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Long-lasting Effect of Penetrating Acupuncture among Responders: Double-blind RCT of Acupuncture for Vulvodynia

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Abstract

Vulvodynia, vulvar pain of unknown etiology, lasting 3 months or longer, affects 7% of American women, and has no consistently effective treatment. We aimed to test the efficacy of acupuncture on vulvar pain and dyspareunia and explore the duration of the effect in a double-blind randomized controlled trial of acupuncture for vulvodynia. 89 women, 19–62 years old (mean 30.2 ± 8.3), 70% White, 20% Hispanic; 91% completed a 13-needle, 10-session standardized acupuncture protocol using double-blind acupuncture needles. Average Pain Intensity of vulvar

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JMS, ADS, NT, WHK, MT, HY, YY, DCF, TJK, and DJW substantially contributed to the conception and design of the work. JMS, ADS, NT, MT, JEG, and DJW were responsible for acquisition, interpretation, and drafting the article. ADS, LAB, HAP, NT, YY, and DJW substantially contributed to the data analysis. JMS, AD, NT, WHK, MT, HY, MLS, MM, KMS, HY, JEG, DCF, TJK, and DJW critically revised the work for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

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pain (API, 0–10 scale) and dyspareunia (Female Sexual Function Index) were measured at baseline and after the 10th treatment. Participants with a clinically important post-treatment improvement reported weekly Tampon Test scores (0–10), a measure of provoked vulvar pain, until they returned to baseline. Percentage of responders was similar: acupuncture 58%, placebo 57%; no significant differences were found between acupuncture and placebo groups on API or dyspareunia upon completion of treatments. Responders showed a consistently higher rate of return to baseline pain during the 12-week post-treatment follow-up in the placebo group compared to the acupuncture group (hazard ratio: 2.72, 95% CI: 1.13–6.54). Effects of acupuncture on vulvodynia may have been underestimated because of the strong placebo response from the skin-touch placebo needles. Among responders, the relatively large placebo effect did not persist for as many participants as the therapeutic effect of penetrating acupuncture during the 12-week follow up. Findings indicate investigations into the effects among acupuncture responders and non-responders are warranted. Findings also merit larger, pragmatic trials.

Perspective

Double-blind RCT of acupuncture for vulvodynia tested vulvar pain and dyspareunia and explored the duration of effect. Penetrating acupuncture and skin-touch placebo needle groups had pain reduction, not significantly different between groups. Pain reduction lasted longer for significantly more responders in the penetrating acupuncture vs. skin-touch placebo groups.

Keywords

Vulvodynia; Acupuncture; Chronic Pain; Placebo; Sham Acupuncture; Double-blind Acupuncture Needles; Placebo Acupuncture

Introduction

Vulvodynia is vulvar pain of unknown etiology that lasts at least 3-months, may have other potentially associated factors, and affects 7% of American women.[1–3] The pain of vulvodynia renders sexual intercourse virtually impossible and devastates intimate relationships.[4–6] Seventy percent of women with vulvodynia report severe pain (greater than 6/10).[7] To reduce their pain 60% use alcohol and 43% use alcohol with analgesics (including opioids).[8] The severe chronic pain of vulvodynia may lead to physical disability[9] and even suicidal ideation.[10] The two most common subtypes of vulvodynia are provoked vestibulodynia (PVD), pain limited to the vulvar vestibule and vaginal introitus that is provoked by touch,[11] and generalized vulvodynia, spontaneous diffuse vulvar pain that can spread to the perineum and inner thighs.[7] Although many have been tried, few therapies have been proven efficacious.[12]

Acupuncture has been shown to be effective in a meta-analysis of 39 high-quality randomized trials of acupuncture in 20,827 patients for the treatment of four chronic pain conditions: nonspecific musculoskeletal pain, osteoarthritis, chronic headache, and shoulder pain (all $p < .001$).[13] In contrast to these four chronic pain conditions,[13] there have been only six acupuncture studies[14–19] of which two had acupuncture sham-control focused on feasibility[17,18] and four[14–16,19] provided some evidence of the effect of acupuncture on

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vulvodynia. In all of them, women who received acupuncture had less pain, better quality of life, improved sexual health, and improved mental health. However, three were single-group uncontrolled acupuncture studies and none were blinded,[14–16] which limits conclusions about the efficacy of acupuncture for vulvodynia.

To address these methodological issues and verify the previous significant pain reduction with penetrating needles compared to a wait-list control group,[19] a placebo-controlled acupuncture trial was conducted with double-blind needles[18,20,21] to examine the efficacy of acupuncture on vulvodynia. Specifically, the study aim was to compare the acupuncture penetrating needle group and the skin-touch placebo needle group for effects on the reduction of vulvar pain, the primary outcome, and dyspareunia and sexual function, the secondary outcomes.[22] A second aim was to describe the duration of the treatment effects in each group's responders until pain returned to baseline levels or up to 12 weeks after treatments ended. The hypothesis was that, controlling for baseline values, at posttest there would be statistically significant less vulvar pain and dyspareunia and more sexual function after five weeks of treatment in the penetrating needle group compared to the skin touch placebo group. It was also expected that fewer responders in the placebo needle group would have persistent effects on vulvar pain than in the penetrating needle group.

Methods

Study Design

As reported previously,[22] the study protocol involved a 10-week double-blind (participant and acupuncturist) RCT with 12-week post treatment follow up. The Institutional Review Board (IRB) at the University of Illinois Chicago (UIC, IRB2017-0885) approved the RCT prior to data collection (Supplementary Material). This trial was registered with ClinicalTrials.gov (NCT03364127). All participants completed informed consent prior to study enrollment.

Setting

The acupuncture research lab at the UIC College of Nursing served as the site for all study activities. Two non-study affiliated private acupuncture clinics in greater Chicagoland were the sites for delivery of free, post-study acupuncture treatments to participants who received placebo acupuncture.

Participants

Recruitment Strategies/Patient and Public Involvement Statement: To promote diversity and inclusiveness in the study sample, participants were recruited from community settings, Chicagoland area medical clinics, healthcare provider referrals, the UIC study website, and Chicago Transit Authority banners displayed in buses and subway cars. Additionally, the National Vulvodynia Association, a non-profit public advocacy group for women with vulvodynia, aided recruitment by advertising this study through their "Participate in Research" section of their website and through e-blasts to their constituency.

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Determining Study Eligibility: Eligibility criteria were: 1) vulvar pain for at least 3-months duration, 2) a vulvodynia diagnosis as determined by gynecologic exam, 3) at least 18 years old, 4) spoke and read English at the initial screening, 5) a Tampon Test self-reported vulvar pain intensity score of 4 or greater on the Pain Intensity Number Scale (PINS 0–10)[23] after inserting and removing a tampon because in women with vulvodynia, the pain of inserting and removing a tampon is significantly correlated with daily vulvar pain and dyspareunia,[24] and 6) be acupuncture naïve to enable participants to be blind to group allocation. At the time of recruitment, participants were not required to be assigned female sex at birth; however, all participants had a pelvic exam to determine study eligibility and were assigned female sex at birth. The detailed gynecologic exam included 1) a cotton swab test of the vulva to assess for allodynia (painful response to a non-painful stimulus), which is present in women with vulvodynia,[2] and 2) a pelvic exam with vaginal maturation index[25] to determine if the potential participant was in menopause and could have pain secondary to atrophic vaginitis. All exams were done by a board-certified urogynecologist or a certified nurse-midwife.

Additional exclusionary conditions included: current vaginitis (candida, bacterial vaginosis, trichomonas vaginalis); inflammatory conditions; neoplastic disorders of the genitals, including cancer or pre-cancer of the vulva, or Paget's disease; neurologic disorders affecting the genitals including pudendal nerve entrapment, or spinal cord nerve compression; genital trauma, history of surgery, radiation, or chemotherapy to the genitals; and hormonal deficiencies. These conditions may cause genital pain or inflammation, but do not constitute a diagnosis of vulvodynia as set forth by the 2014 Executive Council of the International Society for the Study of Vulvovaginal Disease (ISSVD), the Boards of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS).[1]

Women were also excluded if they were pregnant as some of the acupoints in the protocol are forbidden in pregnancy.[26] For this trial, we excluded women if they self-reported a history of comorbid pain conditions to avoid confounding pain outcomes, thus enabling a better understanding of vulvodynia pain only. Therefore, co-morbid pelvic pain conditions including endometriosis and pelvic inflammatory disease were excluded.

Women were also excluded if the following co-morbid conditions were active in the last 6 months: temporomandibular joint disorder, migraine headaches, chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, interstitial cystitis, painful bladder syndrome, atrophic vaginitis, therapies that may decrease stress/pain such as additional acupuncture, massage, and physical therapy. Initially excluded were potential participants older than 45 years old to prevent from enrolling women with atrophic vaginitis. However, these women may not have had atrophic vaginitis and/or vaginal pain due to atrophic vaginitis. Therefore, the exclusion criterion based on age was removed, and women were excluded whose vaginal maturation index indicated atrophic vaginitis (wet mount with greater than 15% parabasal cells).[27]

Determination of the Sample Size: The approach to sample size estimation for Aim 1, comparing the two treatment groups, was conservatively based on mean differences

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between groups at the end of treatment assuming 80% power, alpha=.05, and a two-sided test. A minimum detectable effect size of 0.60–0.63 was estimated based on 80 of 88 participants completing the study, a feasible sample size given the population and resources. This minimum detectable effect size represents a 40–43% reduction of effect size from the pilot study, (Cohen's d = 1.05)[19] necessary to account for the difference between a waitlist control used in the pilot and placebo needles used in the current study.[19] The actual power would be greater in models testing intervention efficacy when controlling for baseline and diagnostic subtype.

Aim 2 was a descriptive aim to describe the variability of treatment duration effects. The prior wait-list controlled study[19] showed that 15/18 (83%) of intervention participants showed a clinically significant reduction in pain intensity of 1.5 points or more, but 3/18 (17%) of the wait-list control subjects met this threshold for pain reduction. Based on these findings a conservative estimate was that 40 (50%) participants from both conditions would show a meaningful improvement following acupuncture or placebo treatment, a number more than sufficient for preliminary estimates of treatment duration variability.

Procedures

All referred individuals consented to initial screening. A 3-step process was conducted to determine study eligibility (Figure 1). The research coordinator determined initial study eligibility at the telephone screening. Potential participants were then scheduled for an appointment for continued eligibility evaluation and possible enrollment. After informed consent was obtained, a urine pregnancy test was completed to ensure that participants did not receive acupuncture if pregnant. For the second step in the eligibility process, potential participants were assessed for the presence of vulvar pain by self-insertion and removal of a regular Tampax® tampon with cardboard applicator as a standard stimulus and reporting their pain on a 0–10 scale (Tampon Test, TT). If their pain was 4 or greater, they were then eligible to complete baseline study measures on a tablet computer. For the third step in the eligibility process, participants were escorted to a private exam room for a gynecologic exam to confirm the presence of vulvodynia, its subtype, PVD or generalized vulvodynia;[1,11] and for a vaginal smear to be taken for microscopy to determine the presence of atrophic vaginitis.[27] Participants confirmed to have vulvodynia without atrophic vaginitis were then randomized via the REDCap[28] randomization module to a needle package number that corresponded to either penetrating acupuncture needles or skin-touch placebo needles. The research coordinator then escorted the participant to a private exam room for acupuncture using the assigned numbered package containing penetrating or placebo needles. The research coordinator, principal investigator, statistician, participants, and acupuncturists were all blind to group assignment.[29] After the 1st and 10th acupuncture session, the participant and acupuncturists completed a questionnaire assessing their perception of which needle was used. Because multiple acupuncturists treated participants over the course of the 10-session, 5-week protocol, due to timing of treatment sessions and logistics, acupuncturists also completed the survey each time they treated a new participant. Upon completion of the 10th and last acupuncture session, participants completed all posttest study measures. Participants reporting at least a 1.5/10 reduction in pain (TT) entered the Duration of Effect portion of the study. Participants inserted and removed a regular Tampax® tampon once per week

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and recorded their vulvar pain intensity scores once per week for up to 12 weeks until they returned to baseline.

Randomization and Blinding: The complete blinding and randomization protocols used for this double-blind RCT have previously been described in detail.[29] Briefly, the REDCap randomization module enabled complete blinding to group allocation based on their gynecologic exam diagnosed status of provoked vestibulodynia (PVD) or generalized vulvodynia.[1] A trained research coordinator used the study-specific randomization program with stratified permutated block randomization, to randomize participants 1:1 to treatment group, separately for PVD and generalized vulvodynia strata.[22,29] Unique treatment group identifiers were used to blind study participants, the principal investigator, the research coordinator, the project manager, and the acupuncturists to treatment group allocation. The study statistician was aware of the treatment group code, but not its meaning. An independent statistician was aware of the meaning of the code (penetrating acupuncture versus skin-touch placebo).

Duration of Effect Phase: After the final acupuncture treatment, if the Tampon Test vulvar pain intensity score was 1.5 points or more below the baseline score, the participant entered the duration of effect phase.[22] In the duration of effect phase, participants completed the Tampon Test pain diary sent automatically from REDCap and accessed via an email once per week for up to 12 weeks or until the provoked pain was equal to or greater than the pre-acupuncture baseline PINS score.[22]

Intervention

Double-blind Acupuncture Needles

To verify the effect of penetrating acupuncture obtained in the prior studies[19–21,30–34] in this rigorous double-blind RCT comparing treatment to placebo,[20] validated double-blind (acupuncturist-participant) acupuncture needles were used. These needles (Figure 2) included penetrating and skin-touch placebo acupuncture needles housed in a device that appears identical.[18,20,21]

The appearance of the penetrating needle and the skin-touch placebo needle are the same except for the needle tip, making it impossible to visually distinguish between the two needles. In addition, the needles are designed to counterbalance any resistance the practitioner felt when inserting them so that the acupuncturist cannot tell which needle is used, both from appearance and from the feel during use. The skin-touch placebo needle provides a sensation similar to that of needle insertion to make the recipient of acupuncture feel they receive real acupuncture. Based on these characteristics, it is possible to perform a double-blind study.[21,35]

The acupuncture needle sets were assembled and packaged for the study by team members in Japan who had no contact with the participant. Each needle package (Figure 3a) had 10 needle packets for 10 treatments and was tagged with a label marked 1 or 2 (needle type identifier).[29] Each needle packet contained the 13 needles for one treatment session. As described elsewhere,[29] after participant randomization, the needle type identifier tag was

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removed and the needle package was labeled with a randomization ID (Figure 3b). This ID was obtained from the REDCap-deployed randomization allocation schedule that was based on specified arm, block random number, sequence number, and vulvodynia subtype group. Therefore, the study staff did not know the participants' treatment group assignment. The research coordinator verified blinded needle types after all data were collected on a randomly selected sample of 23 packets (25%) and recorded A or B for type of needle to distinguish this validity check from the initial needle type assignment while maintaining the blind for the statistician and other team members. All A needles corresponded to arm 1 and B needles to arm 2, with the exception of one unavailable packet that had been recycled after the participant withdrew from the study.

Study Training Including Environmental Control

Led by the principal investigator and Dr. Takakura, the acupuncturists were required to take a 2-day, 5-hour in-person training. Topics included: 1) an overview of the study and general steps, 2) training on needle technique, 3) needle technique practice, 4) training on acupuncture for vulvodynia, and 5) acupuncture protocol practice. During their training in the study procedures, acupuncturists were taught how to use the double-blind needles and that there was a real and a placebo needle. No further information was given (Supplementary Table).

Adherence to the Protocol

For the participants, at the beginning of the study the research coordinator informed participants that they would receive either real or fake acupuncture. Both groups were informed that they would be blind to the participant's group assignment until after study completion. After the session, the research coordinator handed a paper version of the Double-blind Needle Questionnaire for the Acupuncturist to the acupuncturist and asked them to complete it; no further instructions were given. The research coordinator handed the participant a computer tablet to complete the Double-blind Needle Questionnaire with no further instructions.

Fidelity to the Intervention

To control the test environment, the protocol specified that the acupuncturists communicated with participants only as necessary to safely administer the acupuncture treatments. Acupuncturists did not engage in patient-centered or social support before, during, or after the treatments and the treatment room did not include music or aroma therapy. A trained research specialist monitored fidelity to the treatment protocol with a 17-step protocol-specific checklist at each treatment session (Supplementary Table).

Intervention Phase

This trial conformed to the Revised STRICTA Guidelines (Table 1). Used in this trial was the same 13-point acupuncture protocol (Figure 4) from a prior study,[19] which was based on clinical experience treating vulvodynia patients. The acupuncture protocol is detailed in Table 1.

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Measures

Primary Outcome, Vulvar Pain: The primary outcome, vulvar pain with the valid and reliable PAIN*Report*It (Nursing Consult LLC, Seattle, WA), a computerized 1970 version of the validated McGill Pain Questionnaire (MPQ)[36] containing the measures used for this trial.[22] The valid and reliable Pain Intensity Number Scale (PINS; 0 representing no pain, 10 representing pain as bad as it could be)[23] measured vulvar pain as the average pain intensity (API)[37] of current pain and least and worst pain in the last 24 hours.

Secondary Outcomes, Dyspareunia and Sexual Function: The secondary outcomes were assessed with the Female Sexual Function Index (FSFI),[38] including dyspareunia (FSFI dyspareunia) and sexual function (FSFI total). The valid and reliable FSFI[39] is a 19-question self-report measure of six sexual function domains: desire, arousal, lubrication, ability to orgasm, sexual satisfaction, and dyspareunia (pain with intercourse), with a total score that represents overall sexual function.[38,39] On a 0–5 scale, the 3-question dyspareunia subscale measures frequency and level of pain during or following vaginal penetration in the last 4 weeks. Higher scores indicate improved function. Summed domain scores are multiplied by a domain factor ratio and summed to obtain a total score. It is not necessary for women to have sexual relations with a partner to complete the questionnaire. The FSFI defines sexual activity as caressing, foreplay, masturbation, and vaginal penetration.

Duration of Effect Phase Weekly Vulvar Pain Intensity: The Tampon Test[24] was the provoke pain stimulus and its vulvar pain intensity was measured with the PINS. Since participants with provoked pain may have had no pain while completing the study measures, the tampon insertion and removal protocol developed by Foster et al.[24] provides a standard stimulus that enables vulvar pain to be measured in women with generalized vulvodynia or PVD. Provoked pain using the Tampon Test correlated significantly to daily pain ($r = 0.42$), dyspareunia ($r = 0.35$) and vulvar vestibular pain provoked with a cotton swab ($r = 0.38$).[24] Women with vulvodynia reported stable mean Tampon Test scores, 4.6 ± 2.6 (week 2); 4.6 ± 2.7 (week 1); and 4.7 ± 2.8 (week 0); and, moderate week to week reliability (weighted Kappa = 0.52).[24] The acceptability of the Tampon Test has been demonstrated with women performing the Tampon Test 96.3% of the requested time, which was twice as often than measuring pain with intercourse.[24,40] For this study, participants inserted a regular, unlubricated Tampax™ tampon with applicator. The scores determined study eligibility and eligibility to enter the duration of effect phase of this study where tampons were inserted weekly up to 12 weeks.

Assessing Acupuncturist and Participant Blinding: To assess whether the acupuncturist and participant remained blind, the acupuncturist completed the Double-blind Needle Questionnaire for the Acupuncturist and the participant completed the Double-blind Needle Questionnaire for the Participant as described in the procedures.[29] Both acupuncturists and participants 1) guessed what type of needle was used in the treatment, and 2) their confidence in the guess on a scale of 0 to 10, with 0 being no confidence and 10 being complete confidence. A “don’t know” option was not provided. Participants completed this survey after the first and 10th session.

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Statistical Analyses

Preliminary Analyses: Data cleaning to check variable ranges, distributions, coding of write-in variables such as race-other and medications, and amount of missing data was done on the total sample. Further analyses were conducted using randomization group but blinded to meaning of the codes (i.e., penetrating versus skin-touch placebo needles). Descriptive statistics were used to compare the randomized treatment groups on demographic and baseline outcome measures. Fisher's exact chi-square and independent samples t-tests were used to assess treatment group differences for dropout and session attendance. Logistic regression was used to explore predictors of withdrawing from the study before completing the treatment protocol.

Analysis of Treatment Effect and Duration of Effect: The planned main effect analysis for all primary and secondary outcomes was a full-information maximum likelihood analysis of covariance model regressing the outcome at post-treatment on treatment group, the outcome at baseline, and an indicator for vulvodynia subtype used to define strata for randomization. This was conducted with a structural equation model and retained all randomized participants for the intention to treat models. Additional models conducted for sensitivity analysis used a general linear model for complete cases and mixed effect regression models of complete cases assessing the impact of multiple membership,[41] i.e., clustering of participants nested within acupuncturists, using weights that represented the proportion of all sessions provided by each acupuncturist as random effects with identity covariance structure. Effect sizes and 95% confidence intervals were calculated from the intent to treat model by using standardized outcomes.[42]

The duration of effect was described with Kaplan-Meier curves for each treatment group. Survivor functions were tested for equality using a log rank test. A Cox regression was used to test treatment group differences adjusted for vulvodynia subtype. Sensitivity analyses were conducted for 7 right-censored cases with less than 6 weeks of observations using a range of assumptions. Analyses were completed with standard commands using Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Assessment of Participant and Acupuncturist Blinding: A weighted guess score was computed using +1 as an acupuncture guess and −1 as placebo, multiplied by the confidence rating resulting in a potential range of −10 to +10. This range was reduced to 5 levels collapsing −10 to −7 (strongly believe treatment is placebo), −6 to −3 (somewhat believe treatment is placebo), −2 to +2 (do not know), etcetera, to be consistent with the 2 × 5 format recommended by Kohali et al.[43] Bang's Index, developed to be calculated for each treatment group, ranges from −1 to 1 with 0 indicating random blinding (ideal), a positive value significantly different from zero indicates a failure in blinding, and a negative value different from zero may indicate a failure of blinding in the other direction. The Stata package "Blinding: Stata Module to Compute Blinding Indexes"[44] was used to compute Bang's blinding indices at visit 1 and visit 10 for participants and acupuncturists, by treatment group.

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Results

From the 450 women assessed for eligibility, 89 were enrolled between February 23, 2018 and September 24, 2022, when the targeted enrollment was completed. Full details of the screening and retention appear in the CONSORT diagram (Figure 5). Demographics are summarized by treatment group in Table 2. Approximately 9% of randomized participants withdrew from the study and were missing outcomes measurements, six (13%) in the treatment group and two (5%) in the placebo group (Fisher's exact test, p = .266). Those missing at follow-up were retained through the full information maximum likelihood (FIML) analysis approach. None of the demographic, clinical, and baseline outcome measures were associated with study withdrawal (data not shown).

Randomized participants received, on average, 9 of the 10 sessions [range 1–10, Acupuncture 8.91 (2.71), Placebo 9.57 (1.74), t(87) = −1.356, p = .179]. The participants who did not complete the study received an average of 2.5 sessions (range of 1 to 7). Participants saw, on average, 3 (1.0) acupuncturists across 10 sessions. On average, those who completed the study showed improvements from baseline to follow-up of 0.52 standard deviations (SD) for average pain intensity (API), 0.47 SD for FSFI dyspareunia, 0.29 for FSFI total, and 1.14 SD for vulvar pain intensity after tampon insertion (PINS Tampon Test).

Aim 1: Test of penetrating acupuncture versus placebo at the end of treatment

Results from the intention to treat models (Table 3) showed no significant differences between penetrating acupuncture and placebo groups on API, the primary outcome, FSFI dyspareunia scale, and total FSFI score, the secondary outcomes. Results from complete case and multiple membership models were consistent with the intention to treat models (data not shown). Standardized effects were small (.06–.15), and 95% confidence intervals suggested a range of effects in either direction.[45]

Aim 2: Duration of effect

The *a priori* defined minimal clinically important difference (MCID)[46] was 1.5 or greater decrease in the PINS after tampon insertion from before to after treatment. Slightly more than half (n = 51, 57%) of participants met this criterion and were considered responders. The percentage of responders was similar by treatment group (placebo 57% with mean MCID of −2.0, penetrating acupuncture 58% with mean MCID of −2.2). The proportion of responders was not different by group. Most (n = 48, 94%) participated in weekly Tampon Test PINS, for a median of 63.5 days (IQR = 64). Twenty-two out of 48 (46%) returned to baseline PINS level during the follow-up. Those whose PINS Tampon Test did not return to baseline level (right censored cases), provided PINS ratings a median of 84.5 days (IQR = 10). Kaplan-Meier curves by treatment group were parallel with the placebo group showing a consistently higher rate of returning to baseline over the 12-week follow-up period compared to the acupuncture group (Figure 6). This association was supported by the log-rank test [$x^2(1) = 5.68$, p = .017]) and Cox regression (placebo compared to penetrating acupuncture hazard ratio: 2.72, 95% CI: 1.13–6.54), adjusting for diagnostic subtype.

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Sensitivity analyses were conducted due to the small sample size and possible influence of missing data (2 penetrating acupuncture and 1 placebo participants with no follow-up, and 1 penetrating acupuncture and 3 placebo right-censored participants with < 6 weeks data). A follow-up interval was imputed to be +7 days from their last assessment and varied the outcomes in two ways: 1) all individuals with < 6 weeks of data returned to baseline and 2) worst-case scenario against penetrating acupuncture (penetrating acupuncture returned to baseline, placebo did not). For the first scenario, the findings were slightly attenuated but remained statistically significant [log-rank test: $x^2(1) = 5.92$, p = .015; Cox regression: hazard ratio: 2.41, 95% CI: 1.13–5.14]. For the second scenario, the findings were further attenuated and not significant but still showed a large hazard ratio [log-rank test: $x^2(1) = 2.72$, p = .099; Cox regression: hazard ratio: 1.89, 95% CI: .85–4.20].

Double-blind Needle Assessment of Blinding

In this trial, for the RCT sample and the duration of effect subsample, the blinding effect in the penetrating acupuncture group and skin-touch placebo acupuncture group was not even. The placebo group had near ideal values that indicates random blinding, but the penetrating acupuncture group had values that indicated non-random blinding at baseline and after the 10^{th} treatment (Table 4).

Adverse events

No adverse events were reported or observed.

Discussion

In this double-blind, placebo-controlled trial of acupuncture for vulvodynia, API reduction, dyspareunia and sexual function were not significantly different between the penetrating acupuncture and placebo groups. However, the reduction of provoked vulvar pain, with the Tampon Test, after both treatments was larger than the MCID on average. Further among responders, findings showed a statistically significant longer-lasting reduction in provoked vulvar pain with the Tampon Test after the RCT treatment period for more participants with penetrating acupuncture compared to the skin-touch placebo acupuncture. Specifically, the skin-touch placebo responders were at 2.7 times higher risk of returning to their baseline pain level compared to the penetrating acupuncture responders over a 12-week follow-up period. This finding among the responders is the first report of the specific effect of penetrating acupuncture from a multi-needle, multi-session double-blind (participant-practitioner) acupuncture RCT. The study was designed with 80% power to detect a difference of .6 standard deviations or higher. In a meta-analysis published after our study was initiated,[42] the effect of acupuncture versus sham needles was much smaller (effect size = .2 SD). This study's power to detect a .2 SD effect is 14%. While the effect size estimates were very small, the 95% confidence intervals cover a .2 SD effect favoring either type of needle. Therefore, although the difference between groups was not significant for the primary outcome in our sample, the test of superiority for penetrating needles compared to placebo was inconclusive when considering this smaller expected effect size and other potential samples of participants.

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This inconclusive finding is likely due to the placebo effect, which is known to be reversed by naloxone, indicating, in part, an endogenous opioid effect.[47] Historically, the placebo effect is known to be up to 58%.[48,49] Compounding this large placebo rate is the inability, especially in smaller samples, to account for all contributing variables (e.g., participant desire, hope, and other nonconscious activities including the patient-provider relationship).[50–55] Acupuncture investigators have begun to investigate these variables and their role in the placebo effect.[56–59]

In this trial, the role of expectation or any cognitive or emotional factors that may influence the placebo effect[50–60] were not measured, but they were accounted for in the study design.[60] For example, precautions were taken to control the healing ritual contextual effects[61] that are embedded in the therapeutic patient-provider encounter such as acupuncturist expectations, attention, concern, and compassion with intention to allay patient anxiety.[61] In this study, the acupuncturists did not engage in therapeutic social support[61] or play music,[62] and they followed a rigorous replicable protocol for the double-blind needle insertions.[18,22]

Notably, to reduce bias, potential participants were ineligible if they had received previous acupuncture. Furthermore, the principal investigator, research coordinator, statistician, acupuncturists, and participants were blind to group assignment until the duration of effect portion of the study was completed.

However, most of the acupuncturists did not maintain the blind in this double-blind, multi-needle, multi-session study. Therefore, provider expectations, conveyed nonverbally and not measured, may have influenced participant outcomes.[63] The finding that the skin-touch placebo achieved blinding for the participants, thus reducing the risk of bias, is further evidence it serves as an acupuncture placebo.[64]

How meaningful acupuncture was to the participants may have played a role in the strong placebo response, which might be a reason for the lack of a significant difference between penetrating and skin-touch placebo acupuncture after the 10th session. It is known that acupuncture is effective for pain reduction[13] and participants may have exhausted the few treatments available for vulvodynia.[6,8] Participants volunteering for this acupuncture trial may have viewed it as the last chance to get relief from the pain of vulvodynia with a high expectation and belief for a therapeutic effect.[65] Importantly, there are few effective treatments for vulvodynia and both penetrating acupuncture and placebo acupuncture may have provided more symptom relief than their other previous treatments. These expectations and beliefs may have influenced our findings and warrant additional pragmatic trials of acupuncture as a means of managing vulvodynia in a population that has few options for pain relief.

Furthermore, because participants in the placebo group maintained blinding, they may have expected a positive outcome. Also, because some participants in the penetrating needle group maintained the blind, they may have had low expectations for treatment. Previously, a significant reduction in vulvodynia was obtained with a similar penetrating acupuncture treatment protocol compared with the wait-list group in a smaller, open-label study.[19] This

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previous result indicated pain reduction was not likely attributed to spontaneous resolution of vulvodynia that can occur over time and is common.[66–68] Furthermore in this study, the longer lasting effect of penetrating acupuncture for the responders suggests pain reduction observed in both the penetrating and skin-touch placebo groups had a therapeutic effect, and were not attributed to spontaneous resolution of vulvodynia.[60,69,70]

This trial revealed the true efficacy of penetrating acupuncture under a rigorous experimental protocol; however, the control of the treatment environment may not adequately represent the actual clinical benefits for patients receiving acupuncture treatments as part of their care. There may be synergy between the acupuncture effect, the therapeutic effect of the relationship between the acupuncturist and participant, and the calming effect of common rituals, such as playing music,[62] to enhance the efficacy of acupuncture. Therefore, more clinical benefit than that indicated by the results of this study can be expected. Future studies are needed to clarify the potential of such synergies when using penetrating or placebo needles.

In the duration of effect phase of this study, the longer lasting effect of acupuncture is to be expected because it is known that placebo effects do not last as long as treatment effects.[60,71] A single systematic review[72] identified the placebo effect over time for acupuncture treatment periods ranging from 3 to 12 weeks. In the review, the placebo effect increased from baseline up to 12 weeks and then began to decrease. In contrast, findings from the responders after the RCT's 10 sessions over 5 weeks suggest that the placebo effect diminished after 4 weeks, but the acupuncture effect persisted for 12 weeks for more responders. The prolonged duration of the effect of penetrating acupuncture is an important signpost of acupuncture's salutogenic properties, meaning the ability to endogenously restore health in chronic pain patients.[73,74] The findings that acupuncture not only reduced provoked vulvar pain and that it lasted longer in responders than for those receiving placebo is important. These RCT findings offer a viable treatment option for patients with vulvodynia.

Limitations

This trial had several limitations. Although the study was not designed to be a non-inferiority trial, findings demonstrated a very small effect size, and it cannot definitively be stated that there was support for the null hypothesis. Unknown was the blinding status of the 14 participants who did not provide guesses about their treatment allocation. This study did not have a no-treatment control group[52,69,75] (usual care or wait-list control), rendering it impossible to determine if differences in treatment outcomes were attributable to other non-specific effects (e.g. differences in the natural course of vulvodynia or fluctuations in the magnitude of the placebo effect).[52] The study did not include a measure of expectancy and its potential impact on the placebo effect. Self-reported pain measures were completed immediately after the 10th treatment, not after each treatment session or at an interval that would have measured the full effects of the 10 treatments. Therefore, unknown is the amount of pain reduction that can be attributable to one treatment or the cumulative effect of segments of multiple treatments. Further studies are necessary to discover the optimal dosage of acupuncture and outcome measurement interval to obtain and maintain

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long-lasting pain reduction for vulvodynia patients. These findings also raise questions about the appropriate outcome measure for studies of the pain of vulvodynia, which can have provoked as well as unprovoked pain. The average pain intensity (PINS for current pain, least and worst pain in the past 24 hours) may not be as sensitive as the Tampon Test (PINS current pain after a stimulus) for the provoked nature of the pain of vulvodynia.

Conclusion

Clinically important pain reduction was observed on average after the 10 treatments in both the penetrating acupuncture group and the skin-touch placebo acupuncture group, but no statistically significant difference between the groups was revealed. Both groups included participants with MCID in pain who were treatment responders, for whom the therapeutic effect from penetrating acupuncture needles lasted longer for significantly more responders than the skin-touch placebo needle effect. Findings raise additional questions that warrant larger, pragmatic trials designs. Also, future investigation of responders and non-responders to acupuncture for vulvodynia is warranted.

Disclosures

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data generated by this research are available from the corresponding author, Judith M. Schlaeger, upon reasonable request.

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Highlights

- Pain reduction in both the penetrating acupuncture and the skin-touch placebo acupuncture groups
- Vulvodynia pain not significantly different between penetrating acupuncture and placebo groups
- Percentages of responders were similar by treatment groups
- Effect from penetrating acupuncture lasted longer than placebo for significantly more responders
- Effectiveness of acupuncture may have been underestimated due to the strong placebo response

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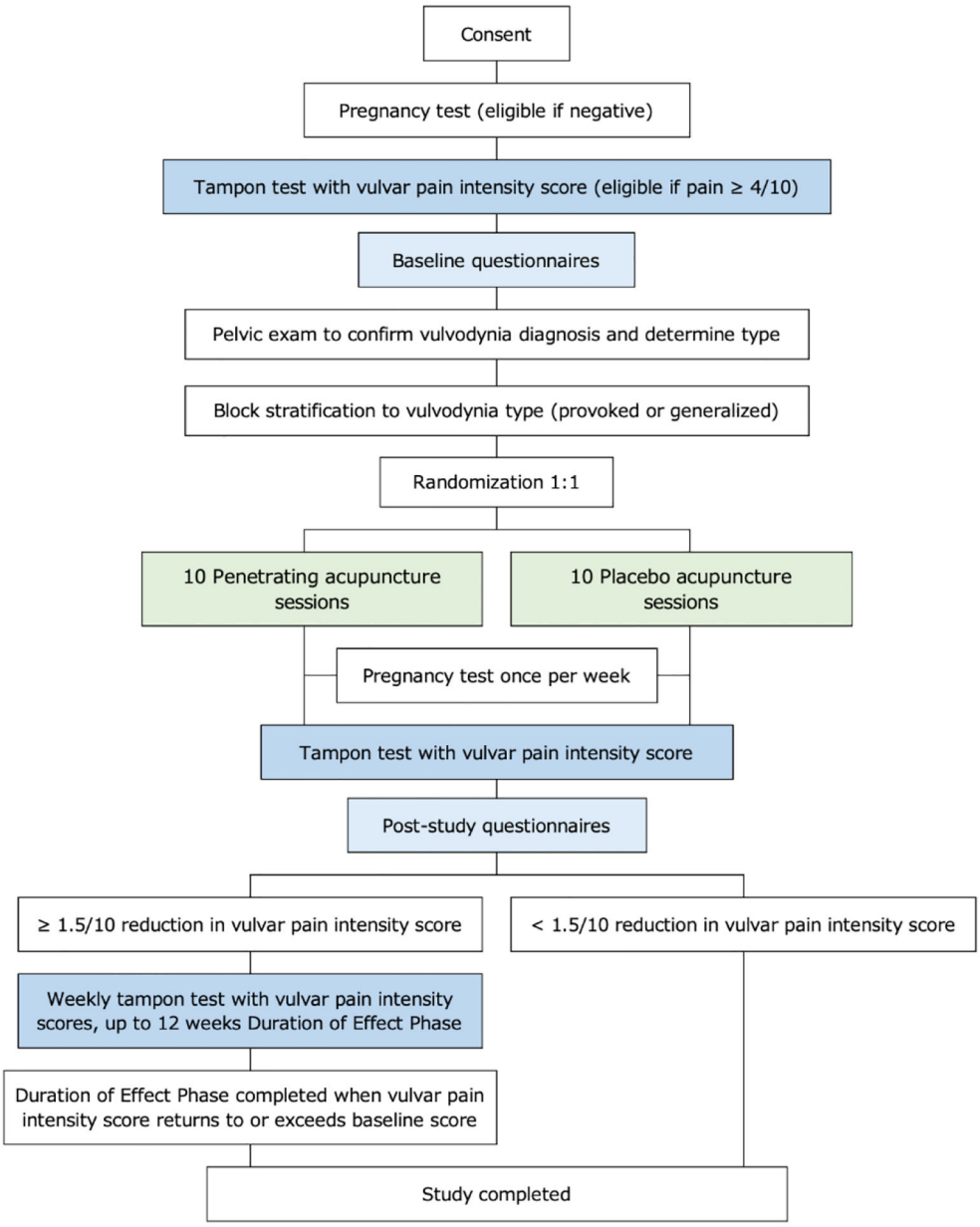

Figure 1.
Flowchart of Study Procedures

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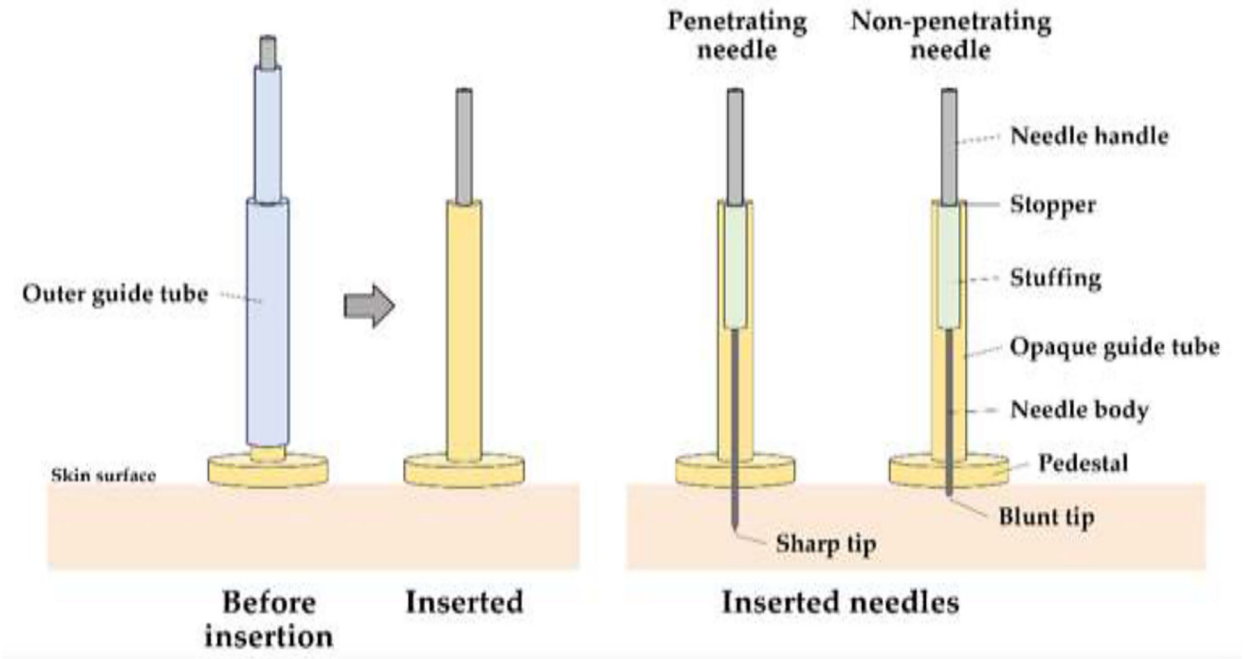

Figure 2.
Double-blind acupuncture needles

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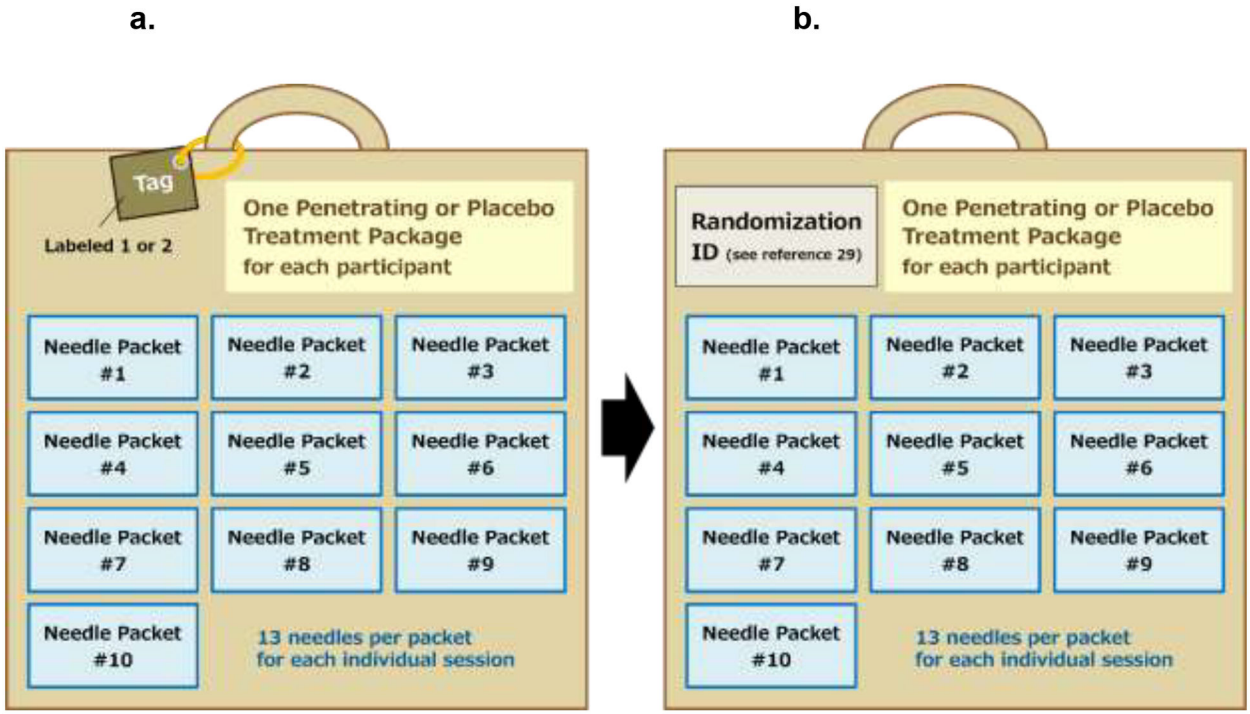

Figures 3.

a. Double-blind needle package with tag

b. Double-blind needle package with tag removed and randomization ID label applied

Each double-blind needle package with tag specifying the needle type as 1 or 2 assembled in Japan (Confidence Co., Ltd., Tokyo). The tag then was removed at UIC by a staff statistician when the randomization ID number was written on a label and applied to the participants' package.

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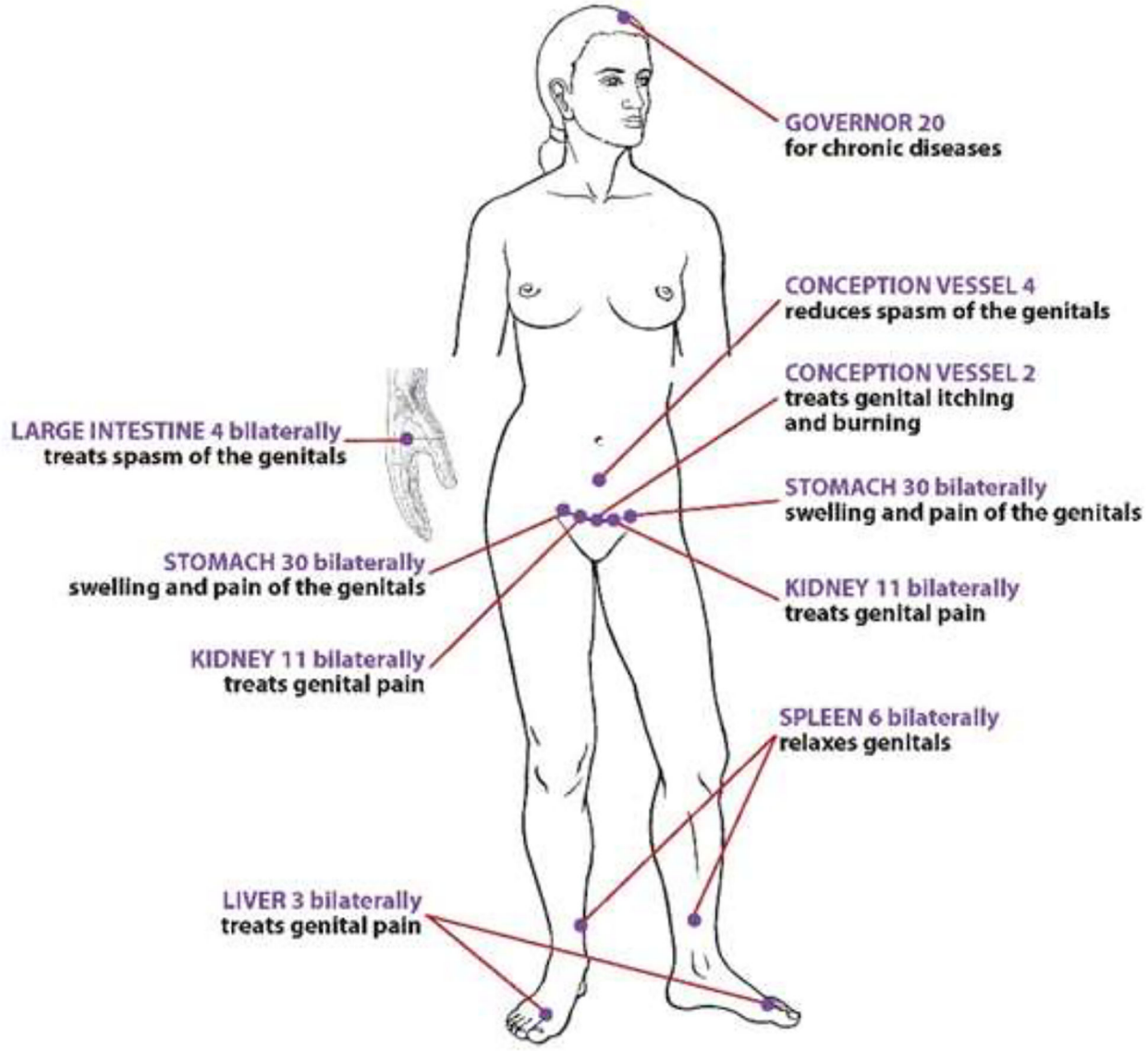

Figure 4.

Standardized 13-point Acupuncture Protocol for Vulvodynia

Figure borrowed from The Journal of Chinese Medicine

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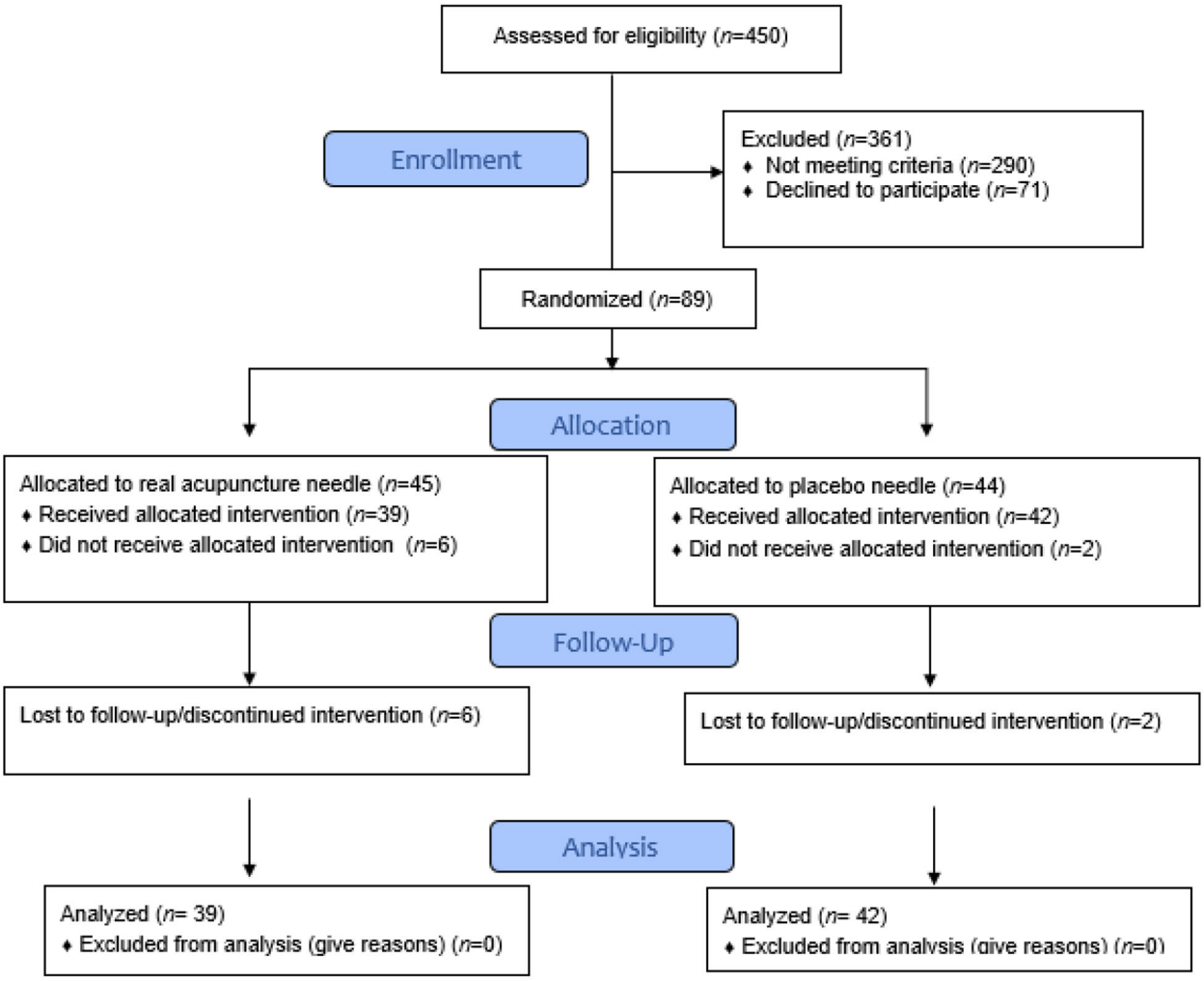

Figure 5.

Double-blind RCT: Effect of acupuncture on patient vulvodynia outcomes CONSORT flow chart

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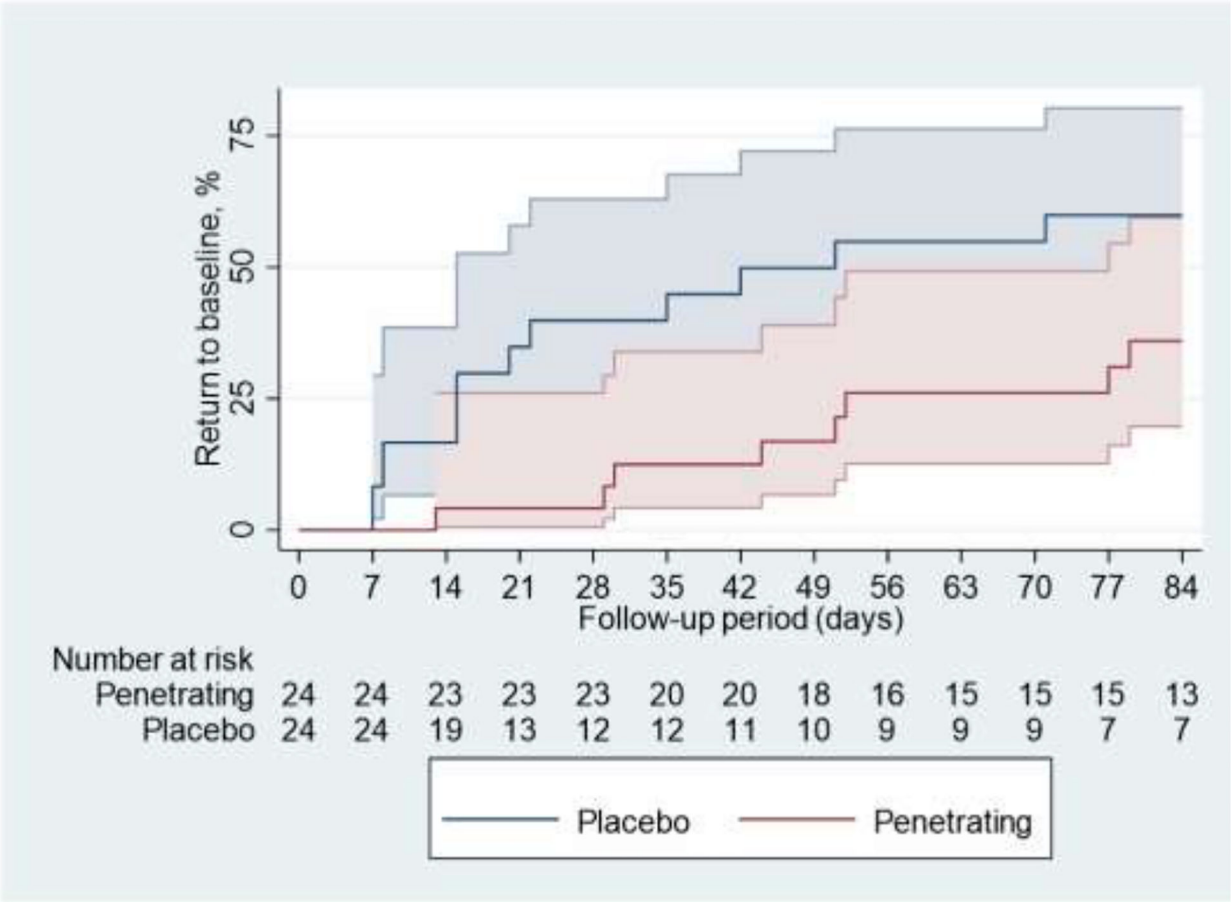

Figure 6.

Kaplan-Meier curves by treatment group

The Kaplan-Meier curves show the proportion of responder-participants returning to baseline pain for both groups over time during the duration of effect part of the study. A larger proportion of the responder-participants in the placebo group returned to baseline pain sooner than the responder-participants in the penetrating needle group. For example, at 28 days half of the placebo group had returned to baseline pain compared to only 1 participant from the penetrating needle group.

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Table 1.

Acupuncture Intervention Reporting Based on Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) Guidelines[36]

Acupuncture rationale	This study used the same acupuncture protocol to evaluate and treat vulvodynia patients developed for our pilot study[19] based on our clinical experience using Traditional Chinese Medicine (TCM) assessments.
Details of needling	**Acupuncture points used:** 13 points which were GV20, CV2 and CV4, and bilateral KD11, ST30, LI4, SP6 and LV3 (Figure 3) based on our pilot study.[19] **Needle type:** The penetrating needle and the matched skin-touch blunt tip placebo needle (0.24 diameter stainless steel needles, Confidence Co. Ltd, Tokyo, Japan) for double (participant-practitioner) blinding.[20] **Insertion depth for penetrating needle or pressing depth for non-penetrating placebo needle:** Insertion depths for the penetrating needles were 5 mm for GV20, 10 mm for LI4 and LV3, 15 mm CV2, CV4, KD11, ST30 and SP6, and the skin-touch blunt tip placebo needle pressed the skin 2 mm.[35,37] The length of each penetrating needle was 44 mm for the 5 mm insertions, 49 mm for the 10 mm insertions, and 54 mm for the 15 mm insertions, and the length of the placebo needle was 41 mm. **Number of needles per participant per session:** 13 needles, which were either all penetrating or all placebo. **Needle stimulation, response sought and retention time:** Acupuncturists inserted all the needles perpendicularly using a tapping-in method and alternating rotating technique while applying downward pressure until the bottom of the needle handle touched the top of the inner guide tube.[38]A “de qi” sensation was not intentionally elicited. All needles were retained for 45 minutes.
Treatment regimen	Participants received 10 acupuncture treatments twice weekly for 5 weeks.
Other components of treatment	No other interventions were administered to enable measurement of the intervention versus placebo. Acupuncturists refrained from talking and no music was played during the treatment to prevent these therapeutic factors from influencing the results.
Practitioner background	The 6 licensed acupuncturists were certified by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) and had been in practice an average of 9 years.
Control interventions	This design intended to eliminate bias for the participant and acupuncturist. Usual acupuncture treatment using verum penetrating needles in our unblinded pilot RCT[19] was significantly effective compared to waiting list controls to reduce vulvar pain and dyspareunia in vulvodynia patients. We therefore designed this double-blind RCT using a non-penetrating blunt-tip placebo needle that does not penetrate the skin compared to a genuine penetrating needle, both concealed by an opaque plastic device, preventing the participant and acupuncturist from seeing the needle type (Figure 2). Also, the stuffing in the inner guide tube enabled the needle insertion to feel the same for both needle types.

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Table 2.

Characteristics of the sample

	Acupuncture (n=45)		Placebo (n=44)		Total Sample (N=89)	
	Median	***IQR***	***Median***	***IQR***	***Median***	***IQR***
Age	28	8	29	9.5	28	9
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
BMI	24.5	5.57	24	5.12	24.2	5.33
	No.	***%***	***No.***	***%***	***No.***	***%***
Diagnostic subtype						
Provoked	17	38	13	30	30	34
Generalized	28	62	31	70	59	66
Gender						
Female	45	100	44	100	89	100
Marital Status						
Single	22	49	22	50	44	49
Married / Partnered	21	47	19	43	40	45
Widowed	1	2	2	5	3	3
No answer	1	2	1	2	2	2
Education						
8th grade or less	1	2	0	0	1	1
High school or less	4	9	5	11	9	10
Associate degree	4	9	3	7	7	8
Bachelor’s degree	22	49	17	39	39	44
Master’s degree	7	16	15	34	22	25
Doctoral degree	6	13	3	7	9	10
No answer	1	2	1	2	2	2
Race						
White	31	69	31	71	62	70
Black/African American	2	4	3	7	5	6
Asian	3	7	4	9	7	8
Native American/Alaska Native	1	2	1	2	2	2
Multi-race/Multi-ethnic	2	4	1	2	3	3
No answer	6	13	4	9	10	11
Hispanic						
No	34	76	35	80	69	78
Yes	10	22	8	18	18	20
No answer	1	2	1	2	2	2
Income						
$10,999 or less	3	7	2	5	5	6
$11,000 – $20,999	4	9	4	9	8	9
$21,000 – $30,999	6	13	5	11	11	12
$31,000 – $40,999	4	9	5	11	9	10

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$41,000 – $50,999	4	9	5	11	9	10
$51,000 – $60,999	5	11	4	9	9	10
$61,000 – $70,999	2	4	5	11	7	8
$71,000 – $80,999	4	9	1	2	5	6
$90,000 – $100,000	3	7	6	14	9	10
more than $100,000	9	20	6	14	15	17
No answer	1	2	1	2	2	2
Have Vaginal Sex						
Yes	27	60	25	57	52	58
No	18	40	19	43	37	42

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Table 3.

Main Effects: Means (Standard Deviations) by Intervention Group and Modeled Between Group Difference

	Acupuncture		Placebo			
	Baseline (n=45)	***After Treatment (n=39)***	***Baseline (n=44)***	***After Treatment (n=42)***	**Between group difference (Effect Size)* (95% confidence interval)**	**p-value**
Primary Outcome						
Vulvar Pain (API)	3.90 (2.39)	2.48 (2.11)	3.51 (2.31)	2.22 (2.09)	−.06 (−.36, .24)	0.702
Secondary Outcomes						
FSFI Dyspareunia	1.22 (0.89)	1.61 (1.76)	1.38 (1.16)	1.83 (1.82)	.06 (−.33, .44)	0.77
FSFI Total†	15.9 (7.05)	17.0 (8.29)	17.4 (5.92)	19.3 (7.71)	.15 (−.22, .51)	0.436
Duration of Effect Eligibility Outcome						
Tampon Test (PINS)	6.14 (1.87)	3.94 (2.27)	6.31 (1.82)	4.31 (2.48)	.04 (−.30, .38)	0.827

*Between group difference (placebo minus acupuncture) and 95% confidence interval adjusted for baseline and diagnostic subtype using intention to treat model with standardized outcome.

†n=43 baseline acupuncture group

API= Average Pain Intensity; FSFI= Female Sexual Function Index

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Table 4.

Blinding by treatment group for participants and acupuncturists for the RCT sample and duration of effect subsample at visits 1 and 10

*Bang's Index: Blinding for the RCT				
	Visit 1		Visit 10	
Group/Rater	**Participants (n=75)†**	**Acupuncturists (n=89)**	**Participants (n=81)**	**Acupuncturists (n=81)**
Penetrating Acupuncture	.35 (.17, .54) p<.001 (Guessed correctly n=32/37)	.43 (.28, .58) p<.001	.34 (.14, .54) p=.002 (Guessed correctly n=31/40)	.58 (.40, .75) p<.001
Placebo	−.03 (−.23, .18) p=.584 (Guessed Correctly n= 16/38)	.08 (−.11, .26) p=.24	−.13 (−.31, 0.4) p=.896 (Guessed correctly n=17/41)	.02 (−.17, .22) p=.421
Bang's Index: Blinding for Subset of Responders Participating in the Duration of Effect				
	Visit 1		**Visit 10**	
Group/Rater	**Participants**		**Participants**	
Penetrating Acupuncture	.27 (.04, .51) p=.028		.35 (.09, .61) p=.014	
Placebo	.07 (−.18, .32) p=.323		−.10 (−.34, .13) p=.765	

*Bang's index mean and (95% confidence interval), value of −1 indicates that all guesses are placebo, 1 indicates that all guesses are penetrating needles, and 0 indicates blinded; p value -- test that the Bang index is significantly different than 0 (p<.05 indicates unblinded).

†Data missing for 14 RCT participants