 indicating highest confidence.

†Hundred-point scales with lower scores favorable. Pain intensity and functional disability were evaluated with the MVK pain and disability scales.

‡The physical and mental health component summaries of the SF-12 Health Survey are standardized scales with mean=50 and SD=10 in the US general population; higher scores are favorable.

Table 2
Observed mean outcomes (±SD) and adjusted mean differences (95% CI) between groups*

				Intervention main effect	Dose main effect	Interaction effect
		8 treatment sessions	16 treatment sessions	SMT–LM (95% CI)	16–8 sessions (95% CI)	SMT and 16 sessions (95% CI)
CGH pain scale†						
Profile	SMT	36.2±19.8	28.4±20.6	−8.1 (−13.3 to −2.8)‡	−1.73 (6.9 to 3.4)	−7.7 (−18.0 to 2.5)
	LM	42.6±16.6	46.9±18.6			
12 wk	SMT	30.8±20.0	29.6±23.7	−10.3 (−18.5 to −2.1)‡	1.2 (−6.9 to 9.3)	−7.8 (−24.0 to 8.4)
	LM	42.0±20.6	49.4±19.0			
24 wk	SMT	33.3±19.7	27.8±26.7	−9.8 (−18.7 to −1.0)‡	0.0 (−8.7 to 8.7)	−9.2 (−26.6 to 8.2)
	LM	41.5±18.2	48.6±21.4			
CGH disability scale†						
Profile	SMT	27.1±24.5	15.9±20.3	−7.9 (−13.2 to −2.6)‡	0.7 (−4.7 to 6.0)	−5.3 (−15.7 to 5.0)
	LM	33.0±22.0	35.0±24.0			
12 wk	SMT	20.4±18.0	18.0±27.5	−10.0 (−18.8 to −1.3)‡	2.0 (−6.9 to 10.8)	−0.6 (−17.8 to 16.6)
	LM	32.2±23.9	35.4±23.8			
24 wk	SMT	22.2±25.0	17.5±22.8	−6.1 (−15.1 to 2.9)	2.9 (−6.2 to 12.0)	−5.8 (−23.5 to 11.8)
	LM	26.7±17.6	33.3±23.4			
CGH number (in last 4 wk)						
Profile	SMT	8.0±6.0	6.9±7.6	−2.6 (−4.5 to −0.7)‡	0.7 (−1.2 to 2.6)	−0.5 (−4.3 to 3.3)
	LM	10.5±7.9	11.5±7.4			
12 wk	SMT	5.8±4.8	6.4±6.8	−3.6 (−6.2 to −0.9)‡	2.1 (−0.5 to 4.7)	−1.9 (−7.1 to 3.3)
	LM	9.8±6.7	12.9±8.8			
24 wk	SMT	7.2±5.3	6.6±8.2	−2.2 (−5.0 to 0.6)	1.5 (−1.3 to 4.3)	−1.8 (−7.3 to 3.8)
	LM	8.7±7.6	10.7±7.5			
Other headache number (in last 4 wk)						
Profile	SMT	1.3±2.2	1.2±1.6	−1.5 (−2.4 to −0.7)‡	0.1 (−0.7 to 0.9)	−0.9 (−2.5 to 0.8)
	LM	2.9±4.0	3.4±4.2			
12 wk	SMT	1.8±3.3	1.2±1.7	−0.9 (−2.1 to 0.2)	−0.1 (−1.2 to 1.0)	−0.8 (−3.0 to 1.4)
	LM	2.8±4.1	2.8±2.5			
24 wk	SMT	1.5±2.4	1.1±1.5	−2.1 (−3.8 to −0.5)‡	0.0 (−1.5 to 1.6)	−1.2 (−4.4 to 1.9)
	LM	3.5±5.2	4.3±5.8			
Neck pain scale†						
Profile	SMT	37.6±24.4	30.6±25.6	−8.7 (−17.5 to 0.1)	−3.6 (−12.3 to 5.1)	−9.3 (−26.6 to 7.9)
	LM	44.9±22.7	47.9±22.2			
12 wk	SMT	36.9±22.9	32.9±24.9	−7.5 (−16.5 to 1.4)	−3.5 (−12.3 to 5.4)	−4.8 (−22.4 to 12.8)
	LM	47.1±24.2	47.2±21.8			
24 wk	SMT	38.3±26.3	28.2±26.9	−9.9 (−20.0 to 0.2)	−3.7 (−13.7 to 6.3)	−13.9 (−33.8 to 6.0)
	LM	42.8±21.6	48.4±23.1			
Neck disability scale†						
Profile	SMT	23.2±23.8	15.2±22.1	−9.1 (−17.5 to −0.7)‡	2.0 (−6.6 to 10.6)	−2.1 (−18.5 to 14.4)
	LM	32.8±25.7	34.3±24.8			
12 wk	SMT	22.9±24.8	14.5±21.4	−11.0 (−19.6 to −2.3)‡	−1.0 (−9.9 to 7.9)	1.9 (−15.1 to 18.9)
	LM	37.5±25.8	33.8±21.9			
24 wk	SMT	23.5±23.6	15.9±23.4	−7.3 (−16.8 to 2.3)	5.0 (−4.8 to 14.8)	−6.0 (−24.8 to 12.7)
	LM	28.3±25.5	34.7±27.6			
Over the counter (times in last 4 wk)						
Profile	SMT	8.5±13.6	6.8±8.4	−3.2 (−6.3 to 0.0)	−1.2 (−4.0 to 1.7)	−0.6 (−6.1 to 4.9)
	LM	9.4±11.6	8.2±8.2			
12 wk	SMT	6.3±8.7	6.9±8.4	−1.8 (−5.1 to 1.5)	0.7 (−2.5 to 3.9)	0.3 (−6.1 to 6.8)
	LM	7.2±9.0	7.3±7.7			
24 wk	SMT	8.1±8.5	7.0±8.6	−6.0 (−10.1 to −2.0)‡	−0.2 (−4.1 to 3.8)	−1.0 (−8.9 to 6.9)
	LM	12.1±12.3	11.7±9.5			

CGH, cervicogenic headache; CI, confidence interval; LM, light massage; SMT, spinal manipulative therapy.

*Outcomes are presented for the 12- and 24-week follow-ups, as well as for the full profile averaged across all follow-ups (4–24 weeks). Original data (mean±SD) are included for the four study groups. The main effects are adjusted mean differences (n=40 per comparison group). The means (with 95% CIs) were adjusted in the analysis for baseline differences between groups: outcome measure, CGH pain score, number of CGH, age, gender, presence of migraine, patient's confidence in SMT versus LM, and expected number of SMT versus LM treatment sessions for optimal CGH improvement. Generalized estimating equations were used to analyze the full profile, and simultaneous regression was used to analyze the 12- and 24-week follow-ups; missing data were imputed. A negative main effect favors SMT over LM and favors 16 treatment sessions over eight treatment sessions. A negative interaction effect shows that a treatment effect favoring SMT is greater for 16 sessions than for eight sessions and that a dose effect favoring 16 sessions is greater for SMT than for LM. See Table 3.

†MVK scale (scored from 0 to 100 points with lower score preferable). The pain scale is the primary outcome.

‡$p<.05$.

profile over all time points. Adjusted pairwise comparisons are included in Table 3. The adjusted mean differences between groups were consistently smaller than unadjusted comparisons because of baseline differences in the covariates.

For the MVK pain scale, the primary outcome, Table 2 shows that there were no clinically important main effects of dose (|AMD|<2). Table 3 further shows that pairwise comparisons were small in magnitude (|AMD|≤5.6). There were, in contrast, clinically important and statistically significant main effects of intervention favoring SMT over LM. The AMD was −8.1 for the entire profile, −10.3 at 12 weeks, and −9.8 at 24 weeks (Table 2). The largest pairwise effects of SMT were found for 16 treatment sessions, AMD=−11.9 to −14.4, as opposed to eight sessions, AMD=−4.2 to −6.4 (Table 3). The effects were smaller for the profile than for the individual time points because the profile included data from 4 weeks, which was only halfway through study care.

Figure 2 shows the adjusted follow-up means for the CGH pain scale for all time points. The baseline value in the figure is the overall sample mean (54.3). It is included here because adjusted pain outcomes are determined relative to this common value for all groups. Inspection of Fig. 2 shows that most improvement in the MVK pain scale was achieved by the end of care at 8 weeks and was durable to 24 weeks. Spinal manipulative therapy performed better than LM at all time points. However, the graphs show further room for patient improvement.

Dose and intervention effects for CGH disability demonstrated similar trends to that of CGH pain. Most AMDs were slightly smaller in magnitude and less likely to be statistically significant because of greater variability in the data.

Headache number

There were statistically significant intervention main effects favoring SMT for the profile (AMD=−2.6) and at 12 weeks (AMD=−3.6) for the number of CGH in the prior 4 weeks (Table 2). Significant intervention effects were also found for 16 sessions in Table 3. Dose effects were smaller,

Table 3
Adjusted mean differences (95% CI) for pairwise group comparisons*

	Intervention effects: SMT–LM (95% CI)		Dose effects: 16–8 sessions (95% CI)	
	8 sessions	16 sessions	LM	SMT
CGH pain scale†				
Profile	−4.2 (−11.5 to 3.1)	−11.9 (−4.6 to −19.3)‡	2.1 (−5.1 to 9.4)	−5.6 (−12.9 to 1.7)
12 wk	−6.4 (−17.9 to 5.0)	−14.2 (−25.8 to −2.6)‡	5.1 (−6.3 to 16.5)	−2.7 (−14.2 to 8.8)
24 wk	−5.2 (−17.5 to 7.1)	−14.4 (−26.9 to −2.0)‡	4.6 (−7.7 to 16.9)	−4.6 (−17.0 to 7.8)
CGH disability scale†				
Profile	−5.2 (−12.6 to 2.1)	−10.6 (−18.0 to −3.2)‡	3.3 (−4.0 to 10.7)	−2.0 (−9.5 to 5.5)
12 wk	−9.7 (−21.9 to 2.5)	−10.3 (−22.6 to 2.0)	2.3 (−10.0 to 14.5)	1.7 (−10.7 to 14.1)
24 wk	−3.2 (−15.7 to 9.4)	−9.0 (−21.7 to 3.6)	5.8 (−6.7 to 18.4)	0.0 (−12.8 to 12.8)
CGH number (in last 4 wk)				
Profile	−2.4 (−5.1 to 0.4)	−2.9 (−5.6 to −0.1)‡	0.9 (−1.7 to 3.6)	0.4 (−2.3 to 3.2)
12 wk	−2.6 (−6.3 to 1.0)	−4.5 (−8.2 to −0.8)‡	3.1 (−0.6 to 6.7)	1.2 (−2.5 to 4.8)
24 wk	−1.3 (−5.2 to 2.6)	−3.1 (−7.1 to 0.9)	2.4 (−1.6 to 6.3)	0.6 (−3.4 to 4.5)
Other headache number (in last 4 wk)				
Profile	−1.1 (−2.3 to 0.1)	−2.0 (−3.2 to −0.7)	0.6 (−0.6 to 1.7)	−0.3 (−1.5 to 0.9)
12 wk	−0.5 (−2.1 to 1.1)	−1.3 (−3.0 to 0.3)	0.3 (−1.3 to 1.9)	−0.5 (−2.1 to 1.1)
24 wk	−1.5 (−3.8 to 0.7)	−2.8 (−5.1 to −0.5)‡	0.6 (−1.6 to 2.9)	−0.6 (−2.8 to 1.6)
Neck pain scale†				
Profile	−4.0 (−16.3 to 8.2)	−13.4 (−25.8 to −1.0)‡	1.1 (−11.1 to 13.3)	−8.3 (−20.5 to 4.0)
12 wk	−5.2 (−17.6 to 7.3)	−9.9 (−22.5 to 2.7)	−1.1 (−13.6 to 11.3)	−5.9 (−18.4 to 6.6)
24 wk	−2.9 (−17.0 to 11.2)	−16.8 (−31.1 to −2.6)‡	3.3 (−10.8 to 17.3)	−10.6 (−24.8 to 3.5)
Neck disability scale†				
Profile	−8.1 (−19.8 to 3.6)	−10.1 (−21.9 to 1.6)	3.0 (−8.7 to 14.8)	0.9 (−11.1 to 13.0)
12 wk	−11.9 (−24.0 to 0.2)	−10.0 (−22.2 to 2.2)	−2.0 (−14.1 to 10.2)	−0.1 (−12.5 to 12.4)
24 wk	−4.2 (−17.5 to 9.1)	−10.3 (−23.7 to 3.1)	8.0 (−5.4 to 21.4)	2.0 (−11.7 to 15.7)
Over the counter (times in last 4 wk)				
Profile	−2.9 (−7.5 to 1.8)	−3.5 (−7.1 to 0.2)	−0.9 (−4.8 to 3.0)	−1.5 (−5.4 to 2.5)
12 wk	−2.0 (−6.6 to 2.6)	−1.6 (−6.3 to 3.0)	0.6 (−4.0 to 5.1)	0.9 (−3.7 to 5.5)
24 wk	−5.5 (−11.2 to 0.1)	−6.5 (−12.3 to −0.8)‡	0.3 (−5.3 to 5.9)	−0.7 (−6.3 to 4.9)

CGH, cervicogenic headache; CI, confidence interval; LM, light massage; SMT, spinal manipulative therapy.

*Outcomes are presented for the 12- and 24-week follow-ups, as well as for the full profile averaged across all follow-ups (4–24 weeks). Adjusted mean differences are presented for comparisons of treatments for both 8 and 16 treatment sessions and for comparison of doses for both SMT and LM. Analysis was conducted as in Table 2. The largest treatment effects of SMT are noted for 16 sessions.

†MVK scale (scored from 0 to 100 points with lower score preferable). The pain scale is the primary outcome.

‡$p<.05$.

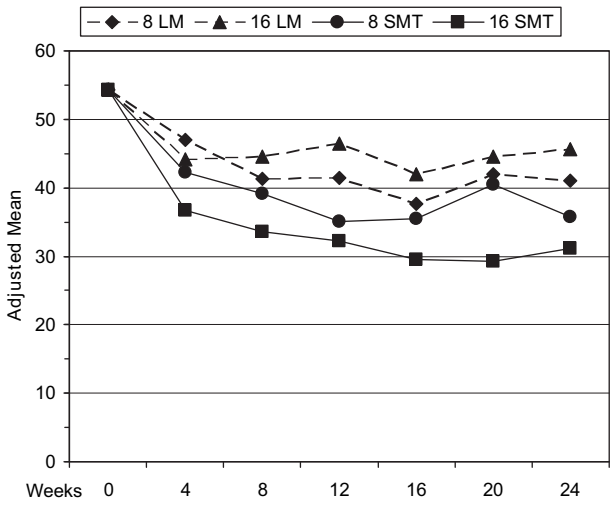

Fig. 2. Adjusted mean cervicogenic headache (CGH) pain. Predicted follow-up means were computed using simultaneous regression analysis adjusted for the baseline covariates. The analysis assumes that all groups start at the grand baseline mean pain (shown at Week 0).

particularly for SMT. Figure 3 shows that the adjusted mean number of CGH was decreased by more than half in participants receiving SMT and that the improvement was sustained to 24 weeks.

"Other" headaches were rare compared with CGH. The mean number at baseline was 3.4 compared with 15.7 in the prior 4 weeks. Findings for other headache numbers paralleled those for CGH. The intervention effects were smaller in magnitude (Table 2) but larger in proportion to baseline number of headaches. Of note was the benefit of SMT over LM at 24 months (AMD=−2.1). At this time point, only SMT patients demonstrated improvement from baseline.

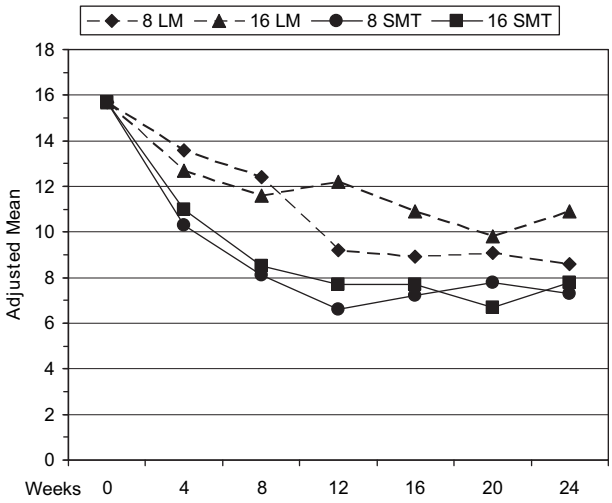

Fig. 3. Adjusted mean number of cervicogenic headaches (CGHs). Predicted follow-up means were computed using simultaneous regression analysis adjusted for the baseline covariates. The analysis assumes that all groups start at the grand baseline mean pain (shown at Week 0).

Neck pain and disability

The main effects were similar to those of CGH pain and disability but generally of lesser magnitude. Dose effects were mostly small, with the exception in Table 3 of a clinically important advantage of higher dose SMT over lower dose SMT. Table 2 showed some statistically significant intervention effects for disability. However, the advantage for SMT in pain and disability consistently reached clinical importance only for the higher dose, 16 treatment sessions (Table 3). The study did not have power to reach statistical significance.

Medication use

Dose effects were unremarkable for oral medication. Table 2 shows that improvement in over-the-counter usage achieved at 12 weeks was only sustained for SMT patients at 24 weeks. The SMT patients were using a third less medication compared with baseline at 24 weeks, and there was a statistically significant advantage for SMT over LM at this time point (AMD=−6.0).

Secondary analysis: 50% symptom reduction

Table 4 shows the percentage of participants who achieved a 50% reduction in outcomes at 12 and 24 weeks and for the profile over all follow-up time points. Dose effects were small. On the other hand, SMT was considerably more likely to achieve a 50% reduction in symptoms (adjusted odds ratio>1.8). In fact, the adjusted odds ratios for CGH pain were greater than 3.0.

Sensitivity analysis

The sensitivity analysis using original data without imputation for CGH pain scale (primary outcome) showed the same general trends presented above in Table 2. However, there were some notable differences from the data in Table 3. A clinically important dose effect was observed favoring 16 SMT sessions over eight SMT sessions: the profile AMD=−9.4 (95% CI=−17.4 to −1.5), 12-week AMD=−13.1 (−27.0 to 0.8), and 24-week AMD=−11.4 (−26.6 to 3.9). In addition, the advantage of SMT over LM was somewhat larger for patients receiving the higher dose of care: 12-week AMD=−20.4 (−33.4 to −7.3) and 24-week AMD=−14.4 (−28.7 to −0.2). Adjusted odds ratios for symptom reduction were also consistent with the findings in Table 4.

Discussion

This was the first randomized trial to study the effect of SMT dose on headache and the efficacy of SMT across dose conditions. There were several notable findings. Regarding dose, there was little difference between 8 and 16 treatment sessions for a battery of headache and neck outcome

Table 4
Patients achieving a 50% reduction in symptoms and adjusted odds ratios (95% CI)*

				Intervention main effect	Dose main effect	Interaction effect
		8 treatment sessions, n (%)	16 treatment sessions, n (%)	SMT/LM, OR (95% CI)	16/8 sessions, OR (95% CI)	SMT and 16 sessions, OR (95% CI)
CGH pain scale†						
Profile	SMT	10 (53)	9 (53)	3.6 (1.6 to 8.1)‡	1.1 (0.5 to 2.4)	1.9 (0.4 to 9.9)
	LM	9 (47)	7 (35)			
12 wk	SMT	6 (38)	6 (35)	3.1 (0.9 to 9.8)	0.5 (0.2 to 1.5)	4.0 (0.4 to 41.2)
	LM	6 (35)	1 (6)			
24 wk	SMT	5 (28)	8 (47)	3.1 (0.9 to 10.3)	1.2 (0.4 to 3.6)	4.0 (0.4 to 37.9)
	LM	5 (28)	3 (16)			
CGH number (in last 4 wk)						
Profile	SMT	16 (84)	15 (88)	2.1 (1.0 to 4.5)‡	1.0 (0.5 to 2.0)	1.2 (0.3 to 4.4)
	LM	13 (68)	14 (70)			
12 wk	SMT	12 (75)	10 (59)	2.6 (0.9 to 7.4)	0.5 (0.2 to 1.5)	1.0 (0.1 to 7.4)
	LM	8 (47)	6 (38)			
24 wk	SMT	10 (56)	11 (65)	1.8 (0.7 to 5.1)	0.8 (0.3 to 2.2)	2.7 (0.4 to 19.5)
	LM	10 (56)	9 (47)			
Neck pain†						
Profile	SMT	7 (37)	8 (47)	2.5 (1.0 to 6.4)	1.2 (0.4 to 3.3)	2.7 (0.4 to 18.4)
	LM	7 (37)	5 (25)			
12 wk	SMT	5 (31)	6 (35)	2.5 (0.7 to 8.3)	1.6 (0.5 to 5.1)	1.3 (0.1 to 13.2)
	LM	3 (18)	4 (25)			
24 wk	SMT	6 (33)	8 (47)	2.9 (0.9 to 9.3)	1.0 (0.3 to 3.1)	6.0 (0.6 to 61.3)
	LM	6 (33)	4 (21)			

CGH, cervicogenic headache; CI, confidence interval; LM, light massage; OR, adjusted odds ratio; SMT, spinal manipulative therapy.

*Outcomes are presented for the 12- and 24-week follow-ups, as well as for the full profile across all follow-ups (4–24 weeks). Original data, n (%) are included for the four study groups. The main effects are adjusted odds ratios (n=40 per comparison group). The odds ratios were adjusted in the analysis for baseline differences between groups as in Table 2. The effects for the individual time points were computed using logistic regression. The profile effects were computed across all follow-up time points using logistic regression with generalized estimating equations. Missing data were imputed except for five patients with no follow-up data. A main effect with OR>1 favors SMT over LM and favors 16 treatment sessions over eight treatment sessions.

†MVK scale (scored from 0 to 100 points with lower score preferable). The pain score is the primary outcome.

‡$p<.05$.

measures. Although somewhat greater improvement was generally seen for 16 SMT visits, the greatest dose effect found for CGH pain did not reach clinical importance in the primary analysis. Still, a dose effect in the range of 8 to 16 treatment sessions for SMT cannot be unequivocally ruled out. The alternative analysis without imputed data did suggest some clinically important differences.

Second, clinically important and statistically significant differences between SMT and LM were observed for CGH pain and disability. The largest intervention effects were found consistently at the higher dose of 16 treatment sessions. However, this pilot study was not powered to evaluate an interaction effect, and the hypothesis that there is a greater advantage for SMT over a control at the higher dose than at the lower dose could not be tested. Overall, the intervention effect sizes (standardized mean differences) for CGH pain were moderate to large for the main effects in Table 2 and for 16 sessions in Table 3 (between 0.5 and 1.0) [52]. The odds ratios for 50% reduction in CGH pain also substantially favored SMT (>3.0).

Third, there was substantial and sustainable reduction in CGH pain and number of headaches concomitant with decreased use of over-the-counter pain medication. This suggests that confounding effects of medication on pain improvement were likely minimal. The decrease in medication use was also only durable to 24 weeks for SMT. This implies that the differences between SMT and control may have been underestimated for follow-up in the longer term.

Finally, Figs. 2 and 3 showed that the average SMT patient could cut the number of headaches in half by 8 weeks. The average higher dose SMT patient could achieve a clinically important improvement (20 of 100 points) [53,54]. However, the figures make it clear that there is further room for improvement in CGH outcomes. This can be explored with study of the inclusion of ancillary modalities and integrative care models.

The prevalence of self-reported migraine headaches was unexpectedly low (28%) at baseline, given the high representation of migraine (>90%) in CGH sufferers observed by Fishbain et al. [27]. The lower prevalence may have been because of advertisement without mention of migraine, type of care offered, and exclusion from the study for prophylactic use of medication. It is interesting to note that migraine appeared to have little effect in this study on CGH pain and disability outcomes for the longitudinal profile (data not shown). This may be attributed to independence of mechanisms [55–57] or the influence of

treatment observed in the study on other headaches (migraine and/or tension type). A clinical benefit for SMT in the treatment of all three headache types has been noted in systematic reviews [15–17,19,58].

Important strengths of our trial design were the inclusion of a control treatment across dose of intervention, as well as control of attention and the effects of touching the patient. The principal limitation was sample size, and our pilot study findings should be considered preliminary. There is reasonable confidence in the analysis of main effects because comparisons had 40 in each group. However, the pairwise comparisons had only 20 per group and were more susceptible to the effects of unmeasured confounding variables and imprecise estimates of group differences (ie, wide CIs).

The absence of blinding made the study susceptible to the confounding effects of patient expectation and the patient-provider encounter. Expectations were balanced at baseline (Table 1). Other analysis, to be published elsewhere, demonstrated that patient perception of chiropractor enthusiasm was also balanced across groups and that both patient expectation and the patient-provider encounter were poor determinants of outcomes (Haas M, Aickin M, Vavrek D. A path analysis of expectancy and patient-provider encounter in an open-label randomized controlled trial of spinal manipulation for cervicogenic headache. J Manipulative Physiol Ther [accepted]).

The medication usage from our study cannot be generalized to that seen in practice. It is underestimated because participants taking analgesics regularly as a preventive measure were excluded from the study. This was necessary to minimize confounding in a trial with pain as the primary outcome. The length of study follow-up was limited by the duration of the grant support. A future study will include follow-up to at least 1 year. Finally, it is unknown at this time what subpopulations and CGH etiologies would most benefit from SMT. This requires further exploration.

Conclusions

Our pilot study adds to an emerging picture of SMT dose for the treatment of headache. It showed that a plateau in intervention effect might be found in the range of 8 to 16 treatment sessions, although a dose effect at these treatment levels cannot be ruled out. The study also adds to the support of SMT in moderate doses as a viable option for the treatment of CGH. What remains to be determined is a more precise estimate of the dose-response relationship with more dose conditions and whether it is dependent on ancillary care and duration of intervention in practice. That is, is short-term concentrated care or long-term care with less frequent visits more effective and cost effective and is there an effect on dose response of physical modalities, lifestyle changes, other ancillary procedures, and an integrative care approach across health care professions?

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