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Pilot, Randomized, Modified, Double-Blind, Placebo-Controlled Trial of Acupuncture for Cancer-Related Fatigue

Judith Balk, MD, MPH, Richard Day, PhD, Margaret Rosenzweig, PhD, Sushil Beriwal, MD

Cancer-related fatigue is a substantial problem for cancer patients and their caregivers, but no effective treatment exists. Acupuncture has been suggested to improve cancer-related fatigue, but no randomized clinical trials have been conducted. We hypothesized that true acupuncture, compared with sham acupuncture, would reduce cancer-related fatigue in cancer patients receiving external radiation therapy. The aim of this study was to determine effect size and feasibility. A modified, double-blind, randomized, placebo-controlled trial was conducted. The subject, clinical staff, and assessor were blinded, but the acupuncturist was not. Subjects received acupuncture once to twice per week during the 6-week course of radiation therapy. Data were collected at baseline, 3 weeks, 6 weeks, and 10 weeks, which was 4 weeks after that last radiation session. Twenty-seven subjects enrolled, and 23 completed the last data collection. Both true and sham acupuncture groups had improved fatigue, fatigue distress, quality of life, and depression from baseline to 10 weeks, but the differences between the groups were not statistically significant. The true acupuncture group improved 5.50 (SE, ± 1.48) points on the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F), whereas the sham acupuncture group improved by 3.73 (SE ± 1.92) points. This difference was not statistically significant (p = .37). All subjects guessed that they were in the true acupuncture group. Our study was underpowered to find a statistically significant difference. To demonstrate a statistically significant improvement between true and sham acupuncture would require 75 subjects per group in a future study. Owing to poor recruitment, the feasibility of a larger trial using the same methodology is low. Despite being underpowered, it appears that subjects receiving true acupuncture may benefit more than subjects receiving sham acupuncture. In the discussion section, we review our experience with using a sham-needle controlled study.

Key words: *acupuncture, cancer, cancer patients, cancer treatment, cancer-related fatigue, depression, quality of life, radiation therapy, sham acupuncture, true acupuncture*

Cancer-related fatigue (CRF) is the most frequently reported symptom of cancer and cancer treatment.[1] Seventy-eight percent of cancer patients reported experiencing fatigue during the course of their treatment,[2] with a prevalence of 60 to 90% estimated in the literature.[3] The fatigue is also persistent; patients diagnosed with cancer more than 1 year before were still experiencing fatigue as frequently as those diagnosed within the previous 6 weeks.[2] Fatigue affects more cancer patients for more of the time than any other symptom and is considered by patients to be more important than either pain or nausea and vomiting.[4] Oncologists generally believe that pain adversely affects their patients more than fatigue (61% vs 37%), but cancer patients report that fatigue impacts their daily lives more than pain (61% vs 19%).[2] Clearly, fatigue is a highly prevalent condition that adversely affects patients.

No definition of CRF is universally accepted. It is often described as "a profound tiredness affecting almost all aspects of life"[5] or a "general feeling of debilitating tiredness or loss of energy."[2] CRF was recently accepted as a diagnosis in the *International Classification of Diseases, 10th Revision-Clinical Modification.*

Treatment is supportive, including rest, eliminating unnecessary activity and stress, and additional sleep. Given that patients follow these recommendations but still experience substantial fatigue, other approaches are necessary. Exercise appears to be helpful to treat CRF,[6] as does energy conservation.[7] Pharmacologic interventions may benefit some patients, although the data supporting interventions specifically for fatigue are limited. Drugs that may be used include

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corticosteroids, megestrol acetate, and psychostimulants such as dextroamphetamine. Each has side effects, and patients may not tolerate these medications or may choose to avoid them because of potential side effects. Nonpharmacologic treatments without significant side effects are attractive to cancer patients.

Recently, Vickers and colleagues conducted a phase II study assessing acupuncture for postchemotherapy fatigue.[8] Patients had completed chemotherapy on average more than 2 years previously. Thirty-seven subjects were enrolled, and 31 completed the follow-up assessment. Subjects had completed chemotherapy and had experienced persistent fatigue. Subjects received either twice-weekly acupuncture for 4 weeks or once weekly acupuncture for 6 weeks. The primary outcome was change in fatigue as measured by the Brief Fatigue Inventory. Mean improvement following acupuncture was 31.1%, and there was no difference between the different regimens. The authors concluded that acupuncture is worthy of further study in the treatment of postchemotherapy fatigue. This study compared two different acupuncture regimens, but it did not have an attention or placebo control group. It also studied subjects who had finished chemotherapy more than 2 years previously; thus, it did not study patients currently undergoing treatment. It is possible that earlier and more aggressive treatment could be more beneficial. This project aimed to begin to fill the research void on acupuncture in CRF. We hypothesized that true acupuncture would reduce CRF in cancer patients receiving radiation therapy when compared with sham acupuncture. Our aim for this pilot study was to obtain feasibility data and to estimate an effect size for the interventions. We also aimed to refine the logistics of recruitment and retention in planning for a larger and longer study.

Methods

The proposed pilot study was a modified, double-blind, randomized, sham-controlled clinical trial of 54 cancer patients. The modified, double-blind aspect was that the patient, the clinical staff, and those doing the assessments were blinded, with only the acupuncturists knowing treatment group assignment. This study was approved by the Institutional Review Board prior to initiation of any study procedures. All study staff completed human subjects training. Dr. Balk, the principal investigator, and Dr. Kalro, an acupuncturist, were both licensed acupuncturists registered with the State Board of Medicine in Pennsylvania.

Eligibility Criteria

Women with localized cancer who had surgery alone or in combination with chemotherapy and were planning to undergo radiation therapy were eligible for this trial. The Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F)[9] was obtained at baseline to determine eligibility, with a score of 44 or lower, indicating worse than average fatigue. The score range is 6 to 52. The subscale measures quantity and quality of fatigue, the fatigue experience, and the impact of fatigue on functional status. Higher scores reflect less fatigue. Patients undergoing radiation were also given the FACIT-F at the beginning of the second and third weeks of radiation; if the subject scored 44 or worse, she was informed about the study and given the opportunity to participate. Subjects were excluded if they had a history of acupuncture treatment, allergy to stainless steel, a pacemaker, anticoagulant therapy or known bleeding disorder, or seizure disorder or if they were receiving a combination therapy of radiation and chemotherapy, jointly. Participants were recruited from the Magee-Womens Hospital Department of Radiation Oncology, and all study visits, including both acupuncture sessions and data collection, occurred in examination rooms in the Radiation Oncology office. Magee-Womens Hospital is a teaching hospital within the University of Pittsburgh Medical Center system.

Randomization

Randomization was accomplished through a computer-generated randomization protocol using permuted blocks of variable size, completed by the study statistician (R.D.). We chose an uneven randomization scheme, with three real acupuncture assignments for every two sham acupuncture assignments. We chose this scheme to focus on the specific effects of acupuncture, to improve recruitment, and because sham needles are expensive. The statistician placed the randomization assignments in sequentially numbered, opaque, sealed envelopes, which were kept in the acupuncturist's locked office. Informed consent was obtained by the study nurse, who notified the acupuncturist (J.B.) once eligibility criteria were confirmed and informed consent was obtained. The acupuncturist opened the sealed opaque envelopes on the first day of acupuncture to reveal the group assignment.

Intervention

After informed consent was obtained, each subject was randomized into one of two groups: (1) true acupuncture and (2) sham acupuncture. Contact with the subjects, techniques of needling, stimulation, and point location were standardized so that they were uniform between acupuncturists. Needles were placed bilaterally, with the exception of LI-4, which was not placed on the side of axillary node dissection, and CV-6, which is a point on the midline. CV-6 was not needled if the subject had had a transrectus abdominis muscle flap reconstruction. The needles were individually

wrapped and sterilized for individual, one-time use. Sterile technique was used. The true and sham needles, along with the Park Sham Device,[10] were purchased together so that they were identical. All needles were manufactured by Dongbang Acupuncture, Inc., Korea. The size of the needles was 0.025 by 40 mm. The heat lamp was a Solmed Plus Heat Lamp (IR 3000 Series, Model KM 702370, Marknew Products, Norwalk, CA), and the electroacupuncture unit was an Ito IC-1107+ (Model numbers 0412000491AB and 0412000481AB, Ito Co Ltd, Tokyo Japan).

Point Selection

The true and sham acupuncture protocols used the following points, chosen in consultation with experienced local acupuncturists trained in traditional Chinese medicine: Ki-3, Sp-6, LI-4, St-36, and Ren-6/CV-6. Ki-3 is located on the medial side of the ankle region, midway between the most prominent aspect of the medial malleolus and the Achilles tendon, in a depression immediately posterior to the pulsation of the posterior tibial artery. Sp-6 is located on the medial side of the leg, posterior to the medial margin of the tibia, 3 cun above the prominence of the medial malleolus. LI-4 is located on the dorsum of the first interosseus space of the hand, at the level of the midpoint of the shaft of the second metacarpal bone, on the belly of the first interosseus dorsalis muscle. St-36 is located on the superolateral aspect of the anterior surface of the leg, 3 cun distal to the apex of the patella and one fingerbreadth lateral to the tibial tuberosity. Ren-6/CV-6 is located on the umbilical region, on the anterior midline, 1.5 cun inferior to the umbilicus.

True Acupuncture

The subject reclined in a supine position on the bed. Needles were in place for 30 minutes per session. Subjects had acupuncture treatments once or twice per week during the 4- to 6-week period in which they were in this trial. Point location used standard cun measurements and palpation, and the depth of insertion followed standard clinical guidelines from the American Academy of Medical Acupuncture training. Depth of insertion varied according to point location. A "needle grab" sensation was attempted by the acupuncturist. The needles at Ki-3 and St-36 were connected to a battery-operated electroacupuncture device. The negative electrode was placed on the Ki-3 point and the positive electrode onto St-36. Points were stimulated using low-frequency electrical stimulation (1 Hz). The subject was told that she might or might not experience *de qi*, a sensation of soreness, aching, or numbness at the needle site, and that she might or might not experience a pulsating sensation. The intensity of the electrical stimulation was increased until either the patient noted that she felt a tapping sensation or to a low-medium intensity on the electrical stimulator. A heat lamp was placed over the CV-6 point on the lower abdomen. The electroacupuncture setting was chosen in consultation with medical and traditional acupuncturists and was used to tonify or strengthen energy.

Sham Acupuncture

For the sham acupuncture, we mimicked the true acupuncture procedure by replicating needle location, needle placement, applying the electrostimulator, and "turning on" the electrostimulator. The Park Sham Needle was used at the same acupuncture points as the true acupuncture protocol. This sham needle, which is a telescoping blunt-edged needle, is validated to be indistinguishable from true acupuncture. The needles were held onto the skin by a plastic apparatus with adhesive to the skin. Alligator clips were placed on Ki-3 and St-36, using the same polarity and technique. However, the wires to the clips were disconnected. Thus, visually, the stimulator appeared to be pulsating. The intensity of the electrical stimulation was increased until either the patient noted that she felt a tapping sensation or to a low-medium intensity on the electrical stimulator. It was not expected that subjects would feel a tapping sensation, but some subjects might have imagined that they did. The acupuncturist examined the needled sites at the end of treatment for evidence of bleeding. The subject was told that she might or might not experience de qi and that she might or might not experience a pulsating sensation. A heat lamp with a thermostat set on low was placed over the CV-6 point on the lower abdomen. The patient felt a minimal sensation of warmth.

Outcomes

The primary outcome was CRF, as measured by the 13-item FACIT-F.[9] The FACIT measurement system measures health-related quality of life across cancer and chronic illness. The FACIT-F measures the fatigue that cancer patients experience. This subscale is valid to stand as a single scale. The FACIT-F baseline was obtained at 3, 6, and 10 weeks. Secondary outcomes were quality of life and CRF distress, using the Short Form-36 (SF-36) and the Cancer Related Fatigue Distress Scale (CRFDS).[11] The SF-36 and CRFDS were obtained at baseline, 6 weeks, and 10 weeks. The SF-36 is a widely used tool measuring health-related quality of life for patients with chronic medical and psychiatric illness. Although the SF-36 does include measurement of quality of life effects on areas that overlap with fatigue (physical functioning, vitality), fatigue is not specifically measured

in the SF-36. The CRFDS measures the amount of distress that cancer patients feel. The FACIT-F, SF-36, and CRFDS, and all confounder measurements were obtained prior to the first radiation session and acupuncture session. Baseline demographic information was also obtained using the sociodemographic questionnaire from the Center for Research in Chronic Disorders. The FACIT-F was completed after 3 weeks of radiation therapy to determine if a difference would be seen fairly early in the course of radiation therapy. The FACIT-F, SF-36, and CRFDS were administered at the end of the 6-week radiation regimen and 4 weeks later, at 10 weeks. Confounders that had a high likelihood of changing during the course of the treatment and follow-up, such as estrogen deficiency and medication use, were reassessed. For the purposes of this study, baseline referred to the period prior to both radiation therapy and acupuncture.

Sample Size Analysis

The primary outcome variable is fatigue as measured by the FACIT-F at the end of the 6 weeks of acupuncture. The mean score for the FACIT-F validation study was 36.8, with a standard deviation of 10.5. The actual effect sizes were unknown, but we postulated that both true and sham acupuncture may affect fatigue. We expected true acupuncture to affect it more, and we considered this to be a specific effect. We predicted that we would see a change of roughly 1 SD with true acupuncture. We expected sham acupuncture to have nonspecific effects and predicted that this would result in a change of roughly 0.25 of a standard deviation. With an $\alpha = 0.05$ and $\beta = 0.20$ using a two-sided hypothesis test, a sample size of 30 in the true acupuncture group and 19 in the sham acupuncture group was required.

Statistical Analysis

Overall differences between the treatment groups with regard to specific scale scores (eg, FACIT-F, Center for Epidemiological Studies Depression Scale [CES-D]) were tested using a repeated measures analysis of variance (ANOVA) in which *treatment* was the between-group factor and *time* was the within-group factor. Difference scores (ie, follow-up minus baseline score) were used in these analyses to adjust for baseline differences in scale scores between the two treatment groups. A p value $\leq .05$ was required to reject the null hypothesis (ie, no overall difference between the treatment groups). For illustrative purposes, several analyses were plotted as figures. The data in the figures include both mean values for the data points and the standard errors, as well as the results of the overall ANOVA analyses.

Confounder Measurements

The confounders that were assessed included psychological distress, as measured by the Brief Symptom Inventory 18 (BSI 18) and the CES-D; iatrogenic estrogen deficiency; type of surgery; use of pharmacologic agents for fatigue; type and length of chemotherapy regimen; anemia; concomitant illness; drug therapy; inactivity as measured by the Physical Activity Questionnaire; and complementary and alternative medicine use.

Credibility

At the 3- and 10-week follow-ups, subjects were asked to which group they believed they were assigned. Choices included "true acupuncture" or "sham acupuncture."

Data Collection

The research nurse, who was blinded to treatment group, was responsible for data collection. She reviewed all forms for completeness and asked subjects about the other confounders, for example, amenorrhea and credibility on the appropriate days.

Results

Subjects were recruited from November 2005 to June 2007. Participants attended a study visit for recruitment at one of the radiation oncology planning visits, once to twice per week for the course of radiation therapy, and then at the 4-week follow-up visit. The mean age of the subjects was 54.1 years and 53.7 years, in the true acupuncture and sham acupuncture groups, respectively. All subjects except one had breast cancer; the one remaining patient had endometrial cancer. No statistical differences occurred between groups regarding chemotherapy status prior to radiation therapy. The demographics are shown in Table 1.

Twenty-seven subjects were enrolled; 11 were randomized to sham acupuncture and 16 were randomized to true acupuncture. Twenty-six of the 27 subjects completed all 6 weeks of acupuncture. One subject in the true acupuncture group withdrew from the study during the acupuncture/radiation owing to changing employment responsibilities. All other subjects completed the 6-week course of both radiation and acupuncture. Four subjects did not complete the week 10 outcome assessments: the one subject, described above, who withdrew during the acupuncture/radiation, and three other subjects who were all in the sham acupuncture group. There were no protocol deviations other than these withdrawals. One hundred percent of subjects guessed that they were receiving true acupuncture. No subjects experienced adverse events.

Table 1. Baseline Levels of Demographic, Clinical, and Outcome Variables by Randomized Treatment Group

	Treatment Group		
Variable	*Real Acupuncture* (n = *16*)	*Sham Acupuncture* (n = *11*)	*All* (N = *27*)
Age (yr)			
Mean (SD)	54.0 (9.1)	53.7 (9.0)	54.1 (9.4)
Group, *n* (%)			
40–49	6 (37.5)	5 (45.5)	11 (40.7)
50–59	7 (43.8)	2 (18.2)	9 (33.3)
60–69	3 (18.7)	4 (36.3)	7 (26.0)
Menopause, *n* (%)			
No	3 (18.7)	0 (0.0)	3 (11.1)
Natural	8 (50.0)	5 (45.4)	13 (48.2)
Chemical	1 (6.3)	3 (27.3)	4 (14.8)
Surgical	4 (25.0)	3 (27.3)	7 (25.9)
Chemotherapy (%)			
Yes	8 (72.7)	7 (43.7)	15 (44.4)
No	3 (27.3)	9 (56.3)	12 (55.6)
FACIT-F score			
Mean (SD)	31.9 (8.1)	36.6 (4.8)	33.8 (7.2)
Median (range)	31 (16–44)	38 (28–42)	34 (16–44)
CES-D score			
Mean (SD)	21.6 (8.4)	21.8 (9.0)	21.7 (8.5)
Median (range)	21.5 (8–36)	16 (13–39)	21 (8–39)
≥ 16 score	12 (75.0%)	8 (72.7%)	20 (74.1%)

Our primary outcome variable was fatigue as measured by the FACIT-F. Those randomized to true acupuncture had more severe fatigue, but differences were not statistically significant (Figure 1). Owing to this baseline difference, the changes from baseline in both groups were calculated (Figure 2). True acupuncture improved more than sham, but the differences were nonsignificant. When applying this effect size for a sample size analysis for a future study, we determined that 75 subjects per group would be required to have adequate power. CRF distress (Figure 3) and both physical (Figure 4) and mental (Figure 5) quality of life scores improved over the course of the study but were not statistically significant between groups or within groups. Depression scores (Figure 6) improved over the course of the study and were significant within groups but not between groups. FACIT-F and CES-D scores were correlated at both baseline ($r = -.485$, $p = .01$) and 6 weeks ($r = -.623$, $p = .003$).

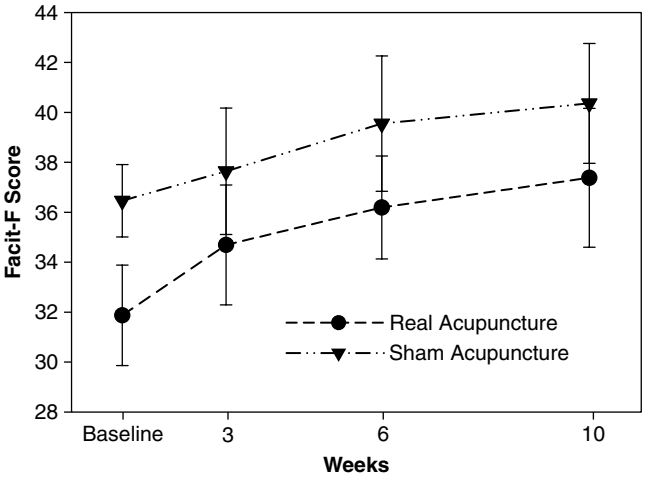

Figure 1. Mean FACIT-F Scale scores and standard errors at baseline and follow-up appointments by treatment group.

Discussion

The purpose of this pilot study was to assess feasibility and to determine an effect size. As part of the feasibility assessment, the eligibility criteria, the recruitment method, and the logistics of providing acupuncture during a patient's visit for radiation were evaluated. First, the feasibility is low for conducting a large-scale trial using the current approach and eligibility criteria. Some of the issues that were faced were a change in office staff and procedures during the study that limited access to the subjects. Owing to the Health Insurance Portability and Accountability Act, researchers depended on the clinical staff to approach potential subjects, but the clinical staff were extremely busy and unable to help. Also, from the time the study was funded to the time it began, one major change happened to the subject availability: many patients

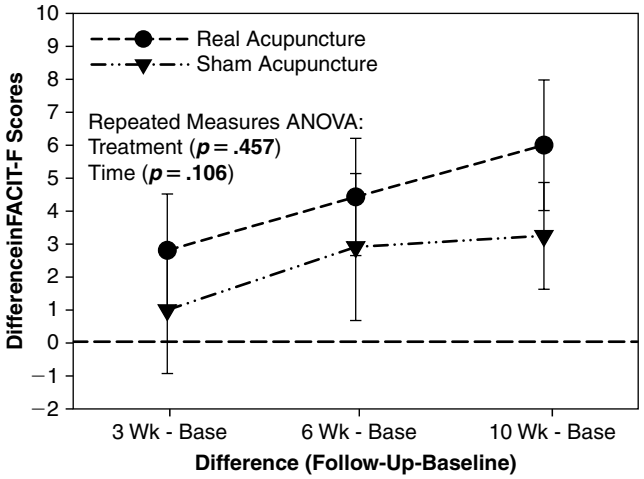

Figure 2. Mean FACIT-F differences over baseline scores for follow-up appointments and standard errors, by treatment group. ANOVA = analysis of variance.

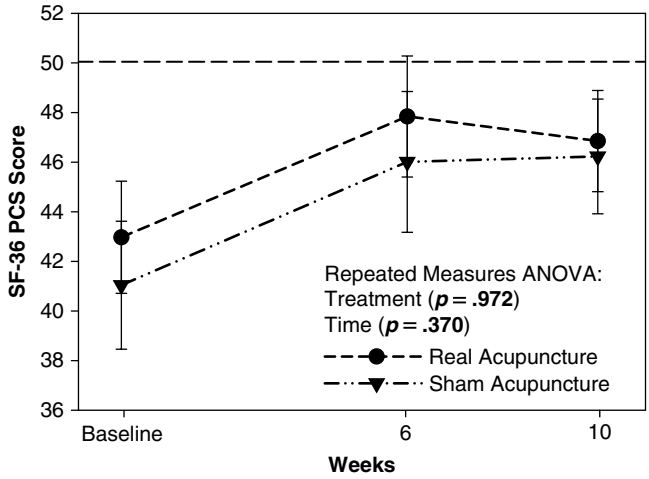

Figure 4. Mean SF-36 physical component summary (PCS) scores and standard errors at baseline and follow-up appointments, by treatment group. ANOVA = analysis of variance.

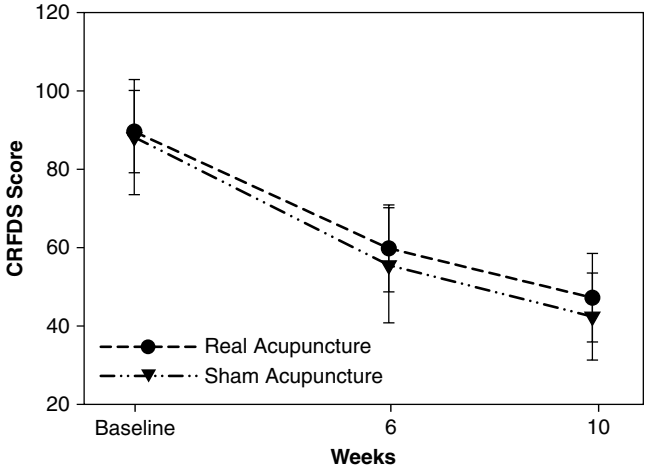

Figure 3. Mean Cancer Related Fatigue Distress Scale scores and standard errors for baseline and follow-up appointments, by treatment group.

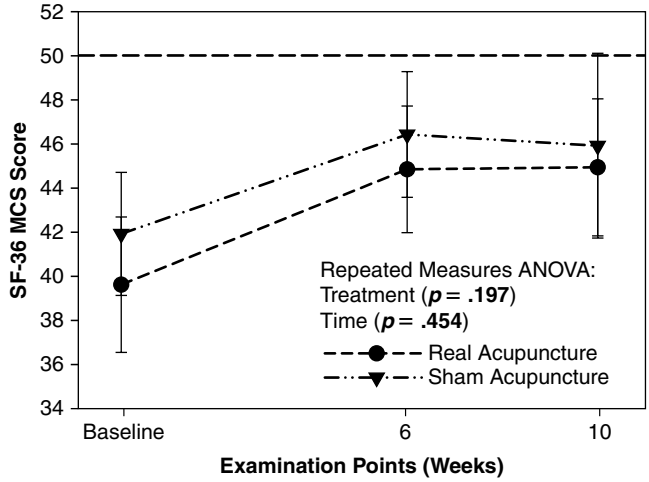

Figure 5. Mean SF-36 mental component summary (MCS) scores and standard errors at baseline and follow-up appointments, by treatment group. ANOVA = analysis of variance.

began to choose Mammosite rather than external radiation. We changed the eligibility criteria to include any subject receiving external radiation to increase enrolment, but this only helped minimally. The eligibility criteria required subjects to be fatigued at baseline; on the one hand, this is appropriate because if subjects are not fatigued, no improvement can be seen. On the other hand, knowing that external radiation is associated with fatigue, it would be reasonable to try to prevent fatigue, and randomization could have equally distributed the fatigue scores. On several occasions, the clinical staff called to inquire if a subject could be enrolled owing to severe fatigue, but if the subject was into her third week of radiation, she did not qualify. Either enrolling all subjects to attempt to prevent fatigue or waiting until radiation was over to enrol those with persistent fatigue would enhance enrolment. Given that fatigue is reported to increase during radiation,[4,12] a decrease in fatigue during the time where one would expect an increase could have clinical benefits. A usual care control group was not used; however, one would be used for a future study. If one was able to prevent the fatigue that commonly occurs with radiotherapy, it is possible that the risk of persistent fatigue would decrease. Our findings are generalizable to all patients receiving external radiation therapy for breast cancer. We did not have sufficient numbers of other types of cancer to determine if our results would be applicable.

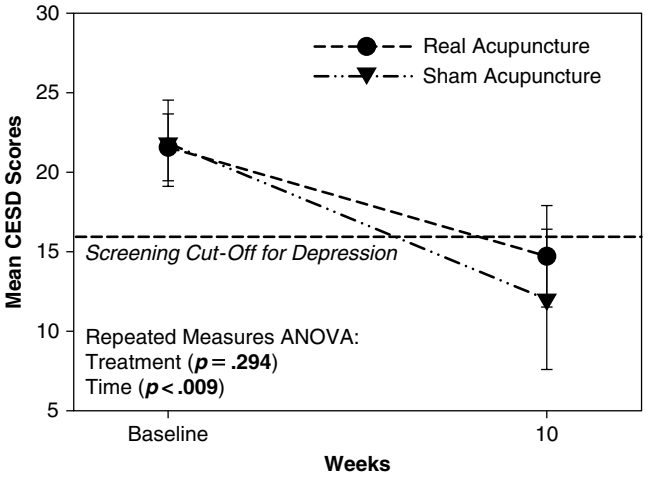

Figure 6. Mean Center for Epidemiological Studies-Depression score at baseline and the 10-week follow-up appointment, by treatment group. ANOVA = analysis of variance.

One aspect of feasibility that was focused on was the use of sham acupuncture with the Park Sham Device. The device was clearly able to blind subjects as 100% of subjects thought they were receiving true acupuncture. However, in the focus to keep subjects blinded, it was determined that the actual goal of the study, true versus sham acupuncture, changed and became a study of a "less than true" acupuncture versus a "more than sham" acupuncture. For instance, a true acupuncture protocol includes feedback from the patient on sensations such as aching, soreness, or warmth, known as de qi. In the quest to keep the patient blinded, however, it was not attempted to have feedback from the patient because the true group would have these sensations, but the sham group would not. If the subject truly never felt anything, the study would be unblinded. Also, the plastic rings and tubes were used as part of the blinding but are never used in true acupuncture. The acupuncturists felt that there was less needle manipulation because of the tubes and rings holding the needle and that because the needles were covered with the tubes, it was difficult to determine the depth of insertion. Thus, it was believed that the true acupuncture was not "true" acupuncture. It was a less than active form of acupuncture. In the same vein, the sham acupuncture was likely not completely inert. At the minimum, acupressure occurred at active acupuncture points. These points were stimulated by both the plastic ring that was adhered to the point and the blunt end of the sham needle. Furthermore, point location occurred as usual in clinical practice, by palpation. Merely touching the skin affected the brain and thus has physiologic effects.[13] Thus, it was concluded that the sham acupuncture was actually "more than sham"; it was an active control, although less active than the "less than true" acupuncture. Other sham interventions may not have this same effect; interventions that do not require that the true intervention be modified or a sham intervention that is physiologically inactive would improve the methodology.

The other goal of this study was to determine an effect size. The sample size was too small to have adequate power, although small, nonsignificant differences were found between changes in fatigue scores in both groups. It was also found that the CES-D scores were highly correlated with the fatigue scores. It is possible that what was thought to be "treated" was the "demoralization" that can be seen with high CES-D scores.[14] Perhaps enrolling in a study and having individual attention improved the demoralization that can occur with cancer diagnosis and treatment. It was believed that the effect size was small because of the small differences between the actual treatments; essentially, the only difference was whether the skin was actually punctured, but acupuncture is much more than whether the needle traverses the epidermis. Future studies should include a truly inert control that does not have a touch component, for instance, waiting control or education.

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