CoRPS CONCEPT PROPOSALS

Abstract

This randomized trial builds on research investigating Fractionated CO2-laser therapy as a treatment for women affected by vulvar lichen sclerosus (LS), a debilitating dermatologic condition that causes silent suffering for millions of people. Our prior studies have shown that Fractionated CO2-laser therapy is as effective as the current gold standard treatment of ultrapotent topical corticosteroid therapy (TCS) with 0.05% clobetasol propionate. In this prior RCT, Fractionated CO2-laser therapy significantly reduced symptoms on patient-reported outcomes and improved the appearance of the vulvar tissues following 3 treatments over a 6-month period. We now know that both Fractionated CO2-laser therapy and clobetasol proprionate treat LS but we do not know if combining these therapies leads to additional improvement. We also do not know how CO2 fractionated laser alters the histologic architecture of the vulvar skin. We are therefore proposing a randomized controlled trial of Fractionated CO2-laser therapy with either topical clobetasol proprionate 0.05% or topical placebo women with LS to achieve the following aims:

- Specific Aim 1: Evaluate if women with LS undergoing Fractionated CO2-laser therapy experience improved treatment response with concomitant TCS with clobetasol proprionate 0.05%, with treatment response measured by Skindex-29 validated questionnaire change score (a questionnaire utilized in dermatologic research to assess treatment response for skin disorders).
- Specific Aim 2: Assess histologic change in the vulvar tissues in response to Fractionated CO2-laser therapy by comparing pre- and post-treatment vulvar biopsy specimens in a subset of women with each participant acting as her own control.

Background and significance

Fractionated CO2-laser has been proposed as a possible treatment modality for patients suffering from LS. A recent randomized trial performed by our group at MedStar directly compared Fractionated CO2-laser to TCS with clobetasol propionate 0.05% ointment and found that Fractionated CO2-laser resulted in significantly more improvement in overall Skindex-29 scores as compared to TCS. Additionally, 89% (23/27) of participants randomized to laser rated their symptoms as "better or much better" on the PGI-I compared to 62% (13/24) of participants randomized to TCS (p=0.07), and participants in the laser group were highly compliant despite the requirement for three treatment visits over a 6-month period. The success of our initial trial is very exciting. Larger studies are needed to replicate our findings and determine whether Fractionated CO2-laser therapy really is safe, valuable and effective in order to help the women suffering from this harmful condition.

Study Design

We are proposing a randomized controlled trial of Fractionated CO2-laser therapy with or without concomitant 0.05% clobetasol proprionate in women with lichen sclerosus.

Study population: Women electing for Fractionated CO2-laser therapy for treatment of lichen sclerosus.

Inclusion Criteria	Exclusion Criteria
• Postmenopausal with suspected lichen sclerosus • English-speaking • Electing to undergo Fractionated CO2-laser therapy	• Prior vaginal mesh • Active genital infection • Known vulvar malignancy or active treatment for other malignancy • Planning pregnancy • Prior pelvic radiation therapy

• Willing and able to undergo vulvar biopsy for diagnostic confirmation • Willing and able to undergo concomitant 0.05% clobetasol proprionate treatment	• Intrauterine device in place • Topical corticosteroid use on the vulvovaginal tissues within past 8 weeks • Contraindication or allergy to clobetasol proprionate 0.05%

Study Visit Schedule: Women interested in participating will be scheduled for a clinical visit with one of the Urogynecology providers (if they have not previously seen one) and those electing for Fractionated CO2-laser therapy will be screened for enrollment. Upon enrollment, participants will be consented, demographic data will be collected (age, race/ethnicity, medical conditions, prior surgeries, urogynecologic history, HRT use, tobacco use, prior treatment for LS) and they will be asked to complete 4 validated questionnaires and undergo a vulvar biopsy. They will then be scheduled to return in approximately 2-3 weeks to undergo the first of three office Fractionated CO2-laser treatments performed 4-6 weeks apart and then return for a final study visit at 6 months.

Intervention: Clobetasol proprionate 0.05% cream or identical-appearing placebo cream applied once daily x 2 months and then daily x 1 month and then up to one daily prn.

Fractionated CO2-Laser therapy protocol: The vulvovaginal SmartXide^2-V2-LR laser system by DEKA fractional CO_2 laser will be utilized. Prior to laser treatment, eutectic local anesthetic (lidocaine 2.5%, prilocaine 2.5% topical ointment) will be applied for 30 minutes then wiped off. Participants will be provided an additional supply of eutectic local anesthetic for any discomfort following treatment as per usual clinical practice. Settings will be as utilized per protocol in our prior study (power 26 Watts, dwell time 800 microseconds, spacing 800 micrometers at normal scan mode for initial treatment and then power 30 Watts, dwell time 1000 microseconds, spacing 1000 micrometers at normal scan mode with smart pulse for second and third treatments). Visually affected areas of vulvar and perianal LS will be treated with single pass, except the glans of the clitoris and clitoral hood will be spared with at least a 5mm margin.

Validated Questionnaires: We will administer the following validated questionnaires at baseline and at 5 months in order to assess vulvovaginal symptoms as well as impact on quality of life and lower urinary tract function.

- Skindex-29 questionnaire: a validated measure of the effect of skin diseases on quality of life designed to minimize participant burden that are widely utilized with dermatologic research to assess effectiveness of different treatments for skin diseases.[11,12] Skindex scores vary from 0 (no effect) to 100 (effect experienced all the time), and responses are aggregated in Symptoms (four items), Emotions (seven items), and Functioning scales (five items).
- Vulvovaginal Symptoms Questionnaire (VSQ): a 21-item survey used to measure vulvovaginal symptoms in postmenopausal women that includes four subscales (symptoms, emotions, life-impact, and sexual impact).[13]
- Female Sexual Function Index (FSFI): a validated questionnaire assessing domains of sexual function (e.g. sexual arousal, orgasm, satisfaction, pain).[14] It is not a measure of sexual experience, knowledge, attitudes, or interpersonal functioning and it was not designed for use as a diagnostic instrument.
- Core Lower Urinary Tract Symptom Score (CLSS) Questionnaire: a 11-item questionnaire used in males and females to LITS including storage, voiding, pain in the bladder/urethra, and burden.[15,16]

Sample size calculation: Our prior RCT required 52 subjects to detect a clinically meaningful difference in Skindex-29 with 80% power between the study groups based on one-sided two-sample t-test with alpha = 0.05, accounting for 10% attrition (non-inferiority design).

Our prior study reports average SKINDEX score of 40.5 ± 22.3 at baseline and 23.7 ± 23.3 at follow up for patients in the Laser group with a total of 14 (51.85%) out of 27 participants randomized to laser having significant improvement (reduction in SKINDEX score of 16 points or more).

- Two-sided design
  If we conduct a sample size calculation based on the proportion of participants in each group who achieve an improvement in symptoms, defined as a significant change (16 point improvement) in the Skindex-29 questionnaire score from baseline to 5 months. Using Power = 80%, Alpha = 0.05 we have calculated the following estimates in the sample size for detecting the following differences in proportion of participants who experience improvement in combined vs laser alone therapy:

Total N	Each Arm N	P1 (combo)	P2 (laser only)	Diff D1
3112	1556	57%	52%	5%
768	384	62%	52%	10%
334	167	67%	52%	15%
242	121	69.5%	52%	17.5%
184	92	72%	52%	20%

Randomization: Randomization will be performed in a 1:1 ratio of control to intervention in random permutated blocks of 4-6 stratified by site. The randomization table will be generated by RedCap consultants and uploaded into RedCap. Allocation concealment will be achieved using RedCap. The study will be double-blinded. Study participants and providers will not be aware of treatment allocation or randomization block size. Participants will receive study drug (0.05% clobetasol proprionate or placebo) in identical appearing tubes.

Feasibility

For our prior RCT we screened 205 patients from 2015-2018 with total enrollment of 52 subjects. As that study was randomizing to laser vs TCS there was a significant number of subjects who declined enrollment as they wanted laser therapy. We anticipate this study will have higher enrollment as it is randomizing those already electing laser to either TCS vs placebo. We will be performing a vulvar biopsy so that may limit enrollment but we plan to incentivize participation with an incentive payment upon completion of the study. We could also consider potentially offering a discount on the laser therapy costs for participation.

Funding

We plan to submit an application through the National Vulvodynia Association as well as the Patty Brisben Foundation for Women's Sexual Health for funding for this proposed multi-center randomized controlled trial comparing Fractionated CO2-laser therapy with and without concomitant TCS with clobetasol propionate 0.05% for women with vulvar LS. The NVA offers grants up to $50,000 and the Patty Brisben Foundation for Women's Sexual Health directs resources and funds research up to $200,000.

Budget

Tier 1

- Study drug supplies and preparation
- Participant incentive payment
- RedCap database setup and maintenance
- Biostatistics support

Tier 2

- Primary Site Research Coordinator / Project Manager
- Individual Site Research Coordinators
- Vulvar biopsy specimen processing and interpretation