

Original Studies

Japanese-Style Acupuncture for Endometriosis-Related Pelvic Pain in Adolescents and Young Women: Results of a Randomized Sham-Controlled Trial

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Abstract. *Study Objective:* To assess feasibility, and collect preliminary data for a subsequent randomized, sham-controlled trial to evaluate Japanese-style acupuncture for reducing chronic pelvic pain and improving health-related quality of life (HRQOL) in adolescents with endometriosis.

Design: Randomized, sham-controlled trial.

Settings: Tertiary-referral hospital.

Participants: Eighteen young women (13–22y) with laparoscopically-diagnosed endometriosis-related chronic pelvic pain.

Interventions: A Japanese style of acupuncture and a sham acupuncture control. Sixteen treatments were administered over 8 weeks.

Main Outcome Measures: Protocol feasibility, recruitment numbers, pain not associated with menses or intercourse, and multiple HRQOL instruments including Endometriosis Health Profile, Pediatric Quality of Life, Perceived Stress, and Activity Limitation.

Results: Fourteen participants (out of 18 randomized) completed the study per protocol. Participants in the active acupuncture group (n = 9) experienced an average 4.8 (SD = 2.4) point reduction on a 11 point scale (62%) in pain after 4 weeks, which differed significantly from the control group's (n = 5) average reduction of 1.4 (SD = 2.1) points (P = 0.004). Reduction in pain in the active group persisted through a 6-month assessment; however, after 4 weeks, differences between the active and control group decreased and were not statistically significant. All HRQOL measures indicated greater improvements in the active acupuncture group compared to the control; however, the majority of these trends were not statistically significant. No serious adverse events were reported.

Conclusion: Preliminary estimates indicate that Japanese-style acupuncture may be an effective, safe, and well-tolerated adjunct therapy for endometriosis-related pelvic pain in adolescents. A more definitive trial evaluating Japanese-style acupuncture in this population is both feasible and warranted.

Key Words. Acupuncture—Endometriosis—Pelvic pain—Sham acupuncture—Inflammatory cytokines

Introduction

Chronic pelvic pain in adolescent girls is the cause of nearly 10% of their outpatient gynecology visits.¹ It is believed that 25–38% of adolescents with chronic pelvic pain (i.e. 3 to 6 months of pain) have endometriosis.² In addition to an increased risk of infertility associated with endometriosis, endometriosis-related chronic pelvic pain in adolescent girls is associated with significant functional morbidity including anxiety, depression, absence from school, and decreases in psychosocial functioning.^{3,4}

Although much research has focused on treatments for women with pelvic pain between the reproductive ages of 25 and 40,⁵ far less attention has been paid to adolescents with this disease. Consequently, treatment options for adolescents are more limited than for adults. Current recommendations as outlined by the American College of Obstetricians and Gynecologists include surgical diagnosis and destruction of visible lesions followed by medical therapy with suppression of ovulation and menses.⁶ These therapies are not

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always effective and a multidisciplinary approach to endometriosis associated chronic pelvic pain may be needed.^{7,8} Moreover, certain hormonal options for adults such as Depo-Lupron are generally not offered to adolescents younger than 16 years of age because of concerns of a potential adverse impact on bone density and development.^{2,6} Therefore there is a pressing need for additional therapies for adolescents with endometriosis-related pelvic pain.

In the West, acupuncture is commonly used as an adjunct therapy in the treatment of both pain^{9–12} and gynecological conditions.^{9,13,14} Recent studies indicate that complementary and alternative therapies, including acupuncture, are increasingly being used and are well received by adolescent patients.^{15–18} However, little research has evaluated acupuncture's efficacy in the treatment of gynecological pain,^{19,20} particularly in adolescent women.²¹

To better evaluate the potential application of acupuncture for endometriosis-related chronic pelvic pain in young women, and to inform the design of a future, more definitive study, we conducted a pilot randomized, sham-controlled trial with the following primary aims: (1) To determine the feasibility of recruiting and retaining adolescents and young women with endometriosis-related chronic pelvic pain into a randomized controlled trial of acupuncture; and (2) To collect preliminary data to evaluate the efficacy of Japanese-style acupuncture in reducing endometriosis-related pelvic pain and improving health-related quality of life in adolescents. A secondary aim of this study was to collect preliminary data to evaluate hypotheses regarding the relationship between endometriosis-related pelvic pain and inflammatory cytokines,²² and the impact of acupuncture on inflammatory cytokine levels.^{23,24}

Materials and Methods

Study Design and Population

This study was a prospective, randomized sham-controlled trial with blinding of patients and outcome assessors; but because acupuncture was manually administered, blinding of acupuncturists was not possible. The trial protocol was approved by applicable institutional review boards and was monitored by an independent data safety and monitoring board. All participants provided written informed consent. Participants less than 18 years old signed an assent form and a legal guardian signed a consent form.

Potential study participants were identified and recruited through a combination of efforts including: direct recruitment of current patients from a senior physician (M.R.L.) at Children's Hospital Boston (CHB), Division of Gynecology; sending letters to former CHB patients with endometriosis identified

through a hospital database; mailings and personal deliveries of study brochures and posters to gynecology, pediatric, and acupuncture clinics in the Boston area; presentations at local medical facilities; advertisements in Boston area public and college-specific newspapers and magazines; and internet listings.

Eligibility criteria for study participants included: 13–22 years old; diagnosis of Stage I, II, or III endometriosis determined by laparoscopic surgery within past 5 years; persisting pelvic pain with an intensity between 2 and 8 on a 10-point numerical scale; post menarchal; intact uterus and at least one ovary; a candidate for, or already using, combination hormonal therapy (oral contraceptive pill, contraceptive patch, or contraceptive vaginal ring); no prior experience with acupuncture; and living within 2 hours of the Boston metropolitan area. Study candidates were excluded from consideration if they: were pregnant or lactating; had a history of drug or alcohol abuse; had used a GnRH analogue such as Depo-Lupron® or Synarel® within the 6 months prior to their participation in the study; or had a co-existing disabling physical or psychiatric condition that the study physician believed might interfere with participation in the study.

Study Procedures

Recruitment, screening, enrollment, and general study procedures are described in Figure 1.

All active and sham acupuncture treatments and study visits were provided to participants enrolled in the study at no cost. Participants were informed that at the end of the study, those randomized to receive sham treatments would be offered a free course of active acupuncture. All parking costs for hospital visits were covered, and participants were reimbursed up to \$200 for study-related transportation costs including taxicab and non-hospital parking fees. Over the course of the study, participants were also remunerated with three \$20 gift certificates to the GAP® clothing store.

Interventions

This study employed a style of Japanese acupuncture developed by Shima and Chace²⁵ and Manaka et al,²⁶ and follows the Japanese acupuncture training curriculum at the New England School of Acupuncture. In comparison to typical traditional Chinese medicine (TCM) acupuncture, Japanese acupuncture uses smaller needles and inserts needles less deeply and with less manipulation.²⁷ For these reasons, we believed Japanese acupuncture would be less invasive than TCM, and thus better received by our adolescent population. Japanese acupuncture has been shown to be effective in treating certain pain conditions.²⁸ The specific acupuncture protocols employed in this

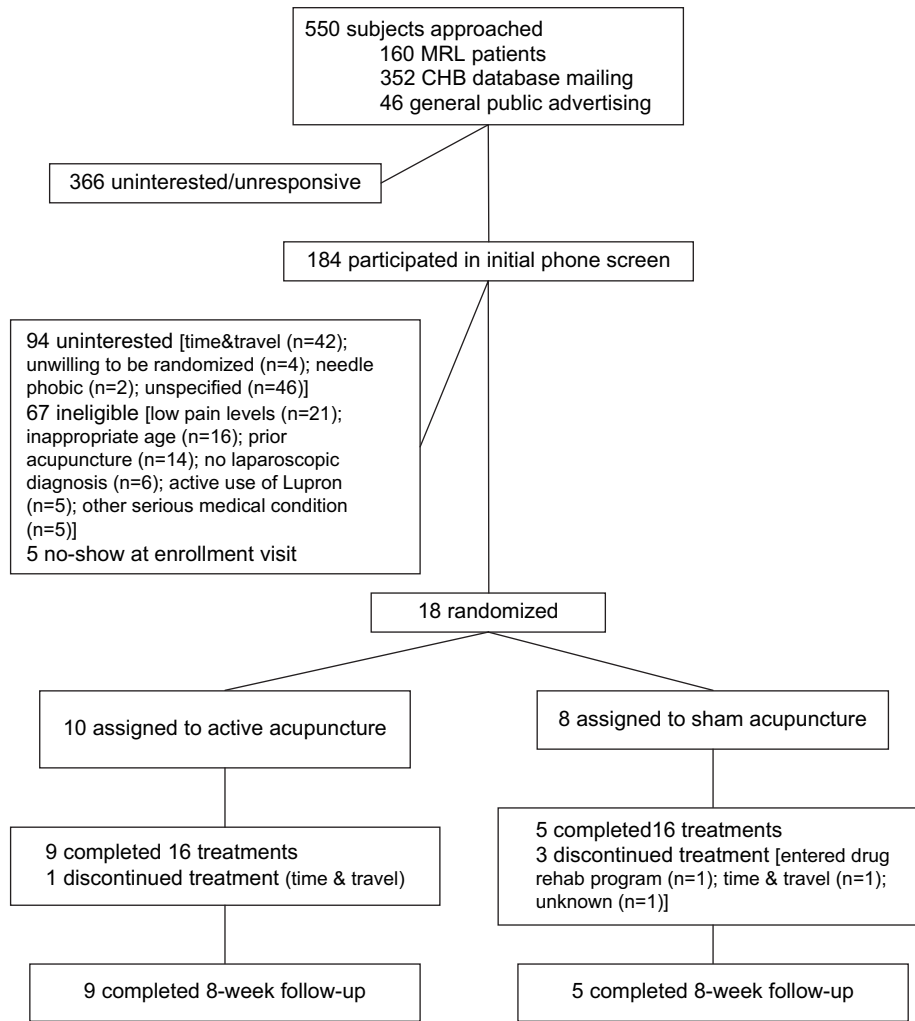


Fig. 1. Flow of study participants.

study are briefly described below and discussed in greater detail in a companion paper.²⁹

Participants assigned to both the active and sham groups underwent a total of 16 acupuncture treatments; 2 per week for 8 consecutive weeks. All but 4 subjects received the entire course of 16 acupuncture treatments. Three of the 4 subjects who did not receive the entire course of treatment dropped out of the study while one subject continued to complete questionnaires and follow-up measures without receiving acupuncture. Treatments were administered by 7 licensed acupuncturists with formal training in this style of Japanese acupuncture. All study acupuncturists received a 6-hour training session during which they were taught the specific active and sham acupuncture protocols employed in this study, as well as standard operating procedures for interactions with patients. To further ensure protocol compliance, study acupuncturists were observed and evaluated during treatment by a member of the research team at least once during the course of the study. Treatments were

conducted either in acupuncturist's private offices, or in the home of study participants for those who opted for home treatments.

Active acupuncture treatments followed guidelines defined and written in a treatment manual developed by three senior practitioners who teach this style of Japanese acupuncture and have an average of approximately 20 years of clinical experience.²⁹ Treatments were individually-tailored according to patients' diagnostic symptoms, using *a priori*-determined decision algorithms. The use of individualized acupuncture protocols based on a treatment manual approach has been employed in a number of randomized controlled trials,^{30–33} and is believed to have both high clinical validity and reliability.^{34–36} Diagnostic elements of the protocol included patient interviews, palpation of radial pulses and the abdomen, and measures of electrical resistance at acupuncture points located at the tips of the fingers and toes (Jing-well points) using a Hibiki-7 device (Asahi Butsuruyooki Research Lab; Kita Kyoto, Japan). Treatment elements of the

protocol included: (1) needling 8–12 points to activate and balance Extraordinary²⁶ and Divergent acupuncture channels;²⁵ (2) burning of small threads of a ‘warming’ herb (moxibustion) on both back shu acupuncture points and sacral areas that affect the pelvic region; and (3) electro-stimulation of reactive auricular acupuncture points using the Hibiki-7 device.³⁷ All needling employed sterile, single-use needles and followed mandated clean needle techniques.

Sham acupuncture was designed to mimic active treatments, while being minimally active. Sham treatments employed a validated sham acupuncture device that does not penetrate the skin. Because this device does not puncture the skin, the effect is minimized. However, the sham acupuncture device may not be completely inactive because the presence of a needle-like device and light contact near a site has not yet been proven to be inert. Designed to look like a real acupuncture needle, upon insertion pressure, the sham needle shaft retracts upwards into the needle handle.^{38–40} This device has been employed in a number of prior trials in which patient blinding with respect to treatment allocation has been maintained.^{32,33} To minimize any therapeutic effect, sham needles were positioned at non-acupuncture points and without meridian palpation. Protocols for sham moxibustion and sham ear stimulation were similarly designed and implemented to mimic the active intervention.²⁹ All other aspects of the sham intervention, including the diagnostic process, and duration and scope of interactions between practitioners and patients, were identical to the active acupuncture protocol.

Outcome Measures

All outcome measures were assessed at baseline, and at 4 weeks, 8 weeks, and 6 months following commencement of acupuncture treatments. Our main treatment outcome measure was change in pelvic pain not associated with menses and sexual activity and was assessed after 8 weeks of treatment. This outcome was based on the pain intensity question contained in the Endometriosis Symptom Severity Scale.⁴¹ Using a numerical analog scale, patients were asked to rate pain severity during their past 4 weeks that was not associated with menses and sexual activity from 0 to 10. The Endometriosis Symptom Severity Scale has been validated and demonstrated to be sensitive to change in endometriosis-associated pelvic pain in adults (but not adolescents) enrolled in clinical trials.⁴¹

Secondary outcomes associated with health-related quality of life (HRQOL) were assessed with four separate instruments: (1) Endometriosis Health Profile-30; (2) The Pediatric Quality of Life Inventory; (3) The Perceived Stress Scale; (4) A participant-generated list of 3 activities made difficult due to pelvic pain.

The Endometriosis Health Profile-30 is a reliable and valid, patient-generated instrument that measures disease-specific HRQOL in women with endometriosis.^{42–44} It includes 30 items in total, which can be analyzed to inform 5 subscales (pain, control/powerlessness, emotional well-being, social support, self image), and has been shown to be sensitive to change in clinical pharmacology trials.⁴³ Total scores range from 0 to 100; a lower score reflects fewer symptoms and better HRQOL.

The Pediatric Quality of Life Inventory is a 23-item instrument for measuring HRQOL in children and adolescents ages 2–18.⁴⁵ The overall instrument and its four subscales (physical health, emotional health, social health, and school participation) have been demonstrated to have good reliability and validity in adolescents exhibiting a variety of health conditions.^{46–48} Total scores on the Pediatric Quality of Life Inventory range from 0 to 100; a higher score indicates better HRQOL.

The Perceived Stress Scale is a measure of the degree to which situations in one’s life are appraised as stressful.^{49,50} We used the 10-item version of this instrument, which has been shown to have good reliability and validity.⁵⁰ Total scores range from 0 to 4; a lower score indicates less perceived stress.

Finally, we employed a single question instrument that assessed the degree to which patients’ pelvic pain interfered with daily activities. Participants were asked to generate a list of three activities made difficult by their pelvic pain, and on a numerical scale of 0–10, to rate how difficult each item is to perform (10, most difficult). This instrument has been used in prior clinical trials evaluating the impact of pain on activities of daily living.⁵¹

In order to conduct a preliminary assessment of whether active Japanese-style acupuncture lowers levels of inflammatory cytokines associated with the progression of endometriosis, subjects’ blood was drawn at baseline, 4 weeks, and 8 weeks at the Children’s Hospital Boston GCRC.²² Serum samples were tested for Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) using Quantikine high sensitivity solid phase ELISA immunoassays (R&D Systems, Minneapolis, MN, USA). Blood was collected in a serum separator tube and allowed to clot for 30 minutes before centrifugation for 15 minutes at approximately 1000 × g. The serum samples were spot frozen at –20°C until being tested at the conclusion of the study, when all samples were batched and tested simultaneously. Samples were assayed in duplicates, and the coefficient of variation (CV) for these duplicate tests were well within 0 to 10 range.

Given the undetectable levels of these two cytokines using the normal range IL-6 kit with a minimum standard range of 3.2 pg/mL, and a normal range

TNF-alpha kit with a minimum standard range of 15.6 pg/mL, high sensitivity test kits were used with a minimum standard range of 0.156 pg/mL, and a minimum standard range 0.5 pg/mL, for IL6 and TNF-alpha, respectively, in retesting the sample. Again, each sample was assayed in duplicates and the CV for these duplicate tests were well within the 0 to 10 pg/mL range.

Participants' beliefs about the outcomes of acupuncture therapy have been shown to modulate treatment outcomes.^{52,53} We assessed patient's expectations using the self-administered Treatment Credibility Scale (scale 0–4, 4 = greatest expectancy) developed by Borkovec and Nau (1972) and modified for acupuncture studies.^{31,32,54} The success of patient blinding was assessed after the second and final acupuncture treatments with a self-administered instrument used in prior acupuncture trials.^{32,54} The instrument asks subjects to indicate the treatment group to which they believed they were assigned by circling the applicable statement: a) I believe I am in the active acupuncture group; b) I believe I am in the inactive, sham acupuncture group; c) I am unsure what group I am in. If they chose response (a) or (b), they were also asked how confident they were of their answer on a 5-point Likert scale.

Statistical Analysis

All calculations were performed using SAS 9.1.3, © 2002–2003, SAS Institute Inc., Cary, NC. Descriptive statistics were computed at baseline and all follow-up time points for the subjects who had data at those times. Difference from baseline calculations were performed only on those subjects who had data at follow-up time points. Differences between sham and active groups at baseline and at each follow-up time point were assessed using Wilcoxon rank sum tests with no adjustment for multiple comparisons. Fisher's exact test was used in testing blinding between groups because of small cell counts.

Results

Eighteen patients were randomized, 10 to active acupuncture and 8 to sham acupuncture. Figure 1 summarizes the flow of participants through the trial.

Baseline characteristics of the 18 subjects did not differ significantly among treatment groups for any variable ($P > 0.05$) (Table 1). All participants were diagnosed with Stage I endometriosis which is consistent with profiles of endometriosis in adolescent populations.⁸ A total of 4 patients discontinued treatments. One participant in the active group withdrew because of travel time. Three participants in the sham group withdrew for the following reasons: entered a drug rehabilitation program, travel time, unknown.

Nine and 5 participants in the active and sham group, respectively, completed all 16 treatments per protocol, as well as all baseline and follow-up testing. All analyses presented below are based on these 14 participants.

Mean pain levels experienced during the 4 weeks preceding each assessment declined between baseline and 6 months (Figure 2, Table 2). At 4 weeks, declines were significantly greater in the active acupuncture group as compared to the control; mean = -4.8 (SD = 2.4) vs -1.4 (SD = 2.1), respectively, on a 11 point scale ($P = 0.004$). After 8 weeks and 6 months, pain reduction in the active group remained slightly greater, but between group differences were not statistically significant.

HRQOL assessed with both the Endometriosis Health Profile and the Pediatric Quality of Life Inventory indicate trends towards improvement in the active, but not in the sham group; however, differences between groups were not statistically significant (Figure 2, Table 2).

Perceived stress improved in the active group by 0.5 (SD = 0.6) points out of 4 at 4 weeks, compared to baseline; differences from baseline were similar at week 8 and at 6 months. In contrast, there was relatively little change in perceived stress in the sham group; differences between groups were not statistically significant (Figure 2, Table 2). Pelvic pain-related limitations in activities showed greater improvement in the active vs. sham treatment group: at 4 weeks, limitations were reduced from baseline by 3.4 (SD = 2.2) points out of 10 in the active group compared to 0.5 (SD = 1.5) points in the sham group ($P = 0.02$). After 8 weeks and 6 months, declines in activity limitation in the

Table 1. Participant Characteristics at Baseline

Baseline Characteristics	Active (n = 10)	Sham (n = 8)
Demographics		
Age, y, mean (\pm SD)	17.8 (2.1)	17.0 (2.1)
Age, range	15-21	13-22
Hispanic or Latino	20.0%	0%
White	100%	87.5%
Student		
Part-time	80.0%	87.5%
Full-time	10.0%	0%
Not a student	10.0%	12.5%
Sexually active	50.0%	50.0%
Clinical status and history		
Pain, mean (\pm SD)	7.7 (2.4)	7.4 (0.9)
Stage of Endometriosis		
Stage I	100%	100%
Time since surgery (months)	7.4(8.9)	9.5(15.9)
Endometriosis Health Profile	36.5 (20.2)	44.9 (16.5)
Pediatric QOL Inventory	65.1 (14.4)	61.9 (13.0)
Activity Scale	6.6 (2.3)	6.3 (2.5)
Perceived Stress Scale	1.6 (0.7)	1.8 (0.6)

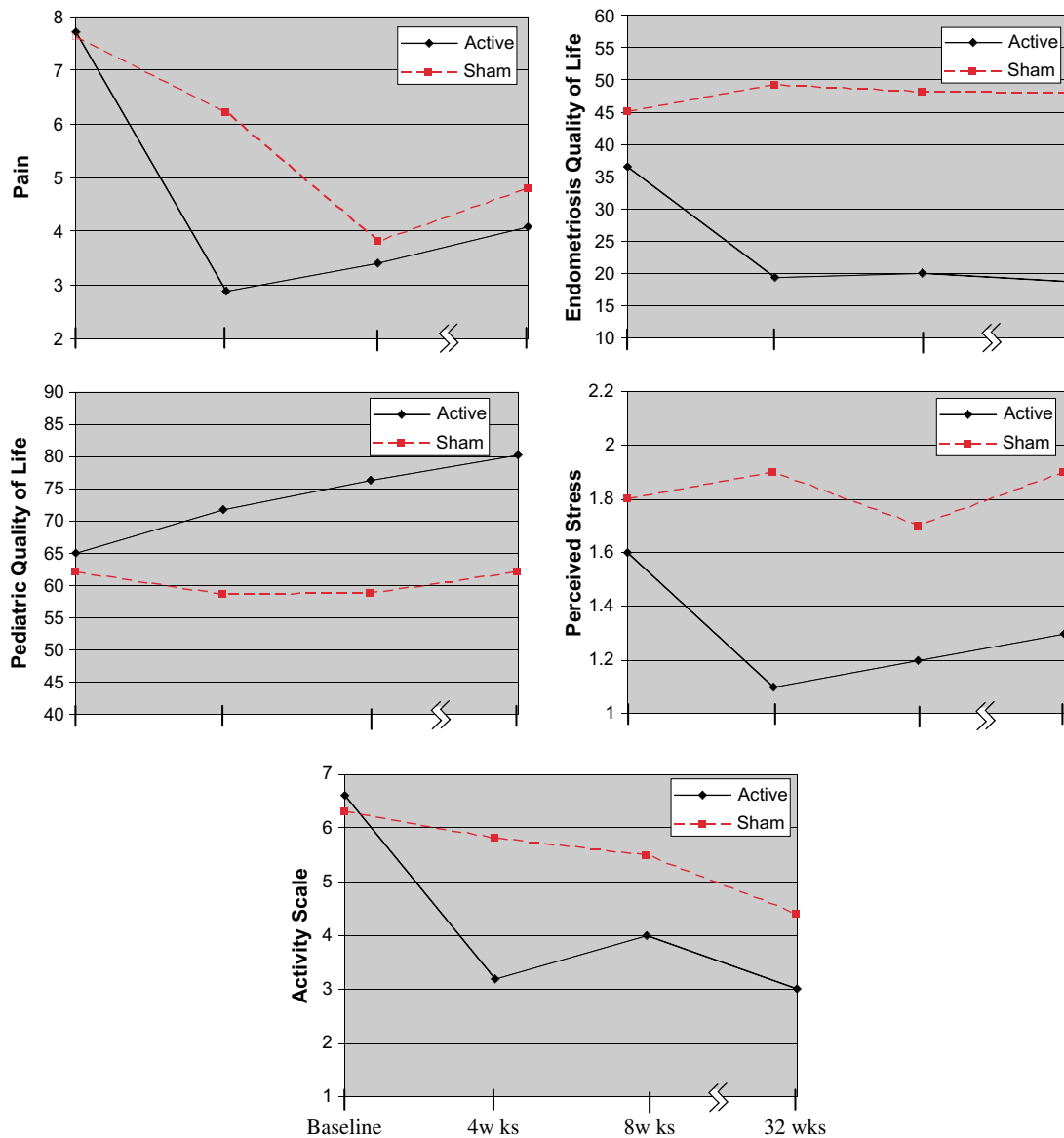


Fig. 2. Impact of active and sham acupuncture on: (A) pain (full scale ranges from 0-10); (B) endometriosis quality of life (full scale ranges from 0-100); (C) pediatric quality of life (full scale ranges from 1-100); (D) perceived stress (full scale ranges from 0-4); and (E) activity limitation (full scale ranges from 1-10). Solid lines are active group; dashed lines are sham group. Symbols indicate group means.

active group remained greater, but between group differences were not statistically significant (Figure 2, Table 2).

There was no significant difference between the active and sham groups' differences from baseline at either 4 weeks (Wilcoxon exact $P = 0.989$) or at 8 weeks ($P = 0.647$) for IL6. One subject's initial IL6 was off the chart; this subject withdrew from the trial to enroll in a drug rehabilitation program and reported using various substances that might bias blood assays. This subject was omitted from IL6 analysis. Analysis of changes in TNF α serum cytokine levels from baseline to 4 weeks and to 8 weeks were based on 10 participants in the active and 8 participants in the sham

groups. There was no significant difference between the active and sham groups' differences from baseline at either 4 weeks (Wilcoxon exact $P = 0.071$) or at 8 weeks ($P = 0.199$) for TNF α .

No serious adverse events were reported by any participants. A total of 9 minor and expected adverse events related to acupuncture were reported over the course of 232 treatments. These included transient light-headedness, minor bruising, and minor burns associated with moxibustion.

The degree to which subjects were blinded to treatment allocation did not differ statistically different between groups. After 4 weeks, 5, 3, and 1 participant in the active group, respectively, stated that they were:

Table 2. Impact of Active and Sham Acupuncture on Pain, Health Related Quality of Life, Perceived Stress and Activity Limitation.

	Baseline		Difference from baseline at week 4			Difference from baseline at week 8			Difference from baseline at 6 months		
	Active	Sham	Active	Sham	<i>P</i> -value	Active	Sham	<i>P</i> -value	Active	Sham	<i>P</i> -value
	BL (n = 10)	BL (n = 8)	(n = 9)	(n = 5)		(n = 9)	(n = 6)		(n = 9)	(n = 5)	
Pain During Last 4 weeks¹	7.7(2.3)	7.6(0.9)	-4.8(2.4)	-1.4(2.1)	0.004	-4.3(3.6)	-3.8(1.7)	0.788	-3.6(3.0)	-2.8(3.8)	0.819
Endometriosis Health Profile²	36.5(20.2)	44.9(16.5)	-17.2(18.3)	4.3(15.0)	0.065	-16.6(24.8)	3.1(13.4)	0.136	-17.9(21.9)	3.0(10.8)	0.282
Pain	36.7(20.3)	44.8(19.4)	-14.6(16.5)	7.1(20.1)	0.083	-14.6(19.0)	5.9(19.8)	0.137	15.7(18.3)	7.1(10.9)	0.438
Powerlessness/control	46.5(26.8)	55.8(23.4)	-25.6(26.0)	2.0(27.1)	0.121	-25.0(35.5)	-3.3(23.2)	0.284	27.2(33.1)	1.0(26.1)	0.226
Emotional well-being	25.8(20.7)	39.6(17.4)	-13.0(25.6)	3.3(6.8)	0.179	-12.5(28.0)	6.9(12.8)	0.118	14.4(21.1)	1.7(16.0)	0.381
Social support	36.3(27.1)	50.8(21.2)	-16.7(22.1)	-1.3(12.0)	0.251	-13.2(28.7)	-7.3(10.8)	0.930	18.1(24.1)	8.8(21.0)	0.417
Self-image	40.8(34.6)	25.0(28.9)	-23.1(24.6)	6.7(22.4)	0.064	-23.1(43.3)	8.3(16.7)	0.120	-17.6(41.8)	15.0(21.6)	0.173
Pediatric QOL Inventory³	65.1(14.4)	61.9(13.0)	6.6(16.0)	-3.5(9.5)	0.137	11.1(19.9)	-3.1(9.7)	0.107	15.1(18.2)	0.2(7.8)	0.147
Physical	74.1(11.4)	74.6(16.7)	-0.7(9.7)	-17.5(8.4)	0.012	0.8(13.4)	-8.3(17.4)	0.137	4.9(14.0)	-15.0(4.6)	0.013
Emotional well-being	63.0(17.8)	60.6(14.7)	7.8(14.4)	-3.0(10.4)	0.220	13.9(23.8)	-8.3(19.9)	0.135	21.7(16.4)	6.0(15.6)	0.204
Social support	89.5(13.8)	89.4(12.9)	2.8(11.8)	-5.0(17.7)	0.820	3.3(16.4)	-6.7(15.7)	0.593	3.3(16.6)	-11.0(10.2)	0.094
School	58.3(26.2)	50.4(18.9)	10.0(27.4)	0.0(3.5)	1.000	14.7(37.9)	4.2(10.7)	0.752	16.7(22.2)	10.0(10.0)	0.725
Perceived Stress Scale⁴	1.6(0.7)	1.8(0.6)	-0.5(0.6)	0.1(0.6)	0.136	-0.4(0.7)	-0.1(0.6)	0.864	-0.3(0.6)	0.1(0.4)	0.254
3-Activity Scale⁵	6.6(2.3)	6.3(2.5)	-3.4(2.2)	-0.5(1.5)	0.029	-2.6(3.2)	-0.8(2.1)	0.272	-3.6(2.6)	-1.9(3.5)	0.253

¹Numerical pain scores potentially range from 0 to 10; lower score indicates less pain.²EHP score and sub-scales range from 0 to 100; lower score indicates fewer negative symptoms.³PQOL score and sub-scales range from 0 to 100; higher score indicates fewer negative symptoms.⁴PSS scores range from 0 to 4; lower scores indicate less stress.⁵Activity scale scores range 0 to 10; lower scores indicate less difficulty participating in activities.

unsure of the group they were assigned to; that they were assigned to the active group; or assigned to the sham group. In the sham group, 1, 1, and 3 participants, respectively, stated that they were: unsure; in the active group; or in the sham group ($P = 0.25$). The pattern was largely unchanged after 8 weeks ($P = 0.43$) and 6 months ($P = 0.41$). Participant's expectancy that treatments would be effective were identical at baseline (Table 1) and remained similar after 4 weeks of treatment ($P = 0.49$).

Discussion

Baseline pain levels in our study population were relatively high. Our results indicate that pain levels declined significantly faster in the active acupuncture group compared to the sham control. After 4 weeks of treatment, pain was reduced by an average of 4.8 (SD = 2.4) points out of 11 in the active group vs. 1.4 (SD = 2.1) points reduction in the sham group ($P = 0.004$). While the reduction in pain in the active group was stable and persisted through the 6 month follow-up assessment, differences between active and sham groups were smaller and not statistically different after 4 weeks. This observed rate and magnitude of pain reduction in the active acupuncture group is clinically very significant.²¹ The results of this current study parallel results we observed in an earlier case series describing the responses of adolescents with endometriosis-related pelvic pain to traditional Chinese medicine style acupuncture.²¹ They also add to results reported in other studies demonstrating that acupuncture can effectively relieve pain in pediatric and adolescent populations,^{18,57,58} and that acupuncture can positively impact adult endometriosis⁵⁹ and related gynecological conditions such as dysmenorrhea.^{20,59,60}

Quality of life in adolescents with chronic pelvic pain is often seriously compromised, and is commonly associated with depression, anxiety, and decreased school attendance and participation in social activities.^{3,4} Improvements in quality of life are of particular importance in this young population as problems in early life can affect normal development.⁶¹ In the present study, average baseline values for the Endometriosis Health Profile (EHP) and the Pediatric Quality of Life Inventory indicate significant impairments in quality of life in our study population. Our observed results suggest clinically significant trends towards improved HRQOL in response to acupuncture that warrant further investigation, though differences between group were not statistically different. These include a 17.2 (SD = 18.3) point improvement out of 100 in the Endometriosis Health Profile and a 6.6 (SD = 16.0) point improvement out of 100 in the Pediatric Quality of Life Inventory.

Changes in Pediatric Quality of Life Inventory of the magnitude we observed have been interpreted as clinically meaningful.⁶² Noteworthy is that for both of these outcomes, differences between active and sham groups persisted (EHP) or even increased (PedQL) during the period following treatment and 6 month follow-up assessment.

A unique feature of this study was the use of a sham control as well as measures of patient blinding and expectation. Use of a validated sham control minimizes the possibility that responses observed in the active group were simply due to attention, to the ritual of receiving acupuncture, or to natural history. Additionally, lack of observed statistically significant differences in measures of blinding as well as participant's expectations regarding the benefits of acupuncture further decrease the likelihood that differences observed between groups were due to placebo-related phenomena.

There are a number of significant limitations to this study that necessitate that we interpret our observed results cautiously. First, the sample we recruited was very small due to the nature of a pilot study of feasibility; consequently, there is a high chance that results we observed are simply due to chance. Our original design intended to recruit 42 participants which, using published data from other studies,²⁰ we estimated would provide 50% power to detect a 2-point difference in change in pain between groups after 8 weeks. In the present trial we were only able to enroll 18 participants over a period of 2 years despite significant effort. A key factor limiting enrollment of many potential participants was the time and resources required by them (and often their families) to travel to the offices of acupuncturists for 16 consecutive treatments. To address this constraint, in January of 2006 (recruitment ended in August of 2006) we modified our protocol to allow for home acupuncture treatments, which resulted in improved rates of recruitment. Three of the 14 subjects who completed the 16 acupuncture treatments received acupuncture in their homes (21%). Additionally, at the same time we expanded the eligible age range for participation (from 14–21 to 13–22), and also embarked on an extensive campaign to more publicly advertise our study; these initiatives also modestly improved recruitment rates. While the difficulty of recruiting adolescents into medical and sociological studies has been widely reported,^{62–65} with the initiatives we developed over the course of this study we believe that recruitment of an adequate sample size in a subsequent, more definitive trial would be feasible. Moreover, our ability to retain participants once they were recruited, and to successfully develop and administer all treatment and outcome protocols further supports the feasibility of a future trial.

A second limitation of this study is that some of the instruments we used to assess outcomes have not been specifically validated in adolescent populations. The Endometriosis Symptom Severity Scale that we used to assess pain and the Endometriosis Health Profile have been validated for populations of adults older than 18 years, but not younger adolescents. Similarly, while the Pediatric Quality of Life instrument has been validated for use in children and adolescents between the ages of 3 and 18, it has not been validated for adolescents and young adults between the ages of 19 and 22 years. The limitations of current instruments for characterizing HRQOL in adolescents with endometriosis was highlighted in a recent review article.⁵⁶ Although the similar trends in our QOL measurement results suggest the existence of concurrent validity between the instruments we employed, future studies with larger sample sizes are required to formally evaluate the validity of these instruments for this population.

An important finding of this study is that once enrolled in the study, adolescents were comfortable and receptive to acupuncture treatment. Loss to follow-up was 22%, which is comparable to acupuncture trials studying diverse populations and medical conditions.^{32,33,66} It is possible that the use of Japanese-style acupuncture, with its thinner/smaller needles and limited needle stimulation, contributed to the favorable response by participants. A number of other recent studies also suggest that acupuncture is well received by adolescent and pediatric populations for treatment of pain as well as other conditions.^{15–18,58,67,68}

A secondary goal of this study was to explore the effects of one style of Japanese acupuncture on blood levels of inflammatory cytokines. The basis for investigating acupuncture's effects on inflammatory cytokines comes from two sets of observations. First, numerous studies have reported associations between inflammatory cytokines in the pathogenesis of endometriosis, and serum concentrations (IL-6 and TNF-alpha) have been used to predict endometriosis diagnosis.^{22,69–71} Second, some research suggests that acupuncture exerts anti-inflammatory effects by modulating serum concentrations of inflammatory cytokine levels,^{23,24} and thus may provide one mechanistic pathway through which acupuncture influences endometriosis-related pain. In this study, we did not observe any trends regarding the effect of acupuncture on either IL-6 or TNF-alpha levels. However, because of the very small sample sizes we employed, these results should be considered inconclusive.

Conclusion

The small sample sizes employed in this pilot study of feasibility limit the conclusions that can be drawn.

Nevertheless, our results indicate that Japanese-style acupuncture may be an effective, safe, and well-tolerated adjunct therapy for endometriosis-related pelvic pain in adolescents. Further, our findings suggest a more definitive trial evaluating Japanese-style acupuncture in this population is both feasible and warranted.

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