

The Effect of Spinal Manipulation on Pain and Prostaglandin Levels in Women with Primary Dysmenorrhea

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ABSTRACT

Objective: The primary objectives of this study were to compare the effect of spinal manipulation vs. sham manipulation on a) circulating plasma levels of the prostaglandin F_{2a} metabolite, 15-keto-13,14-dihydroprostaglandin (KDPGF $_{2a}$), b) perceived abdominal and back pain and c) perceived menstrual distress in women with primary dysmenorrhea.

Design: This randomized clinical pilot study investigated the outcome measures before and after either a spinal manipulation treatment (SMT) or a sham manipulation.

Setting: All subjects were treated at the National College Chiropractic clinic, a private chiropractic clinic in the suburban Chicago area.

Participants: Forty-five women with a history of primary dysmenorrhea were recruited from the local community. The volunteers ranged in age from 20–49 (mean age = 30.3 yr), and were entered into the study between April 1990 and January 1991. Twenty-four were randomly assigned to the spinal manipulation group and 21 were assigned to the sham group.

Interventions: Subjects treated with spinal manipulation were placed in a side-lying position with the bottom leg straight and the top leg flexed at the knee and hip. They received a high-velocity, short lever, low-amplitude thrust to all clinically relevant vertebral levels within T10 and L5-S1 and the sacroiliac joints. In the sham manipulation, subjects were placed in a side-lying position with both hips and knees flexed. Their manipulation consisted of a similar thrust administered to the midline base of the sacrum.

Outcome Measures: Perceived abdominal and back pain were measured with a visual analog scale, and menstrual distress was measured with the Menstrual Distress Questionnaire. Both were administered 15 min before and 60 min after treatment. Blood samples were collected by venipuncture for the determination of plasma levels of KDPGF $_{2a}$ at the same times. The plasma was then assayed for KDPGF $_{2a}$ by radioimmunoassay.

Results: Analysis of covariance and paired Student's *t* tests were used for the statistical evaluation. Immediately after treatment, the perception of pain and the level of menstrual distress were significantly reduced by SMT. This reduction was associated with a significant reduction in plasma levels of KDPGF $_{2a}$ in the SMT group. A significant and similar reduction in plasma KDPGF $_{2a}$ also occurred in the sham group, indicating that a placebo effect was associated with a single sham intervention.

Conclusions: This randomized pilot study suggests that SMT may be an effective and safe nonpharmacological alternative for relieving the pain and distress of primary dysmenorrhea. However, the large change in KDPGF $_{2a}$ observed in both treatment groups clearly indicates that further studies with more subjects, studied over a longer time frame, are needed to resolve the question of a placebo effect. (*J Manipulative Physiol Ther* 1992; 15:279–285).

Key Indexing Terms: Dysmenorrhea, Spine, Chiropractic, Prostaglandins, Pain

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INTRODUCTION

Primary dysmenorrhea (PD), defined as painful menstruation in the absence of organic pelvic pathology, is estimated to affect up to 50% of women of childbearing age, and, of these, 10% experience incapacitating pain for 1–3 days every month. Because of its recurrent nature, this condition has an enormous socioeconomic impact as well as personal and family consequences. Absenteeism among the severe sufferers is believed to cause approximately 600 million lost working hours at a cost of \$2 billion annually (1).

Compelling evidence supports the hypothesis that a principal cause of PD is increased production and release of endometrial prostaglandin E₂ (PGE₂) and prostaglandin F_{2a} (PGF_{2a}) during menstruation. Excess release of prostaglandins (PG) during menstrual shedding of the endometrium causes increased uterine smooth muscle contraction and vasospasm of uterine arterioles, leading to ischemia and the cramp-like pain of dysmenorrhea (1–3).

The most widely used drugs for the relief of the pain of PD are the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen and mefenamic acid, which act by inhibiting PG synthetase, a collective name for the enzymes in the cyclooxygenase pathway of arachidonic acid metabolism to prostaglandins. NSAIDs are effective in relieving pain in 70–85% of women with confirmed PD (4). The reason why 15–30% of PD cases are refractory to NSAIDs is unclear at present, although increased activity of the 5-lipoxygenase pathway leading to leukotrienes has been suggested (1). Oral contraceptives (OC) are also used in the treatment of PD (1, 5). OCs reduce the levels of PGs in menstrual fluid by blocking ovulation and perhaps, in the case of gestagen-dominated OCs, by reducing uterine sensitivity to vasopressin and PGF_{2a} (6). Both NSAIDs and OCs, however, 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 (7–9), although the appearance of these side effects is relatively rare. OCs may cause adverse effects on the liver, diminished glucose tolerance and hypertension (10). Oral contraceptives are also contraindicated in women over 30, especially smokers, because of the risk of thrombotic disease, and also in women who wish to become pregnant or who do not wish to use OCs for personal or religious reasons. Therefore, investigation of alternative nondrug therapies is warranted. Of particular importance is the investigation of those nondrug therapies currently in use for which only empirical

evidence exists to support their effectiveness.

Nondrug therapies for PD that have been studied include transcutaneous electrical nerve stimulation (11, 12), subcutaneous peripheral nerve stimulation (13), acupuncture (14, 15) and exercise (16, 17). In these studies, the outcome measures for treatment efficacy were subjective evaluation of pain reduction by the patients, generally assessed through a questionnaire. The levels of PGE₂, PGF_{2a} or their metabolites were not determined, although some authors speculated that increased production of endogenous opioids might be responsible for the alleviation of symptoms. Osteopathic and chiropractic manipulative therapies are also used to treat PD. However, reports of the efficacy of these therapeutic modalities are largely anecdotal and almost exclusively confined to the chiropractic literature (10, 18–21). The study by Thomason (22) in 11 subjects is the only report in which a control group was included. These studies also documented relief of symptoms by using a questionnaire. None of these studies reported the measurement of plasma PG or their metabolites. Despite the virtual absence of scientific evidence demonstrating lower plasma PG and only empirical evidence to support claims of pain reduction by spinal manipulation, chiropractic and osteopathic physicians routinely treat women with PD in this manner.

In an initial effort to provide scientific rationale for the treatment of PD with spinal manipulative therapy (SMT), we report here the results of a small randomized clinical trial to compare the effect of spinal manipulation or sham manipulation on plasma levels of the PGF_{2a} metabolite, 15-keto-13, 14-dihydroprostaglandin F_{2a} (KDPGF_{2a}), in women with PD, as well as on the associated perceived changes in menstrual pain, measured by means of a visual analog scale (VAS), and menstrual distress, measured by means of the Menstrual Distress Questionnaire (MDQ). The VAS is a demonstrably reliable instrument frequently used in trials involving the treatment of any ailment that has pain as a manifestation, including PD (23, 24). The MDQ, developed by Moos to assess the effect of menstrual distress on activities of daily living, has high internal consistencies for pain (0.83) and autonomic function (0.94), as estimated by Cronbach's alpha (25). For measuring PGF_{2a} in vivo, KDPGF_{2a} is considered the most appropriate analyte because it has a longer half-life, occurs in higher concentrations in plasma than the parent compound, forms no artifacts during collection and preparation of samples and accurately reflects the rate of synthesis and release of the parent compound into the circulation (26). Furthermore, plasma concen-

trations of this metabolite are significantly higher in dysmenorrheic women than in eumenorrheic women on the first day of menstruation (27–29).

MATERIALS AND METHODS

Subjects

Women with a history of PD were recruited for this study from the local community through advertisements and posters in local health clubs or were referred to us by local chiropractors and gynecologists. During their initial visit to the clinic, complete medical and gynecological histories were taken and a self-administered questionnaire concerning each subject's menstrual history was completed. A complete physical examination, which included a pelvic examination, was then performed. (Subjects who provided medical documentation of a normal pelvic examination within the preceding 12 months were allowed to forego the pelvic examination.) Subjects who qualified for inclusion and agreed to participate in the study signed a consent form approved by the Institutional Review Board. The criteria for inclusion in the study were a) a history of primary dysmenorrhea that began within 2 yr of menarche; b) menstrual pain beginning the day before or just after the onset of menstrual flow; c) menstrual pain experienced each cycle and rated as moderate, severe or disabling on the menstrual history questionnaire; and d) regular cycles (within ± 3 days). Women were excluded from participation in this study for the following reasons: a) pelvic abnormality revealed upon pelvic examination, b) history of endometriosis, c) use of birth control pills or an intrauterine contraceptive device within 6 months prior to entry into the study or d) presence of contraindications to SMT such as osteoporosis, fracture or other bony pathology. The patients agreed not to take any analgesic medication during the course of their participation in the study, and they also agreed to abstain from exercise and sexual intercourse for 24 hr before treatment. Exercise relieves menstrual pain in some women and has no effect or aggravates the discomfort in others. Since the direct physiological mechanisms are unknown, we chose to control for the effects of exercise so it would not be a confounder. No SMT was permitted for 72 hr prior to treatment.

Procedures

Qualifying subjects were randomly allocated to one of two treatment groups: a) SMT or b) sham manipulation. On the first day of her next menstrual cycle, each woman returned to the clinic and completed a

VAS to rate abdominal pain and another VAS to rate back pain. A MDQ was used to rate menstrual distress. The questionnaires were self-administered 15 min before and 60 min after treatment. The VAS used in this study consisted of a continuous line marked at one extreme "no pain" and labeled at the other "pain as severe as it could be," with numbers from 0–10 above the line. Subjects were instructed to circle the number on the line to indicate their perceived level of pain. Blood samples were collected by venipuncture for the determination of plasma levels of KDPGF_{2a} at the same times. The 60-min post-treatment blood sampling time was selected because it takes approximately 1 hr for preexisting metabolites of PGF_{2a} to clear from the circulation (30). The blood was centrifuged at $1000 \times g$ for 10 min and the plasma was stored at -20°C until it was assayed for KDPGF_{2a}.

Experimental Interventions

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 knee and hip were flexed and not in contact with the table (Figure 1). This posture ensured that 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 delivered to all clinically relevant vertebral levels within T10 and L5-S1 and the sacroiliac joints. These vertebral levels are associated with the sensory and motor neural supply to the uterus and low back (10, 21), and it is postulated that any may be dysfunctional in dysmenorrheic women (22, 31). In contrast, the sham treatment consisted of positioning the subject on one side with bilateral flexion of the knee and hip joints (Figure 2). 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, personal communication). In this sham procedure, a high-velocity, short lever, low-amplitude thrust, in an intended posterior to anterior direction, was administered to the midline base of the sacrum. The force of the thrust and offsetting moment caused by the leg position, opposite that induced by the manipulation, were intended to cancel each other, or at least substantially reduce the mechanical effect of the SMT. Normally, during manipulation, one bone of the articulation to be manipulated is believed to be fixed by the nature of patient positioning, while the other is mobile (32). Theoretically, in the sham treatment, both bones in the articulation are mobile, due to their position in mid range.



Figure 1. Depicting SMT: subject was placed on one side with the bottom leg straight and the top knee and hip flexed. A true manipulation force was applied to all clinically relevant vertebral levels within T10 and L5-S1 and the sacroiliac joints.

Furthermore, this sham procedure was intended to decrease the subject awareness of differences between treatment groups because the sham treatment appears very similar to a true spinal manipulation. Therefore, all subjects, regardless of past experience with manipulative therapy, could participate and be blinded to their treatment group. No ancillary therapeutic modality such as transcutaneous electrical nerve stimulation or soft tissue therapy (massage) was included in this trial.

Radioimmunoassay

Plasma samples were assayed for KDPGF_{2α} by using a minor modification of the radioimmunoassay (RIA) described by Granstrom (33). The standards we used consisted of KDPGF_{2α} (Calbiochem, San Diego, CA) at

concentrations ranging between 5 and 320 pg/ml dissolved in 0.05 M phosphate-buffered saline (pH 7.5) containing 0.1% gelatin. To maintain interassay consistency, we made each concentration of standard for all RIAs performed in this study at one time from a stock solution and then stored the standards at -70°C in aliquot lots sufficient for each assay. For each assay, 100 μl of rabbit anti-KDPGF_{2α} (Accurate Chemical & Scientific Corp., Westbury, NY), 100 μl of [³H] KDPGF_{2α} (Amersham, Arlington Heights, IL) and 4 μl of normal rabbit serum (Calbiochem) were added to triplicate tubes containing either 200 μl of a standard or 200 μl of the unknown plasma sample. The samples were mixed gently on a vortex mixer, then incubated at 4°C for 48 h. After this incubation, 1.0 ml of 10% goat anti-rabbit gamma globulin (Calbiochem) in polyethylene glycol buffer (5% polyethylene glycol in a

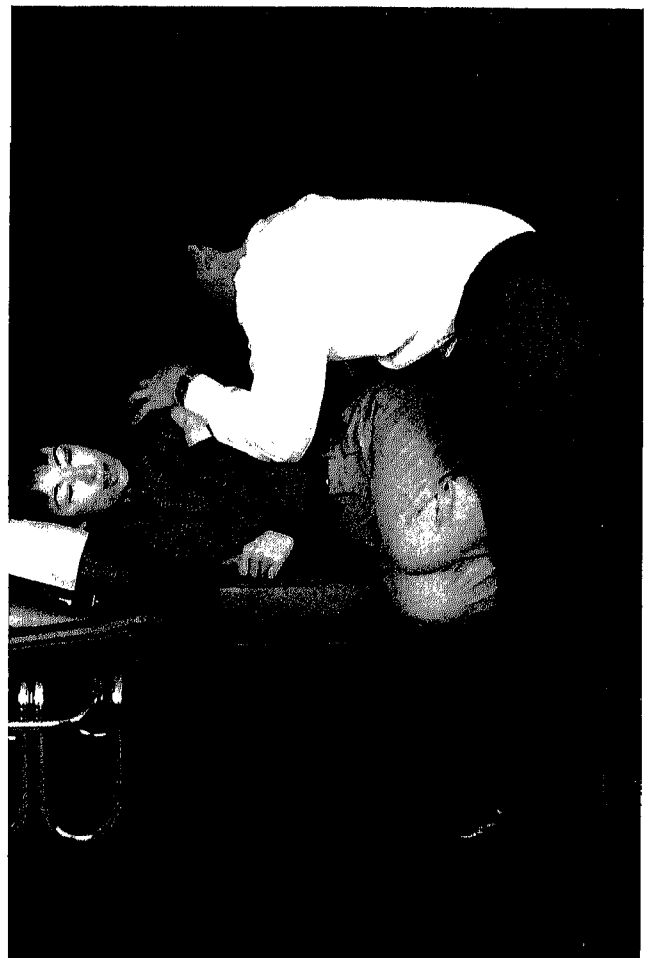


Figure 2. Depicting sham manipulation: subject was placed on one side with flexion of both knees and hips. A manipulation force was applied to the midline base of the sacrum.

0.05 M phosphate buffer, pH 7.4) was added to all samples with the exception of the total count tubes, and the tubes were incubated at 4°C for 3–4 hr. Following this second incubation, the tubes were centrifuged at 2000 × *g* for 60 min at 4°C. The supernatant was discarded and the pellet resuspended in 1.0 ml of deionized water, which was then added to 4 ml of Ultima-Gold scintillation cocktail (Packard Instrument Co., Downers Grove, IL). Each sample was counted in an LKB Rackbeta liquid scintillation counter (Pharmacia LKB, Gaithersburg, MD) interfaced with a Compaq 286 computer (Compaq, Houston, TX) for 2 min. The standard curve was fitted with a four-parameter logistic algorithm by means of the LKB RIACalc software, which, in turn, converted the raw counts/minute to pg/ml. Laboratory personnel performing the RIA and data analysis were blinded to the subjects and their treatment groups. The lower limit of sensitivity for this RIA is 2 pg/ml. In our hands, the interassay coefficient of variation was 1.3% on tests with the same pool of normal human plasma, and the mean intra-assay coefficient of variation was 11.5% ± 1.6%.

RESULTS

Forty-five subjects between the ages of 20 and 49 (mean age = 30.3 yr) were entered into the study between April 1990 and January 1991. Twenty-four were randomly assigned to the SMT group, and 21 were assigned to the sham group. A clerical error resulted in the loss of pain perception and menstrual distress data from one subject in the SMT group. Plasma KDPGF_{2a} levels were not available for four subjects in the SMT group or for two subjects in the sham group because of early technical problems encountered with the RIA. The results for the remaining subjects are described below.

Figure 3 and Table 1 show the pre- and post-treatment group means for plasma levels of KDPGF_{2a} for both the sham and SMT groups. Table 1 also shows the pre/post-treatment mean differences. Regardless of treatment, the plasma KDPGF_{2a} levels significantly declined after intervention, and overall, the differences between plasma levels of KDPGF_{2a} before and after intervention were statistically significant (*t* = 3.276; *p* = .002). However, an analysis of covariance (ANCOVA) indicated that the sham treatment group and the SMT group were not significantly different from one another (*F* = 0.14; *p* = .71).

Pre- and post-treatment means and mean differences in pain and menstrual distress scores are shown in Table 2. The results of the perception of abdominal and back

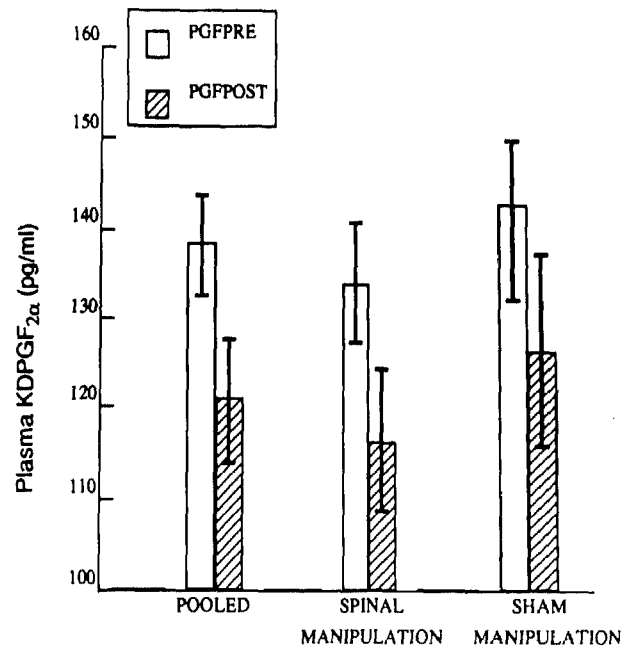


Figure 3. Pre- and post-treatment group means (±SE) for plasma levels of KDPGF_{2a} in spinal-manipulated (*n* = 20), sham-manipulated (*n* = 19) and pooled (*n* = 39) subjects.

TABLE 1. Pre- and post-treatment means and mean differences in plasma KDPGF_{2a}

Treatment	Pretreatment Means	Post-Treatment Means	Mean Differences	SD
Spinal manipulation (<i>n</i> = 20)	133.86	116.18	17.68	32.253
Sham manipulation (<i>n</i> = 19)	142.82	126.27	16.55	33.948

TABLE 2. Pre- and post-treatment means and mean differences in pain and menstrual distress scores

Outcome Measure and Intervention	Pretreatment Means	Post-Treatment Means	Mean Differences	SD
Abdominal pain ^a				
SMT (<i>n</i> = 23)	5.87	3.78	2.09	2.30
Sham (<i>n</i> = 21)	6.00	5.19	0.81	1.50
Back pain ^a				
SMT	4.83	2.96	1.87	1.94
Sham	5.21	4.43	0.78	1.57
Menstrual distress ^b				
SMT	44.22	25.17	19.05	15.36
Sham	47.86	37.57	10.29	11.27

^a 10 cm VAS; 0 = no pain.

^b MDQ; 0 = no distress.

pain (VAS) and menstrual distress (MDQ) before and after treatment were compared by using an ANCOVA. No significant interaction effects were determined be-

tween the pretreatment scores and the intervention groups for perceived abdominal pain and menstrual distress.

For perceived abdominal pain, there was a statistically significant difference between the pre- and postintervention scores of the two groups, with the sham treatment group having significantly higher postintervention scores than the SMT group ($F = 5.92$; $p = .019$). A statistically significant difference between groups was also determined for the menstrual distress scores. Again, the ANCOVA indicated that the group receiving sham treatment had significantly higher MDQ scores after treatment than the group receiving SMT ($F = 9.97$; $p = .003$).

A significant interaction effect was found between the pre-VAS scores for back pain and the treatment groups. Thus, individual regression lines were fitted. The slopes of these lines, which describe the relationship between changes in back pain scores for the two treatment groups, were significantly different from one another ($F = 4.44$; $p = .041$).

DISCUSSION

This randomized pilot study suggests that SMT may be an effective and safe nonpharmacological alternative for relieving the pain and distress of primary dysmenorrhea, at least for a short period of time after treatment. The data presented here support the anecdotal claims of women that SMT reduces the pain and symptoms associated with menstruation. The perception of pain (measured by the VAS) and the level of menstrual distress (measured by the MDQ) are significantly reduced by SMT. This reduction is associated with a significant reduction in plasma levels of KDPGF_{2a}. A similar reduction in plasma KDPGF_{2a} is noted in both treatment groups; however, pain and menstrual distress reductions were approximately twice as great in the SMT group as in the sham group. In most patients, increased PG production during menstruation is believed to constitute the biochemical basis for primary dysmenorrhea. Other suggested etiological factors include increased levels of circulating vasopressin during menstruation (29) and increased activity of the 5-lipoxygenase pathway (1), which results in increased leukotriene production. It is possible that SMT may have an effect on vasopressin levels or on the lipoxygenase pathway, in addition to its effect on plasma KDPGF_{2a} levels, which could account for the increased relief of pain and menstrual distress reported by women in the SMT group.

The reduction in plasma KDPGF_{2a} observed in subjects who received a sham treatment could stem from

higher pretreatment KDPGF_{2a} levels that were measured in the sham group. A second possibility is that some subjects assigned to the sham treatment group may have received manipulation forces close to those administered in a true manipulation. The sham procedure reported here was based on alterations in posture and force application sites to biomechanically reduce the effect of the manipulation thrust. When this trial was conducted, we had not, as yet, determined the threshold force that treating clinicians should not exceed in administering sham treatment procedures. We now know that a force of less than 400 N is necessary in a sham manipulative procedure (34). Finally, it is possible that physiological measures of organic pain are not as clearly related to the perception of pain as is commonly believed.

CONCLUSION

Regardless of the reason, the large change in KDPGF_{2a} levels in both the SMT and sham-treated groups that we observed is similar to the placebo effect observed by Fedele et al. (35) in a trial of naproxen, pirofen and placebo. They found that all three interventions were 80–85.7% effective in relieving pain during the first menstrual period, but the placebo was effective in only 29% of the women during the second menstrual period and in only 16% by the third. Clearly, further studies with more subjects studied over a longer time frame, with rigorous control of the threshold force in the sham manipulation, are needed to resolve these questions.

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