Title: DOUBLE-BLIND PHASE 2 RCT: EFFECT OF ACUPUNCTURE ON PATIENT VULVODYNIA OUTCOMES

RESEARCH PROTOCOL
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Background and Purpose:
Our long-term goal is to demonstrate the effects of acupuncture for the treatment of vulvodynia. Up to 14 million American women have vulvodynia,[1,2] a debilitating pain syndrome characterized by pain (burning, irritation, stinging or rawness) in the vulva and dyspareunia that renders sexual intercourse virtually impossible[1,2] and leaves these women desperate for relief. Not only are women in pain, but they often lose their partners or have relationship difficulties due to their inability to have sexual intercourse.[3,4] No therapies have been proven efficacious and rapid pain relief is unpredictable and rarely possible.[1,2] After exhausting Western Medicine options, these women often turn to acupuncture.[1,2] But in contrast to other pain conditions,[6] there have been no acupuncture sham control studies of vulvodynia.

Only four studies, including one of ours,[7] provide some evidence of the effect of acupuncture on vulvodynia. In three, single-group acupuncture studies, women had less pain, better quality of life, improved sexual health, and improved mental health.[8–10] Our randomized wait-list controlled pilot study of 36 women with vulvodynia showed great promise. We found a statistically significant and clinically meaningful reduction in vulvar pain and dyspareunia, and an increase in overall sexual function after a 5-week, 13-needle, 10 session acupuncture protocol.[7] This newly developed, standardized acupuncture treatment protocol[7] is the first breakthrough in the treatment of this puzzling disorder.[2] It includes acupuncture points that relieve pain in the genitals. The results of our initial pilot study provided the first evidence from a two-group design that the acupuncture protocol could reduce pain intensity, pain during intercourse, and increase overall sexual function. Our findings, however, warrant stronger evidence to support the inference that the effect is indeed due to the acupuncture since ours or no other study included a sham control or provided follow-up data beyond immediate posttest, which means that the duration of the acupuncture effect is unknown. Our recent feasibility study paves the way to overcome this gap by use of double-blind acupuncture needles. Findings from these two studies support our proposal for the world's first double-blind randomized controlled trial (RCT) of acupuncture for vulvodynia while exploring its duration of effect.

We will conduct a phase 2 double-blind, pretest/posttest RCT to compare effects of penetrating needles or the skin touch placebo needles on vulvar pain in our 13-needle, 10-session acupuncture treatment protocol. A sample of up to 130 women, with a diagnosis of vulvodynia, either generalized or provoked vestibulodynia, will be recruited. Subjects will be stratified by type of vulvodynia, and will be randomized 1:1 either to the penetrating needle group or the skin touch placebo needle group. These double-blind needles will provide a strong sham procedure (placebo) to mask both the acupuncturist and subject to the type of needle used for the 10-treatment protocol.

Specific aims are to:
Aim 1. Compare the penetrating needle group and the skin touch placebo needle group for effects on the: (a) primary outcome: vulvar pain (PAINReportIt® average pain intensity, 0-10), and (b) secondary outcomes: dyspareunia (FSFI dyspareunia) and sexual function (FSFI total). We hypothesize that controlling for baseline values, at posttest there will be statistically significant less vulvar pain (primary) and dyspareunia and better sexual function in the penetrating needle group compared to the skin touch placebo group.

Aim 2. In subjects with a clinically meaningful reduction in pain intensity (at least 1.5 points) at posttest compared to pretest, describe the duration of the acupuncture treatment and placebo effects weekly until pain returns to pretest or up to 12 weeks after posttest. We will describe the variability over time in vulvar pain intensity (0-10) after a tampon insertion-removal stimulus and thereby explore the duration of the effect by intervention group, vulvodynia subgroups, and demographic subgroups (e.g., age, race, occupation). These findings will provide insights to guide future research on initial and maintenance acupuncture for vulvodynia.

References

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Study design:
We will conduct a pretest/posttest, randomized, placebo controlled phase 2 efficacy study on 130 subjects with vulvodynia, with high scientific rigor. In this adequately powered study, we will compare two groups (penetrating acupuncture needle [treatment] group and skin touch needle [placebo] group) in a 13-needle, 10-session acupuncture protocol delivered twice/week for 5 weeks for effects on vulvar pain (primary outcome), and dyspareunia and sexual function (secondary outcomes). Subjects will be stratified by type of vulvodynia (generalized or provoked) and randomized 1:1 either to the penetrating needle group or the skin touch placebo needle group. These double-blind needles will provide a strong

sham procedure to mask both the acupuncturist and subject to the type of needle used. The acupuncturist will be well-trained in the study protocol and will be observed for fidelity. We will obtain measures at 2 time points (baseline and immediately post 10th acupuncture treatment [5 weeks]). Duration of effects will be measured weekly beginning one week after posttest for up to 12 weeks.

Subject identification, recruitment and consent:
The subjects will be women with a diagnosis of vulvodynia, who are 18 – 45 years of age. Potential participants will be recruited from clinical and community settings in Chicago, such as the UIC campus and surrounding communities, gynecologists, certified nurse-midwives, family physicians, and women's health physical therapy practices. Recruitment will also be conducted via a link on the National Vulvodynia Association (NVA) website. We will also recruit through social media like Facebook, in addition to through phone calls and emails. We plan on recruiting up to 130 women to ensure that we have full data on 80 subjects after screening and attrition. We will strive to enroll a racially and ethnically diverse sample of women.

The consent process will be completed at the UIC College of Nursing. It may also be completed at another UIC or other private location chosen by the potential subject to go over the details of the study and informed consent. All study procedures will be conducted at the UIC College of Nursing in fully equipped, clinical research exam rooms on the second floor. The screening gynecological screening exam will take place in one of the exam rooms in the CON or at Dr. Kobak's office in the UIC hospital.

Procedures:
The research specialist (RS) will determine initial eligibility by screening potential participants during an initial telephone or in-person interview according to the inclusion and exclusion criteria. Women deemed to be eligible and interested in participating will be scheduled to go over the consent process and will then receive a gynecological screening exam by Dr. William Kobak, a urogynecologist with expertise in changes in pelvic floor tissue related to vulvodynia, or Dr. Judith Schlaeger, a practicing certified nurse-midwife with over 29 years of experience and a practicing acupuncturist specializing in the treatment of vulvodynia patients for 15 years. This exam will confirm the diagnosis and subtype of vulvodynia (provoked or generalized). Potential participants will also be asked to insert and remove a tampon as a standardized stimulus to provoke vulvodynia pain and women will be eligible if they report a pain level of 4 or higher. We will always use a regular size Tampax™ tampon with applicator as part of the standardized procedure. Participants determined to be ineligible after the above steps will not be able to continue study participation.

Based on the gynecological exam results, participants will be assigned to the generalized or to the provoked vulvodynia group. Eligible women will be able to start the study procedures immediately or at a future visit. Right before the first acupuncture session and once a week before an acupuncture treatment, a urine pregnancy test will be administered. If it is positive, the subject will be discontinued from the study.

Participants will be assigned at random to the experimental group, who will be treated with penetrating needles, or the control group, where the needles have a blunt tip that pinches but does not penetrate the skin. The special needles used in this study are inside an opaque insertion tube so that both the acupuncturist and participant remain blind to group assignment. The actual acupuncture needles,

however, are regular needles used in routine acupuncture. All participants will be informed that they will receive either real or fake acupuncture and they will not be told what kind of needles they are receiving until they complete the duration of effect portion of the study. Participants in the control group will be offered 10 free real acupuncture sessions with regular (not double-blind) acupuncture needles administered by a second acupuncturist after the end of the 17 weeks. The double blind needles are manufactured by Dr. Takakura, the inventor of the double blind acupuncture needle, and will be sent to us sterilized and packaged to maintain sterility.

All participants will receive 10 acupuncture session, two sessions per week over an approximately 5 week period. Each session will last about one hour. The first and last sessions only, where participants will complete the study questionnaires, are expected to last an additional 30 - 60 minutes. Each acupuncture treatment will consist of 13 acupuncture points, of which 12 points specifically treat problems with the genitals. Once the 13 needles are inserted or placed on the skin in the 13 points, they will remain in place for 45 minutes. The RS will remain with the subjects during the treatment session.

At pre-test, before the first acupuncture session, and at post-test, after the 10th acupuncture treatment, participants will be asked to insert and remove a regular Tampax™ tampon with applicator as a standardized pain stimulus, and will complete the three study measures of vulvar pain and sexual function on a computer or tablet:

1) PAINReportIt® computerized program to assess pain intensity as well as collect demographics and medications information
2) Female Sexual Function Index (FSFI) to assess dyspareunia and sexual function
3) Vulvar Pain Functional Questionnaire to describe the physical dimension of impairment in women with vulvodynia
4) At post-test, participants will also complete the Double-Blind Needle Questionnaire for the participants to report whether or not they remained blinded to the type of needle used (penetrating or skin touch placebo).

Weekly for up to 12 weeks after the 10th treatment session, the subjects will be asked to insert and remove a regular Tampax™ tampon with applicator from their vagina and complete the weekly vulvar pain diary to record their vulvar pain, so that we can determine the duration of the treatment effects.

Sample size:
We plan to recruit 130 women to ensure that we obtain full data for 80 subjects.

Anticipated risks:
This study has minor risks. There is a small risk of mild bruising, soreness or bleeding after the real acupuncture needle is withdrawn. There is a risk that participants may experience a negative reaction from acupuncture and thereby experience worse symptoms from participation in the study. Participants may feel mild discomfort upon needle insertion, but this dissipates once the needle has been inserted. To avoid or minimize these risks only experienced licensed acupuncturists will perform the acupuncture. There is a risk that some of the questions in the questionnaires may make the participants uncomfortable, nervous or tired, but they don't need to answer any question they don't wish to answer. There is also the risk of loss of privacy or confidentiality, but we will avoid this risk as much as possible.

Anticipated benefits:
There may be no benefit to individual subjects, but the knowledge gained from this study is expected to provide important insights to guide future research on initial and maintenance acupuncture treatment protocols for control of vulvodynia pain.

Inclusion criteria:
Potential participants must fulfill the following:

a) a previous diagnosis of generalized vulvodynia or provoked vestibulodynia
b) 18 to 45 years old
c) a pain now score 4 or higher with tampon insertion and removal performed at the initial screening exam
d) speak and read English

Exclusion criteria:
Potential participants will be excluded if any of the following is true:

a) infectious conditions
b) inflammatory conditions
c) neoplastic disorders
d) neurologic disorders
e) trauma to the genitals
f) iatrogenic
g) hormonal deficiencies
h) co-morbid pelvic pain conditions (to avoid confounding pain outcomes)
i) pelvic inflammatory disease
j) endometriosis
k) menopause
l) pregnancy
m) women receiving concurrent therapies that may decrease stress and/or muscle tension (i.e., concomitant physical therapy, biofeedback, massage, or other acupuncture sessions) will also be excluded

Data collection and management:
Some of the research data will be collected electronically using a laptop computer. The PAIN*Report*It computerized pain assessment program developed by Dr. Wilkie to collect subjects' pain information will be completed online. Subjects' data will be written directly to the College of Nursing server and will not reside, even temporarily, on the laptop computer. HTTPS will be used for data transfer to the CON server and the transfer from the tablet to the server is encrypted. The application will be located in a secure College of Nursing server with restricted access, with access only to the immediate study

personnel. The other questionnaires (Female Sexual Function Index (FSFI), Vulvar Pain Functional Questionnaire, and the Double-Blind Needle Questionnaire) will be completed on paper.

All participants will be assigned a code number and their data will be identified only with that code number. The link of the code numbers to the subject identifiers will be kept separate from the study data. Only the investigators and key personnel will have access to the code/master key. The computerized data will be stored in a controlled access computer database in a secure College of Nursing server. All hard data collected will be stored in a locked office in the College of Nursing.

Data management procedures will be supervised by Dr. Steffen, the statistician.

Data analysis:
Dr. Steffen will supervise all data analysis procedures. Prior to data collection and entry, a codebook will be created with the variable names, descriptions, and value codes of each variable. Missing data will be minimized through our retention efforts but are inevitable, to some degree, in any longitudinal study. We will address missing data by intention to treat analyses (ITT), using the full information maximum likelihood (FIML) approach, which has been shown to produce unbiased parameter estimates and standard errors. To begin to phenotype subjects with emotional disturbances we will explore the emotional dimension of pain at baseline and after the 10^{th} acupuncture treatment using the well-known Pain Rating Index-Affective (PRI-A) score from PAINReportIt®.

Safety monitoring:
The study is low risk. However, the research team will monitor the safety of subjects during study procedures. In the event of injury related to this research, treatment will be available through the UIC Medical Center. However, the patient or third party payer, if any, will be responsible for payment of this treatment. Patient subjects will remain under the care of their usual provider, who will be available to give them usual care if needed. Any unanticipated problems related to the study procedure will be immediately reported to the IRB.