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Spinal manipulative therapy versus a low force mimic maneuver for women with primary dysmenorrhea: a randomized, observer-blinded, clinical trial

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Abstract

Non-drug therapies for women with primary dysmenorrhea are primarily based on anecdotal evidence and small-scale clinical studies. This randomized, observer-blinded, clinical trial evaluated the efficacy of spinal manipulative therapy (SMT) in the treatment of women with primary dysmenorrhea. Women were recruited from the Chicago metropolitan area and evaluated for inclusion through four screening levels. One hundred thirty eight women, ages 18–45, with primary dysmenorrhea diagnosed by participating gynecologists, were randomly assigned to either SMT or a low-force mimic (LFM) maneuver. No treatment occurred at menstrual cycle 1. Treatment for both groups took place on day 1 of cycles 2, 3 and 4, and prophylactic treatment of three visits took place during the 7 days before cycles 3 and 4. Main outcome measures were the Visual Analog Scale (VAS) and plasma concentration of the prostaglandin $F_{2\alpha}$ metabolite, 15-keto-13,14-dihydro-prostaglandin $F_{2\alpha}$ ($KDPGF_{2\alpha}$), measured 15 min before treatment and 60 min after treatment on day 1 of four consecutive menstrual cycles. The Moos' Menstrual Distress Questionnaire (MDQ) was also administered after treatment on day 1 of each cycle. At cycle 2, the post-treatment VAS scores decreased for both groups, with no statistically significant difference in pre- to post-treatment scores between the two groups ($P = 0.44$). The changes in pre- to post-treatment $KDPGF_{2\alpha}$ levels were not statistically different between the SMT and LFM groups ($P = 0.15$). No treatment effects were detected over the three cycles for VAS, $KDPGF_{2\alpha}$ or MDQ ($P = 0.65$, $P = 0.61$ and $P = 0.78$, respectively). However, there were statistically significant linear time effects for VAS ($P = 0.008$), MDQ ($P < 0.001$), and borderline significance for $KDPGF_{2\alpha}$ ($P = 0.054$); these decreases were not considered clinically meaningful. The LFM maneuver used in this study was designed to act as a 'placebo-like' control treatment in comparison with SMT. Although it is possible that the trial did not continue long enough for any placebo effect of the LFM to wash out, it seems more likely that this maneuver was indistinguishable from SMT. Therefore, the postulated superior benefit of high-velocity, short-lever, low-amplitude, high-force spinal manipulation to a low-force maneuver is not supported by the results of this study.

Keywords: Primary dysmenorrhea; Manipulation; Prostaglandins; Pain measurement; Randomized controlled trial

1. Introduction

The socioeconomic impact of primary dysmenorrhea is enormous. Half the women of childbearing age are believed to be affected and, of these, 10% experience incapacitating pain for 1–3 days every month (Dawood, 1985, 1988; Avant, 1988; Jamieson and Steege, 1996). Estimates of the number of work hours lost per year in the US from absenteeism due to primary dysmenorrhea varies between 100 and 600 million (Dawood, 1984, 1986; Treybig, 1989a,b,c; US Department of Commerce, 1989). Moreover, women who do work when they have dysmenorrhea tend to have a reduced work capacity and a lower work output (Bergsjo, 1979; Dawood, 1988). As women constitute an increasingly larger percentage of the work force, the economic impact of primary dysmenorrhea will continue to exist.

Compelling evidence supports the hypothesis that prostaglandins are involved in the etiology of primary dysmenorrhea (Pickles, 1957; Pickles et al., 1965; Rosenwaks and

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Seegar-Jones, 1980; Dawood, 1985, 1986, 1990). Non-steroidal anti-inflammatory drugs (NSAIDs) are, at least partially, effective in relieving primary dysmenorrhea in about 90% of sufferers and completely effective in 55–70%. The reason why 10–30% of cases are refractory to NSAIDs is unclear at present, although increased activity of the 5-lipoxygenase pathway leading to leukotrienes has been suggested (Dawood, 1990). Oral contraceptives (OCs) are also widely prescribed for controlling primary dysmenorrhea. Both NSAIDs and OCs reduce the levels of prostaglandins in menstrual fluid to below those found in eumenorrheic women (Chan et al., 1981); however, both classes of drugs have side effects and their use is not without some risk. NSAIDs may cause gastrointestinal disturbances, nausea, vomiting, constipation, headache, vertigo, fatigue and allergic reactions. Oral contraceptives may cause adverse effects on the liver, diminished glucose tolerance and hypertension. Oral contraceptives are also contraindicated in women over 35, especially smokers, due to the risk of thrombotic disease (Mishell, 1991; Lindegaard, 1998). In addition, many women wish to become pregnant or do not wish to use OCs on personal or religious grounds. Therefore, investigation of alternative therapies is warranted.

Non-drug therapies for primary dysmenorrhea that have been studied include behavioral therapy (Cox and Meyer, 1978; Denney and Gerrard, 1981; Quillen and Denney, 1982; Amodei et al., 1987), transcutaneous electrical nerve stimulation (TENS) (Lundeberg et al., 1985; Mannheimer and Whalen, 1985; Neighbors et al., 1987; Lewers et al., 1989; Dawood and Ramos, 1990; Milsom et al., 1994), subcutaneous peripheral nerve stimulation (Walker and Katz, 1981), acupuncture (Helms, 1987; Xiaoma, 1987), and exercise (Golub et al., 1968; Israel et al., 1985; Izzo and Labriola, 1991). Prostaglandin levels were not determined in these studies, although some authors speculated that increased production of endogenous opioids might be responsible for the alleviation of symptoms.

Osteopathic and chiropractic manual therapies are also used to treat primary dysmenorrhea. However, reports of the ‘efficacy’ of these therapeutic regimens are largely anecdotal and almost exclusively confined to the literature outside of the major biomedical indexes (Hitchcock, 1976; Thomason et al., 1979; Wiles, 1980; Arnold-Frochot, 1981; Wiles and Diakow, 1982; Radler, 1984; Liebl and Butler, 1990; Kokjohn et al., 1992; Boesler et al., 1993). Only the studies by Thomason et al. (1979) and Kokjohn et al. (1992) included a control group of subjects. Despite the virtual absence of evidence demonstrating lower plasma prostaglandins following manipulative therapy for primary dysmenorrhea, and only empirical evidence to support claims of pain reduction by spinal manipulation, chiropractic and osteopathic physicians routinely treat women with primary dysmenorrhea with manual therapy. In 1992, we reported the results from a pilot study comparing the effect of one spinal manipulative maneuver with a low force (sham) intervention on plasma levels of the prostaglandin $F_{2\alpha}$ metabolite, 15-keto-13,14-dihydro-prostaglandin $F_{2\alpha}$ ($KDPGF_{2\alpha}$), pain perception and menstrual distress, before and after treatment at one menstrual cycle (Kokjohn et al., 1992). The results of this study indicated that in women with primary dysmenorrhea, plasma levels of $KDPGF_{2\alpha}$ measured on the first day of menstruation are lower 60 min following spinal manipulation of the lumbar spine than they are before treatment. A significant reduction in pain perception and in menstrual distress was also observed. Not unexpectedly, our sham treatment group experienced a reduction in both pain perception and $KDPGF_{2\alpha}$ similar to the early beneficial effect observed in control subjects receiving a placebo in drug trials (Mehlisch, 1988; Fedele et al., 1989). Consequently, in evaluating the efficacy of manual therapy for women with primary dysmenorrhea, it is important to conduct studies of sufficient duration to account for possible non-specific effects.

1.1. Purpose

The research hypothesis for the present study was that SMT, compared with a LFM maneuver, will reduce the subjective reporting of pain, determined with a visual analog scale and decrease the plasma $KDPGF_{2\alpha}$ concentration. Treatment and follow-up over four menstrual cycles allowed us to account for possible non-specific effects of manual therapy, which we found in our pilot study (Kokjohn et al., 1992). Primary outcomes were evaluated with respect to acute treatment effects, as well as with respect to prophylactic plus acute treatment effects. As a secondary outcome, we assessed the perceived effect of menstrual distress on activities of daily living with the MDQ.

2. Methods

2.1. Power calculation

A sample size of 68 subjects in each treatment group allowed for an overall 0.05 level of significance with 80% power, assuming standard deviations consistent with those observed in the pilot study, to detect effect sizes of 15 mm on the visual analog scale and 20 pg/ml for plasma $KDPGF_{2\alpha}$ levels with respect to the acute and prophylactic plus acute treatment effects.

2.2. Recruitment and screening of subjects

Potential subjects responded to local advertisements in Chicago metropolitan newspapers. Respondents were screened by telephone and scheduled for clinic visits from February 1994 to May 1996. The telephone survey (S1) was designed to exclude subjects based on the criteria that were listed in the advertisements. Eligible women were invited to attend the National College Chiropractic Center (NCCC), a chiropractic college outpatient clinic, for the second screening level (S2), which included the collection of basic demographic information, a past medical history and a physical examination by a licensed doctor of chiropractic (DC), and a blood sample was taken to determine ovulatory measures of $KDPGF_{2\alpha}$. Women who were eligible at S2 and agreed to further screening were scheduled for a detailed gynecological history, physical examination and Papanicolaou smear (S3) by one of the six Board certified medical specialists in obstetrics and gynecology at the Midwest Women's Center. Finally, subjects who attended NCCC on the first day of their next menstrual cycle (baseline – cycle 1), for measurement of primary and secondary outcomes and a 60-minute no treatment clinic visit (subjects sat quietly in the treatment room), were eligible for randomization at cycle 2. All subsequent evaluations and treatment took place at NCCC. A schematic of the study protocol is shown in Fig. 1.

At S2, subjects were thoroughly instructed in the aims and details of the trial, an information sheet was provided, and informed consent was obtained. Women signed the consent form at S2 with the understanding that the third screening level might result in their exclusion from the opportunity to participate in the trial. The National College of Chiropractic Institutional Review Board reviewed and approved the proposal and consent procedures.

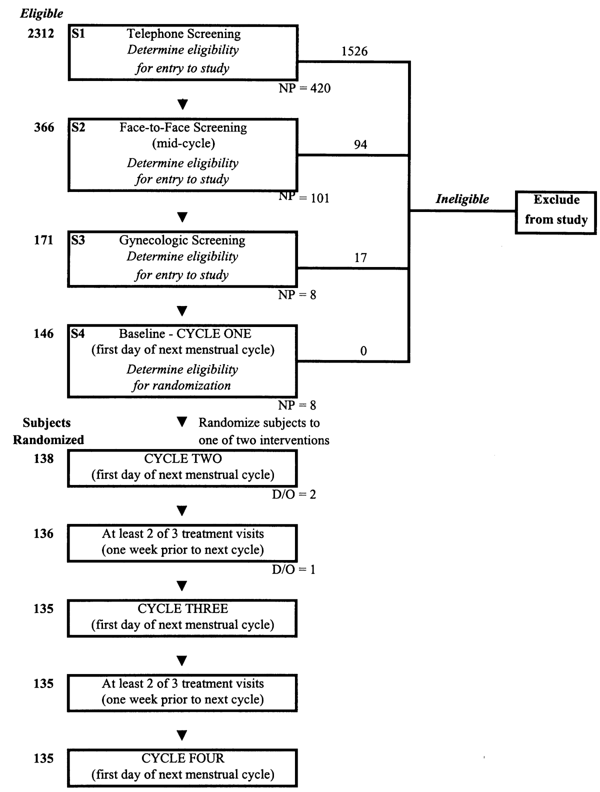

Fig. 1. Study protocol and number of subjects at each visit. S, screening level; NP, non-participants; D/O, drop-outs.

2.3. Inclusion criteria

For inclusion in the study, women were required to be sexually active, non-pregnant, in general good health, 18–45 years of age, with regular menstrual cycles accompanied by moderate to severe pain, and with a diagnosis of primary dysmenorrhea. Study subjects could have no signs of cervical dysplasia on a Papanicolaou smear, taken before they began the study. Inclusion also required that subjects agreed to refrain from the use of an IUD, or OCs for the duration of the study, and from the use of NSAIDs or other analgesics with prostaglandin synthetase-inhibiting activity the week before the expected onset of each menstrual period.

2.4. Exclusion criteria

Subjects with a likely diagnosis of secondary dysmenorrhea due to any identifiable gynecologic condition, including endometriosis, ovarian cyst, pelvic inflammatory disease, uterine cancer, or pre-cancerous lesions and subjects who were taking psychotherapeutic drugs or agents with prostaglandin synthetase-inhibiting activity on a regular basis, were excluded. Subjects who had used OCs, 'Depo-Provera' contraceptive injection, the 'Norplant' implant, or an intrauterine device, or who had received treatment by a chiropractor for low-back pain during the preceding 6 months, were also excluded from the study, as well as women who were currently seeking or receiving care at any facility for low-back pain, or currently seeking compensation for a work-related injury or personal injury case. Subjects were excluded if there was any contraindication to SMT, such as osteoporosis or other bony pathology, or morbid obesity. If there was a question regarding contraindications to SMT, radiographs were obtained to assist in ruling out these contraindications. Eight women had plain film radiographs and none were excluded. Potential candidates were excluded if they planned to get pregnant during the next 6 months or were unable to keep appointments for the three screening levels (S1–S3) and the baseline visit at cycle 1.

2.5. Random treatment allocation

At day 1 of the second menstrual cycle, when complete eligibility was established, study participants were randomly assigned to one of two groups: (a) SMT or (b) LFM. The sequence of assignment was a predetermined block randomization scheme with blocks of size 12. Subjects were randomized by means of sealed, opaque, sequentially numbered envelopes that contained assignments to either SMT or LFM. All study personnel were blinded to block size and were unaware of the next treatment assignment when interviewing and assessing eligibility of study participants.

2.6. Interventions applied

2.6.1. Clinician training

Clinicians were licensed doctors of chiropractic (DC) practicing at the NCCC. The majority of physical examinations (77%) and treatments (66%) were delivered by four

DC orthopedic residents who served overlapping 2-year residency programs at NCCC during the trial. In total, 14 clinicians participated in this study, including five senior staff clinicians, each with more than 10 years of practice experience, six clinicians from the orthopedic residency practice, and three family practice residents.

For training purposes, we measured the table reaction force during manipulative maneuvers using a specially constructed treatment table equipped with a force plate. A priori definitions for the force magnitude of the LFM maneuver were established based on previous work in our laboratory, which suggested a force threshold for an enhanced respiratory burst of isolated polymorphonuclear neutrophils to respond to a particulate challenge (Brennan et al., 1991; Triano et al., 1991). Following initial training in both manipulative procedures and effleurage, rehearsal and retraining occurred at regular intervals throughout the study.

2.6.2. Spinal manipulative therapy and the low force mimic maneuver

For all subjects and on all treatment visit days, clinicians conducted a brief regional low-back assessment and used manual palpatory findings to identify the spinal segments – from T10 to L5 and the sacroiliac joints – to be manipulated. These vertebral levels are associated with the sensory and motor neural supply to the uterus and lower back, and it is postulated that any level may be dysfunctional in dysmenorrheic women (Thomason et al., 1979; Wiles and Diakow, 1982). Brief (3–5 min) pretreatment superficial effleurage was delivered to subjects in both treatment groups before administering SMT or LFM.

Subjects treated with SMT were placed in a side-lying position with the bottom leg straight and in contact with the treatment table. The opposite or top hip and knee were flexed and not in contact with the table to ensure the manipulative treatment resulted in the exertion of unopposed force at the selected joint. The manipulation consisted of a high-velocity, short-lever, low-amplitude thrust, greater than 750 N, delivered to all clinically relevant vertebral levels from T10 to L5 and the sacroiliac joints, bilaterally.

The LFM maneuver consisted of positioning the subject on one side with bilateral flexion of the hip and knee joints. This posture is believed to minimize the mechanical torque on the longitudinal axis of the spine associated with a true manipulation thrust (J.J. Triano, pers. comm). Theoretically, in the LFM treatment, both bones in the articulation are mobile due to their position in the mid-range. The LFM was intended as a sham maneuver and was delivered to the left L2/3 vertebral level, with a high-velocity, short lever, low-amplitude thrust of at least 200 N and not to exceed 400 N.

2.7. Outcome assessments and blinding

2.7.1. Visual analog scale

Women were asked to rate 'the intensity of pain associated with their menstrual period' on a 100 mm visual analog scale (VAS), with the anchors 'no pain, 0' at one end and 'worst pain imaginable, 100' at the other end. This instrument is frequently used in trials involving the treatment of any condition in which pain is a manifestation, including primary dysmenorrhea (Lundeberg et al., 1985; Fraser and McCarron, 1987; Jaeschke et al., 1990). Previous studies in our facility have demonstrated the reliability and validity of the VAS for the assessment of clinical improvement (Triano et al., 1993, 1995).

2.7.2. Radioimmunoassay

Blood samples were collected in EDTA vacutainer tubes (Beckton Dickinson, Mountain View, CA) 15 min before and 60 min after treatment. The 60-min post-treatment sampling time was selected as it takes approximately 1 h for preexisting $KDPGF_{2\alpha}$ to clear from the circulation (Granstrom et al., 1982). The blood was refrigerated until the plasma was isolated by centrifugation at $700 \times g$ for 15 min. The plasma was collected and stored at −20°C for later assay for $KDPGF_{2\alpha}$. Laboratory personnel performing the assays for $KDPGF_{2\alpha}$ were unaware of treatment assignment, visit number and treatment phase of collected samples.

The radioimmunoassay (RIA) we used was a modification of the RIA for $KDPGF_{2\alpha}$ described by Granstrom and co-workers (Granstrom and Kindahl, 1982, 1983; Granstrom et al., 1982; Granstrom, 1986) and described in detail elsewhere (Kokjohn et al., 1992). In our hands, the interassay coefficient of variation (CV) was 5.5% on tests with the same pool of normal human plasma, and the mean intraassay CV was 9.6% ± 0.70%. The average CV for 1357 samples run in the RIA was 4.22 ± 6.88%.

2.7.3. Moos' Menstrual Distress Questionnaire

The MDQ is suitable for repeated assessment of women's reactions over time (Moos, 1985). Each participant completed the MDQ during the 60 min rest period between pre- and post-measures of the primary outcomes on day one of four consecutive menstrual cycles. The MDQ consists of 47 symptoms and feelings, and women are asked to rate the severity of their symptoms on a five point ordinal scale (Moos, 1968). Moos (1985) reported high internal consistencies for pain (0.83) and autonomic function (0.94) with the MDQ, as estimated by Cronbach's alpha. In our pilot study, we found a significant difference in post-treatment MDQ scores between groups receiving SMT and sham treatment (Kokjohn et al., 1992).

2.8. Schedule of interventions and outcome measures

To begin the study, eligible subjects returned to NCCC on day 1 of their next menstrual cycle (cycle 1) for baseline determinations of plasma $KDPGF_{2\alpha}$ from blood samples collected before and after a 60-min no-treatment session. A VAS was completed by each subject before and after the 1 h no-treatment session to assess pain perception on the 1st day of cycle 1. The pre-60 min sample allowed us to compare the groups for dysmenorrhea before any active treatment, and the post-60 min sample allowed for comparisons following 1 h of 'no active intervention.' The MDQ was administered during the 60-min (quiet time) interval to assess the effect of menstrual distress on activities of daily living.

All subjects returned on day 1 of cycle 2 (within 48 h of the onset of pain) and, after randomization, began their intervention schedule. Blood samples were collected and the VAS and MDQ were administered as described above.

Subjects were treated and released three times during the week before the expected onset of menstruation for the next two cycles (cycle 3 and 4). Treatment times were recorded by study personnel and averaged 7–8 min for all subjects in both groups. On the 1st day of cycle 3 and 4, the women were treated again and measurements were made as described for cycles 1 and 2.

2.9. Data analysis

The pre- and post-treatment VAS scores and $KDPGF_{2\alpha}$ levels for cycle 2 were compared between the SMT and LFM groups by means of a two-sample *t*-test on the raw changes. To assess whether treatment effects in the LFM group diminished over time relative to the SMT group, we modeled the immediate pre-post changes over cycles 2, 3 and 4. Proc Mixed (SAS/STAT Software, 1996) was used to fit a linear model to each treatment group with random intercept and slope effects to allow for different slopes over cycles for each group. The covariance matrix of the random effects was unspecified, as was the within-subject covariance structure.

The analyses of the pre-treatment VAS scores and $KDPGF_{2\alpha}$ levels and the post-treatment MDQ scores over cycles 2, 3 and 4 were done on an intention-to-treat basis. Compliers were defined a priori as women who attended the baseline visit, who attended two of the three post-randomization outcome measure visits, who attended at least two of the three scheduled visits for prophylactic care and who used medications only according to the study protocol. Proc Mixed (SAS/STAT Software, 1996) was used to specify an appropriate within-subject covariance structure and fit a model including parameters for cycle, treatment, compliance, all two-way interactions with treatment, and the respective baseline covariate (i.e. VAS, $KDPGF_{2\alpha}$ and MDQ, respectively). Likelihood-ratio tests were used to compare among covariance structures and determine the appropriate covariance structures for the overall model described above. Reduced models were then fit for the chosen covariance structures.

3. Results

3.1. Characteristics of subjects

From February 1994 to May 1996, 2312 women completed the telephone screen; 71% of these were determined to be ineligible at one of the screening levels (Fig. 1). At S1, 66% of the women were ineligible. Approximately one-half of those ineligible at S1 had menstrual pain beginning too early (2 or more days before menstruation) or too late (1 or more days after menstruation begins) to be consistent with a diagnosis of primary dysmenorrhea. In addition, 24% of these ineligible subjects reported use of oral contraceptives in the previous 6 months. Other reasons for exclusion at S2 included cycle irregularity, use of psychotherapeutic medications or other medications that would interfere with the prostaglandin assay, morbid obesity or systemic conditions that could potentially affect the musculoskeletal system, such as fibromyalgia, thyroiditis, hypothyroidism, muscular dystrophy and cardiovascular and cardiopulmonary disorders. Of the 171 women eligible at S3, 17 (10%) were diagnosed with secondary dysmenorrhea or required further diagnostic testing to rule out underlying pathology. These women were excluded.

Of the 786 eligible women at the telephone screen, 537 declined participation at some point in the screening process. Fifty-three, 37, 5 and 5% of the women eligible at each of the four screenings, respectively, declined to participate. The willingness of eligible women to participate was not related to menstrual characteristics or severity of menstrual pain as reported at the telephone screen. The principal reason for declining to participate was unwillingness to commit to the study for four menstrual cycles.

One hundred and thirty-eight subjects entered the study. The data in Table 1 show that baseline characteristics of subjects in the two treatment groups were similar. The overall mean age of the subjects was 30.4 years and 88 (63.8%) subjects had never been pregnant. Baseline characteristics are also similar to those reported for women in drug trials for primary dysmenorrhea (Dawood, 1988; Dawood, 1990; Benassi et al., 1993; Zhang and Li Wan Po, 1998) and in textbook descriptions of primary dysmenorrhea (Lumsden and Norman, 1997), in that the disorder is more prevalent in nulliparous women.

Entrance history and physical examinations on all subjects were either normal or showed minor unrelated findings that would not interfere with the study. All 138 subjects completed the visits at cycle 1 and cycle 2. The pre- to post-scores on the VAS and the $KDPGF_{2\alpha}$ at cycle 1 showed only a slight decrease in $KDPGF_{2\alpha}$ in the LFM group and no other changes (Table 2). Three subjects were lost to follow-up in the study: one subject (SMT) was lost after cycle 2 due to pregnancy; one subject (LFM) refused to travel from the city after cycle 2; and one subject (SMT) received treatment from a chiropractor outside of the study group just before cycle 3. Eighty-seven percent of the subjects complied with the study protocol.

3.2. Acute treatment effects

The mean pre-treatment VAS scores were 42.8 and 38.0

mm for the SMT and LFM groups, respectively. A decrease was seen in the post-treatment scores for both groups, but there was no statistically significant difference in pre- to post-treatment scores between the two groups ($P = 0.44$) (Table 2). The mean pre-treatment $KDPGF_{2\alpha}$ levels were 128.6 pg/ml and 130.2 pg/ml for the SMT and LFM groups, respectively. The changes in pre- to post-treatment $KDPGF_{2\alpha}$ levels were not statistically different between the SMT and LFM groups ($P = 0.15$) (Table 2).

3.3. Assessment of pre-post changes over time

The raw changes from pre- to post-treatment VAS scores for cycles 2, 3 and 4 were 10.08, 7.77 and 5.30, respectively, in the SMT group and 8.01, 11.14 and 7.62, respectively, in the LFM group. The raw changes from pre- to post-treatment $KDPGF_{2\alpha}$ levels for cycles 2, 3 and 4 were 4.29, 3.90 and 1.71, respectively, in the SMT group and 10.99, 2.57 and 2.97, respectively, in the LFM group. The fitted slopes for the pre- to post- treatment raw changes over cycles 2, 3 and 4 did not differ between the groups for either VAS ($P = 0.29$) or $KDPGF_{2\alpha}$ levels ($P = 0.32$).

Table 1

Baseline characteristics of 138 subjects with primary dysmennorhea

Demographics	SMT ($n = 69$)	LFM ($n = 69$)
Mean age (range)	31.1 years (18–45)	29.7 years (18–45)
Mean body mass index (range)	25.9 (18–41)	24.9 (17–38)
Marital status (%)		
Married	40.6	44.9
Divorced/separated	15.9	5.8
Never married	43.5	49.3
Race (%)		
White	92.8	91.3
Black	4.4	2.9
Other	2.9	5.8
Education (%)		
High school	37.7	34.8
College or professional	53.6	53.6
Employed (%)		
Yes	82.6	80.5
No, student	7.3	7.5
No, not student	10.1	11.9
Menstrual History		
Mean age at menarche (range)	12.3 (9–17)	12.5 (9–16)
Mean age at onset (range)	13.7 (10–20)	13.4 (9–18)
Mean number of days in cycle	28.8	28.7
Mean number of days, menstrual flow	4.8	4.8
Number of pregnancies (%)		
0	57.9	69.5
1	10.1	7.3
2+	31.9	23.2
Other history		
Medication use for symptoms (%)	25.6	29.0
Smoking history (%)		
Never	44.9	59.4
Former	34.8	30.4
Current	20.3	10.2

3.4. Prophylactic treatment effects

The following intention-to-treat analysis does not include the three subjects who dropped out of the study. There were no significant differences seen in VAS, $KDPGF_{2\alpha}$ or MDQ in compliers versus non-compliers. Therefore, the models were reduced to include only treatment, cycle, treatment by cycle interaction, and the respective baseline covariate scores. Figs. 2–4 show the least squares means and results for each model. There were no time by treatment interactions over the three cycles for any of the primary outcome variables. There were statistically significant linear time effects for both VAS and MDQ ($P = 0.008$ and $P < 0.001$, respectively); the linear time effect for $KDPGF_{2\alpha}$ was borderline significant ($P = 0.054$). However, no treatment effects were detected for VAS, $KDPGF_{2\alpha}$ or MDQ ($P = 0.65$, 0.61 and 0.78, respectively).

3.5. Adverse effects

Two women in the LFM group and three women in the SMT group reported soreness in the low back region 24–48 h following intervention at one visit. All women reported that the soreness was self-limiting and disappeared within 24 h. No other adverse effects were reported by women in either treatment group.

4. Discussion

The results of this randomized, observer-blinded clinical trial show that although both spinal manipulative therapy and a LFM maneuver relieve the pain associated with primary dysmenorrhea as measured with a VAS, the decreases are probably not clinically meaningful. In trials of drugs for the relief of the pain associated with primary dysmenorrhea, pain reduction from baseline is substantially greater than we observed (Zhang and Li Wan Po, 1998). In addition, there are no statistically significant differences between the two interventions. Similarly, both treatments decrease the level of circulating plasma prostaglandin $F_{2\alpha}$, the putative mediator of dysmenorrhea to the same extent (Table 2, Fig. 3). The results at cycle 2 of the present study are similar to the results of our pilot study (Kokjohn et al., 1992) in that no significant differences between the two treatment arms were observed and both treatments reduced the subjective perception of pain and the plasma levels of $KDPGF_{2\alpha}$. In designing

Table 2

Pre-post changes at baseline (menstrual cycle 1) and menstrual cycle 2

Outcome measure	Menstrual cycle	Treatment group	*n*	Mean pre-post change	SE	95% CI for pre-post change
VAS (mm)	1	SMT	69	–0.17	1.63	(–3.37,3.02)
		LFM	66	2.70	3.37	(–2.01,7.40)
VAS (mm)*	2	SMT	68	10.09	1.84	(6.48,13.70)
		LFM	69	8.01	1.96	(4.17,11.85)
KDPGF$_{2\alpha}$ (pg/ml)	1	SMT	67	2.45	2.40	(–4.15,9.05)
		LFM	67	7.69	3.24	(1.34,14.04)
KDPGF$_{2\alpha}$ (pg/ml)**	2	SMT	67	4.29	2.83	(–1.26,9.84)
		LFM	67	10.99	3.67	(3.80,18.18)

CI, confidence interval; SE, standard error of the mean change; VAS, visual analog scale; KDPGF$_{2\alpha}$, 15-keto-13,14-dihydro-prostaglandin F$_{2\alpha}$; **P*-value for group differences, 0.44; ***P*-value for group differences, 0.15.

the present study, we anticipated that any non-specific effects would diminish over the course of four menstrual cycles. This did not occur.

Proponents of spinal manipulative therapy, principally chiropractors, postulate that the characteristic high-velocity, short-lever, low-amplitude thrust delivered to vertebral levels associated with the sensory and motor neural supply to the uterus and low back will modify the autonomic nervous system balance and/or activity (Jamison et al., 1992), affect the superior hypogastric plexus (Thomason et al., 1979) and the referred pain patterns from these levels (Arnold-Frochot, 1981). The low force maneuver used in this study was designed to act as a ‘placebo-like’ control treatment. This treatment was used in an earlier trial of manipulative therapy for chronic low-back pain in our facility and was perceived by patients as a credible chiropractic maneuver (Triano et al., 1995). It is possible that the present trial did not continue long enough for any placebo effect of the low force procedure to wash out, however, this seems unlikely in light of the results reported by Fedele et al. (1989). They found a placebo effect in only 16% of women by the third menstrual cycle compared with 80% in the first. It seems more likely that the low force maneuver employed in this study was indistinguishable from spinal manipulative therapy. Therefore, the postulated superior benefit of spinal manipulation is not supported by our results. Interestingly, our results are consistent with other recent reports that fail to show a superior effect of spinal manipulation compared with placebo or sham treatment for the treatment of non-musculoskeletal conditions (Balon et al., 1998; Bove and Nilsson, 1998).

In this study, women with a likely diagnosis of secondary dysmenorrhea were excluded based on a clinical history and physical findings, as well as a pelvic examination performed by a Board-certified medical specialist in obstetrics and gynecology. We accepted the clinical judgement of the participating gynecologists. There were four potential subjects for whom a definitive diagnosis was in sufficient question, that an ultrasound or endometrial biopsy was required; these women were excluded from participation. If the use of well-established clinical criteria and a pelvic examination resulted in the occasional misclassification of a subject, any resulting bias was unlikely to favor SMT. In addition, misclassification was expected to occur at the same rate in

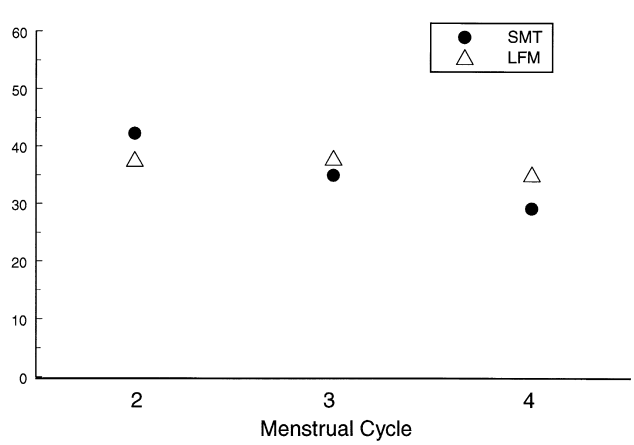

Fig. 2. Least-squares pre-treatment VAS means (mm) at cycles 2, 3 and 4 for each treatment group based on the model with terms for treatment ($F_{1,134} = 0.21$, $P = 0.645$), cycle ($F_{2,249} = 4.97$, $P = 0.008$), treatment by cycle interaction ($F_{2,249} = 2.37$, $P = 0.096$) and baseline VAS ($P < 0.001$), and a compound symmetry covariance structure.

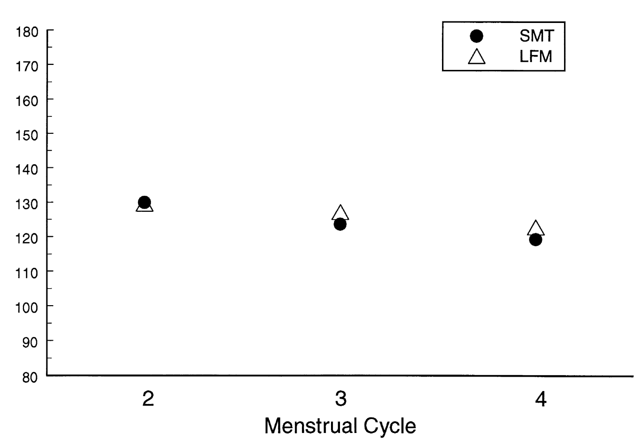

Fig. 3. Least-squares pre-treatment KDPGF$_{2\alpha}$ means (pg/mL) at cycles 2, 3 and 4 for each treatment group based on the model with terms for treatment ($F_{1,133} = 0.26$, $P = 0.611$), cycle ($F_{2,256} = 2.96$, $P = 0.054$), treatment by cycle interaction ($F_{2,256} = 0.20$, $P = 0.819$) and baseline KDPGF$_{2\alpha}$, ($P < 0.001$) and a compound symmetry covariance structure.

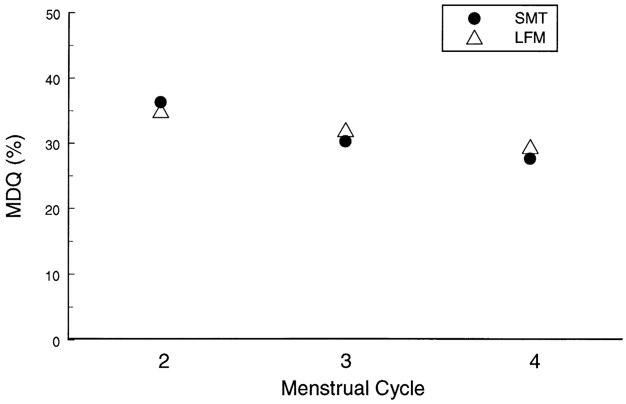

Fig. 4. Least-squares post-treatment MDQ means (%) at cycles 2, 3 and 4 for each treatment group based on the model with terms for treatment ($F_{1,134} = 0.08$, $P = 0.776$), cycle ($F_{2,259} = 11.39$, $P < 0.001$), treatment by cycle interaction ($F_{2,259} = 0.75$, $P = 0.472$) and baseline MDQ ($P < 0.001$), and an unstructured covariance.

our study as it would in a physician's practice. As a result, we believe, that use of the diagnostic criteria outlined in this study enhanced the generalizability of the results.

The nature of manual therapy maneuvers makes it difficult to blind the subjects to the intervention. As noted above, we developed a LFM maneuver that was intended to create a credible sham intervention for comparison with spinal manipulative therapy. A limitation of this trial is that formal assessment of the success of blinding subjects to these interventions was not conducted. However, when women who completed the trial were asked during debriefing whether they received a 'real' or a 'sham' manipulation, most indicated that they received a real manipulation. This suggests that blinding was effective. Incorporating a waiting list control group of subjects was considered, however, the level of funding precluded this treatment arm. We believe a strength of this study was maintenance of observer blinding for assays of $KDPGF_{2\alpha}$ and VAS and MDQ scoring. In addition, only five women complained of slight muscle soreness following LFM (two) or SMT (three), indicating that side effects from this treatment are minimal or non-existent.

The prophylactic treatment regimen provided fewer treatments than the number of treatments reported used for primary dysmenorrhea by chiropractic physicians in the general practice setting (Arnold-Frochot, 1981; Liebl and Butler, 1990) and fewer than the number administered by Thomason in a pilot study conducted in a chiropractic college clinic (Thomason et al., 1979). Hitchcock's report in the osteopathic literature mentions delivering manipulative therapy twice a week but addresses neither the time the treatments were administered in relation to the menstrual cycle, nor the length of time over which the treatments were provided (Hitchcock, 1976). Consequently, in the absence of a standard, other than clinical judgement, for determining the frequency of treatments and when they should be administered, the schedule we proposed was reasonable for an efficacy trial. In light of this treatment regimen, we elected not to include a group who received NSAIDs in this study since NSAIDs are used primarily during the acute episode after either pain or menstruation begins rather than before (Dawood, 1985). Only recently have studies focused on the potential of NSAIDs to prevent the pain of primary dysmenorrhea (Benassi et al., 1993; Pedron Nuevo et al., 1998). Although the null effects in this study may preclude future studies, to our knowledge, this is the only randomized controlled trial of manual therapy conducted for women with primary dysmenorrhea and therefore, cannot be definitive in its conclusions. Nevertheless, we believe that the careful conduct and reporting of our trial, along with the null results, are strong evidence that either the LFM maneuver was an insufficient placebo treatment or, in fact, that manual therapy does not relieve the pain in women with primary dysmenorrhea.

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