Fractional CO2 Vaginal LASER Therapy for Recurrent Urinary Tract Infection

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Background

Urinary tract infections (UTI) are common in women with over 50% of women having a UTI at some time in their lifetime.[1] As the most common bacterial infection in women, UTI's have a significant financial and social burden on women, with an estimated greater than $1 billion spent per year in lost work alone.[2] Recurrent UTIs (rUTI) are defined by 3 UTI's in 1 year, or 2 UTI's in 6 months.[1] Up to 10% of menopausal women will be treated for UTI each year, with 5% of them developing a recurrence within 1 year. Recurrent UTI is a common clinical problem seen by the Urologist and Urogynecologist, who have limited options in terms of treating and preventing further infections in these women. Recurrence of UTI can be difficult to treat due to antibiotic resistance and comorbidities associated with repetitive antibiotic usage.

Most UTIs are caused by uropathogenic bacteria that originate from the gastrointestinal tract with *Escherichia coli* responsible for the vast majority of infections. Menopausal women are at higher risk of developing infections as their vaginal flora shifts with significant decrease in *Lactobacillus* and increased pH. This degenerative shift in flora and lack of estrogen to the vagina is also responsible for the symptoms associated with genitourinary syndrome of menopause (GSM). GSM symptoms include vaginal dryness, painful intercourse, vaginal burning, irritation and dysuria. Approximately 50% of menopausal women are affected by GSM. Currently, vaginal estrogen is an effective treatment for menopausal women with GSM and also for prevention of rUTI. In a randomized controlled trial of vaginal estrogen to placebo for women with rUTI, Raz et al showed a significant decrease in UTI from 5.9 episodes per patient-year to 0.5 episodes per patient year. ($p<0.001$) Restoring estrogen to the postmenopausal vaginal skin may work by regenerating the vaginal microbiome and protective environment from uropathogens. However, its impact on the urinary microbiome has not been studied. Novel sequencing techniques allow us to now investigate the urinary microbiome which previously has been thought to be non-existent.[3]

Fractional CO2 LASER vaginal therapy has recently been studied for the treatment of GSM. LASER therapy is currently commercially available and has FDA clearance for use in gynecology. Current evidence shows that with treatment, histologic changes of the vaginal epithelium have shown regeneration to a premenopausal state, along with subjective improvement in GSM symptoms and sexual function. Using LASER therapy, Zerbinati et al described response by the vaginal epithelium with thickening, superficial shedding and renewing of stratified epithelium, which was maintained 2 months after treatment.[4] Athanasiou et al also described the impact of LASER therapy on the vaginal flora, decreasing the vaginal pH to 4.7 ($p<0.001$) and increasing the Lactobacillus colonies from 30% to 79%.[5] Based on the impact this promising new regenerative therapy has on the vaginal epithelium and microbiome, we anticipate this may have a positive impact on women with rUTI.

1. **We therefore hypothesize that fractional CO2 LASER vaginal therapy is non-inferior to topical vaginal estrogen therapy for the treatment of rUTI.**
    a. **Primary Outcome: Improvement in recurrence of culture positive UTI**

2. **We also hypothesize that LASER therapy will improve the urinary and vaginal microbiome, decreasing the uropathogenic presence and increasing Lactobacillus.**
    a. **Measurement 1: The number of UTI with UPEC isolated from patients**
    b. **Measurement 2: The pH of the vagina as a proxy for presence of *Lactobacillus* sp.**
    c. **Measurement 3: Categorize vaginal and urinary microbial communities**

Methods

We propose a randomized controlled trial to evaluate the clinical difference between the LASER and topical vaginal estrogen in treating patients with rUTI. We expect to enroll 94 patients, to power this study to 80% with type I error of 5%, expecting a recurrence in UTI of 16% and non-inferior margin of 20%. This is accounting for a 10% drop out rate. While this clinical margin is wide, this project will provide us with ample data to apply for external funding, along with a wealth of microbiome data to evaluate in Aim 2. Menopausal women with rUTI will be recruited from the Departments of Urology and Gynecology. If they meet inclusion criteria, they will be randomized to treatment of topical vaginal estrogen or LASER therapy. LASER therapy will be applied 6 weeks apart for a total of 3 treatments. Topical vaginal estrogen will be prescribed per the patient's formulary and preference. Patients will be monitored for recurrence of culture positive UTI.

Laser Therapy protocol:

Mona Lisa Touch is a fractional CO2 LASER that has applications for treatment of the vulva and vagina. Patients randomized to this arm will undergo 3 treatments, 6 weeks apart. Patients will be advised to avoid any vaginal creams, lubricants or ointments, along with vaginal intercourse 48 hours prior to and 48 hours following LASER treatments.

Speculum examination will be performed and pH obtained. Any existing vaginal discharge will be removed prior to therapy. 2.5% lidocaine and 2.5% prilocaine will be applied to the external vulva for 30 minutes to 1 hour prior to procedure. This cream will be removed from the vulva prior to LASER application.

Internal treatments settings:

- First treatment: Power 30W, Dwell time 1000us, Spacing 1000um, Smart Stack 1
- Subsequent treatment: Power 30W, Dwell time 1000us, Spacing 1000um, Smart Stack 3

External treatments settings:

- Power 26W, Dwell time 800us, Spacing 800um, Smart Stack 1

Any deviation from these settings will be at the discretion of the provider performing the LASER therapy and will be documented in the patient's medical record.

Vaginal Estrogen Protocol

Women randomized to vaginal estrogen therapy will be offered vaginal cream. Two FDA approved formulations exist and patients will be offered the choice between the two, which may also be dependent on their insurance formulary preference.

1. Conjugated estrogen (Premarin): 0.5 gm per vagina twice weekly

2. Estradiol (Estrace): 1gm per vaginal twice weekly

Specific Aim 1: Evaluate the number of culture positive, symptomatic UTI in women following randomization to vaginal estrogen and vaginal LASER therapy.

Methods: Following randomization and treatment initiation, patients will be monitored for recurrence of UTI. Patients will be encouraged to call the treating physician for treatment antibiotics according clinical judgment. Standard urine cultures will be obtained along with information about what type of antibiotic treatment was administered. Validated questionnaires will also be collected to monitor symptoms of GSM and also of urinary incontinence symptoms (Appendix A and B). Patients will be followed for 6 months with evaluations at baseline, 4 months, and 6 months.

Specific Aim 2: Characterize the urinary and vaginal microbiome at baseline and at 4 months of patients in each group.

Methods: Baseline vaginal and catheterized urine samples will be collected along with samples at 4 months. Standard catheterized urine cultures will be performed and if symptomatic, treated appropriately (per Aim 1). Microbiome of urine and vaginal environments will then be analyzed using 16S ribosomal DNA sequencing along with shotgun metagenomics. For this study, we will perform sequencing and metagenomics on the first 16 patients in each arm (32 patients total). The remaining collection will be biobanked for future analysis. These techniques will allow us to measure the abundance of different bacteria, but also evaluate the genetic variation and evolutionary effect from treatment. This will also allow us to evaluate for the differences in the microbiome between responders and non-responders in each treatment arm, considering factors such as UTI, symptoms, pH, etc.

Vaginal Estrogen arm	Baseline	4 months	6 months (if can be completed within the funding period)
Informed consent	X		
Vaginal pH	X	X	X
Vaginal swab collection	X	X	X (banked)
Urine collection	X	X	X (banked)
MESA questionnaire	X	X	X
DIVA questionnaire	X	X	X

LASER arm	Baseline	1st treatment	6 weeks (2nd treatment)	3 months (3rd treatment)	4 months	6 months (if can be completed within the funding period)
Informed consent	X					
Vaginal pH	X	X	X	X	X	X
Vaginal swab collection	X				X	X (banked)
Urine collection	X				X	X (banked)
MESA questionnaire	X				X	X
DIVA questionnaire	X				X	X

Inclusion Criteria:

- Female patient >18 years old
- Postmenopausal status, documented by prior bilateral salpingo-oophorectomy, or absence of menses >12 months
- Recurrent urinary tract infections as defined by 3 culture positive urine cultures in the last 12 months, or 2 positive urine cultures in the last 6 months.
    - Positive urine cultures defined by >100K colony forming units of 1 or 2 bacterial species on clean catch sample, or >1000 colony forming units of 1 or 2 bacterial species on sample via straight catheterization.
- Patients on vaginal estrogen must undergo a 1 month washout period prior to initiation of the trial.

Exclusion Criteria:

- Hematuria without appropriate workup
- Pelvic organ prolapse beyond the hymen
- Clinically relevant urinary retention
- Pelvic reconstructive surgery within 6 months
- Reconstructive pelvic surgery with “mesh kits”
- Clinically relevant nephrolithiasis
- History of breast cancer
- Contraindication to topical estrogen therapy
- Anticoagulation therapy
- Prior pelvic or vaginal radiation therapy
- Prior gynecologic malignancy
- Undiagnosed genital bleeding

Subject Recruitment

Patients will be recruited from both the Departments of Gynecology and Urology. We estimate that the two departments evaluate >200 women with rUTI per year. We anticipate realistic recruitment of 1/3 of these patients that meet inclusion criteria. We will recruit 94 patients per power calculation described above and anticipate completion of recruitment in 2 years. For Specific Aim 2, we will perform microbiome analysis on 1/3 of these patients for a total of 32 patients. Further collection of samples will be frozen for future analysis once external funding is secured.

Patients may also be recruited from Social Media, either from a Mayo-approved Facebook ad or from Twitter.

Subject Randomization

Patients will be randomized using 6 as a block size to make sure the balance of the randomization at any time point. The randomization will be created by [redacted] and stored in REDcap. The coordinator who is going to do the randomization will get access to the REDcap randomization schedule and get the treatment assignment from there for the eligible patients.

Data Collection

Demographic information will be collected, which will include age, race, and comorbidities. Urinary cultures will be collected from prior to studies and subsequent to enrollment, with details of results documented. MESA questionnaire will be used to assess baseline and subsequent urinary symptoms to evaluate for change following the procedure as a secondary outcome. DIVA questionnaire will assess change to sexual function and symptoms of GSM at baseline and following treatment. All the data will be collected and entered in the REDcap database.

Statistical Analysis

The 4-month rUTI prevalence and 6-month rUTI prevalence will be estimated using binomial method and compared between the two groups using Chi-square test or Fisher's exact test when applicable. The 6 month rUTI recurrence rate will be estimated using Poisson method and compared between the two groups using GEE method.

Overdispersion will be evaluated and if presented, negative binomial method will be used to estimate the rUTI recurrence rate.

Time to first recurrent UTI will also be compared between the two groups using log-rank test.

The MESA responses, DIVA responses and vaginal histology changes over time will be summarized and compared between the two groups using general linear mixed model or generalized linear mixed model when appropriate.

Clinical outcomes

Microbiome analysis

Whole population DNA will be extracted directly from vaginal and urine samples for both 16S and shotgun-metagenomic sequencing. Sequenced reads will be mapped to the human genome, in order to remove any host DNA contamination. For both 16S and shotgun-metagenomic sequences, reads not aligning to the human genome will then be assigned taxonomic grouping using the Kraken software package. Abundance of taxa/species will be determined by calculating counts per million reads. Changes in microbiome composition will then be determined by comparing the Shannon's diversity index between treatments and sampling timepoints using ANOVA (Yang et al, 2016).

This type of analysis will allow us to further identify the unique microbiome that exists in the urinary bladder. This would not be possible with standard urinary cultures, as without an abundance of 1-2 species, urinary cultures are limited in identifying an existing low count microbiome. This study will add to the microbiome literature in several ways. This type of analysis has not been described using vaginal cultures in patients with rUTI. Furthermore, analysis of change with treatment has not been described in this population as well, from both the urinary and vaginal microbiome perspective. Understanding this information has potential to develop new therapies that may help in treating menopausal women with rUTI.

Recurrent UTI

Our goal is to test the hypothesis that LASER treatment is non-inferior to vaginal estrogen in rUTI patients. If LASER is found to be effective, it would offer clinicians a modality of treatment for these patients that avoids antibiotics and hormone

replacement. It would also offer hope to patients for whom hormones are contraindicated.

Strategic Initiatives

This translational clinical study fulfills multiple strategic initiatives of the Mayo Clinic Enterprise. This novel therapy provides a new service line in regenerative medicine treating women with genitourinary syndrome of menopause with LASER therapy. Expanding the clinical utility based on level 1 evidence that we would provide would fulfill the clinical goals of the Center for Regenerative Medicine. Given that 50% of menopausal women experience symptoms of GSM, this research has potential to impact millions of women in the US and throughout the world.

Incorporating microbiome analysis to this clinical trial opens up further hypotheses of how we can affect an aging microbiome to create a more favorable one within the human body utilizing regenerative technology. This metagenomic data will allow us to better understand this specific population, menopausal women with rUTI, and we may be able to identify avenues to create novel individualized therapies depending on the findings of the microbiome analysis. This fulfills the Center for Individualized Medicine's goals of targeted therapy.