Safety, Tolerability and Short-Term Efficacy of Transvaginal Fractional Bipolar Radiofrequency Therapy for Symptoms of Stress and or Mixed Incontinence in conjunction with Genitourinary Syndrome of Menopause

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Abstract

Introduction: Radiofrequency energy has been utilized to treat conditions such as vaginal laxity, atrophy, and stress urinary incontinence (SUI). Contact RF energy heats the mucosal surface of the vagina uniformly to deliver electrothermal energy to the connective tissues in the vaginal wall. This RF energy application stimulates collagen and elastin remodeling to restore the rigidity, elasticity, and moisture of the superficial vaginal mucosa. The limitation of this surface treatment is in the penetration depth of the energy to the vaginal tissue layers. This is the first study to report on the use of microneedling to deliver RF energy to the vaginal canal similar to what has been used to treat the skin surface of the face, neck, and chest. Microneedling increases the response of the collagen contraction and neocollagenesis in deeper layers of tissue, thus increasing the support to the surface. The novel intravaginal microneedling device used in this study allows penetration of the needles to 1 mm, 2 mm, or 3 mm.

Objective: A prospective pilot study to evaluate the outcome of a single fractional RF treatment of the vaginal canal in a series of women with coexistent stress or mixed incontinence (MUI) and genitourinary syndrome of menopause (GSM).

Methods: Twenty women who had symptoms of SUI and or MUI in conjunction with GSM were given a single vaginal treatment that consisted of fractional bipolar RF energy using the EmpowerRF platform with the Morpheus8V applicator (InMode). RF energy was delivered into the vaginal walls via 24 microneedles, at a depth of 1 mm, 2 mm, and 3 mm. Outcomes were evaluated by “cough” stress test, questionnaires (MESA SI, MESA UI, iQoL, UDI-6) and evaluation of vaginal tissue through the VHI scale at 1-month, 3-months, and 6-months post-treatment compared to baseline. Biopsies were performed at baseline and 3-months on 5 patients for histological reference and tissue evaluation.

Results: Eight out of eight outcomes measured from baseline to 6-months post-treatment showed improvement. The parameters scored in the questionnaires including frequency, urgency, nocturia, urge incontinence, and stress incontinence showed significant improvement in all areas at the 1-month, 3-month, and 6-month follow-up sessions compared to baseline.

Conclusions: The results showed significant evidence that fractional RF energy delivered vaginally is safe, well tolerated, and helps treat symptoms of SUI and or MUI in conjunction with GSM.

Introduction

Stress urinary incontinence (SUI) is the involuntary leakage of urine with exertion, sneezing, or coughing. SUI often coexists with an overactive bladder and is termed mixed incontinence (MUI)[1]. Lowered estrogen levels after menopause and lack of the effect of estrogen stimulation to the vaginal tissue cause loss of collagen and elastin. The vaginal walls become thinner, more friable and have less vaginal secretions [2], resulting in the symptom complex of GSM. SUI and GSM very commonly coexist. The demand for in-office, minimally invasive treatments for these conditions is increasing as awareness of non-surgical options becomes more prevalent [3].

Until now, RF treatments have been available for surface and superficial treatment without an option for fractional RF vaginal treatment. RF energy heats the connective tissue of the vaginal wall, triggering a micro inflammatory activation of fibroblasts to stimulate collagen contraction, neocollagenesis and neo elastogenesis to revitalize and restore the strength, elasticity and moisture of the vaginal mucosa [4]. The role of the transvaginal application of continuous bipolar RF energy has previously been shown to be efficacious and safe in treatment of vaginal laxity and atrophy [4], as well as SUI [5] and pelvic floor restoration [6]. Continuous RF energy is applied to the vaginal mucosa to heat the underlying connective tissue to a temperature of 43^0C, causing collagen remodeling and soft tissue contraction to improve strength and elasticity of the vaginal wall and mucosal lubrication. Studies performed on the face and body have shown that microneedling with fractional RF energy devices that deliver RF energy to depths from 0.5 to 3.5 mm below the surface of the skin induce additional thermal stimulation which provides superior additional neocollagenesis than that seen with surface applications of RF energy alone [7-9].

Our goal was to evaluate the safety and efficacy of a novel transvaginal RF microneedling device which penetrates the vaginal mucosa and vulvar skin to deliver fractional RF energy to depths of 1 to 3 mm for treatment of women with coexistent SUI or MUI and GSM.

Methods

We conducted an IRB-approved prospective study at a single site. All procedures were performed by one of two board certified gynecologists.

Twenty female patients between the ages of 35 and 75 with symptoms of SUI, stress and/or mixed incontinence in conjunction with GSM, were recruited from a single private practice from October 2020 through May 2021. An examination of the treatment area was performed to complete the Vaginal Health Index (VHI) and multiple questionnaires were provided (iQOL, UDI-6, and MESA) pretreatment and at 1-, 3-, and 6-months post treatment. Medical history, demographic information, a bladder diary and questionnaires were collected at the baseline visit. Women who were included had a score of at least 18 out of 27 for the Stress Incontinence Questions and were confirmed as having predominant SUI on the Medical, Epidemiologic, and Social Aspects of Aging Urinary Incontinence (MESA). These parameters were evaluated through MESA Stress Incontinence (SI) and MESA Urinary Incontinence (UI) scales. All subjects were also required to have not used any other aesthetic treatment methods for the 6-months prior to the study or during the entire study period. Exclusion criteria included presence of a pacemaker, internal defibrillator, or any other active electrical implant anywhere in the body, pregnancy, current condition of cancer, or any active condition in the treatment area, or any

surgery in the treated area within 3-months prior to the treatment.

Subjects were pre-treated with Lidocaine 23% - Tetracaine 7% cream for 20 minutes prior to the procedure. Five study subjects had a baseline biopsy of the vaginal mucosa taken prior to the treatment. The treatment procedure was conducted by applying fractional bipolar RF energy through the EmpowerRF Morpheus8V device (InMode) using a stamping method with 50% overlap along the full length of the vagina to the introitus at 9, 10:30, 12, 1:30, 3, 4:30, 6, and 7:30. Two passes were conducted for each depth of 1mm, 2mm, and 3 mm. The Morpheus8V applicator is shown in Figure 1.

Figure 1. Morpheus8V applicator

After treatment the patients were given a voiding diary to complete for the remainder of the study. At 1-month, 3-month and 6-month follow-up visits, the voiding diary was collected, and the patient had a physical examination to assess the tissue and filled out the Urogenital Distress Inventory (UDI-6) questionnaire. For the patients who had a baseline biopsy, another biopsy was taken at 3-months post treatment.

Results

Based on a variety of outcome data measured at various time points, the treatment with Morpheus8V System for symptoms of SUI and vulvovaginal atrophy was statistically effective. In all, 20 patients were recruited into the study, with the average age being 52.7 years. All outcome data were measured at two, three, or four time points; for outcomes with only two time points, paired sample t-tests were employed to determine if the means improved. For outcomes with more than two measurements, repeated measures ANOVA tests were employed.

Repeated Measures ANOVA Results (Outcomes with Three Measurements)

The MESA additive SI battery instrument ranged with scores from 1-27, with lower values (1-9) indicating mild symptoms, and higher values (19-27) indicating severe symptoms. Measurements were taken at baseline, 3-months, and 6-months. The omnibus test was statistically significant $F(2, 36) = 30.52$, $p < 0.001$. Scores decreased from baseline to 3-months, then stayed flat at 6-months, which indicates that symptoms maintained their improved status from 3- to 6-months.

The MESA additive UI battery instrument ranged with scores from 1-18, with lower values (1-6), indicating mild symptoms, and higher values (13-18) indicating severe symptoms. Measurements were taken at baseline, 3-months, and 6-months. The omnibus test was statistically significant $F(2, 36) = 41.22$, $p < 0.001$. Scores decreased from baseline to 3-months, then stayed flat at 6-months, which indicates that symptoms maintained their improved status from 3- to 6-months.

The iQoL final instrument ranged with standardized scores from 1-100; it is a composite score of 22 questions, each of which was assessed at 1 (extremely) to 5 (not at all) scale. Thus, the higher the value of the score, the better the patient's assessment is of improvement after the treatment. Measurements were taken at baseline, 3-months, and 6-months. The omnibus test was statistically significant $F(2, 38) = 13.24$,

$p < 0.001$. Scores increased from baseline to 3-months, then stayed flat at 6-months, which indicates that symptoms maintained their improved status from 3 to 6-months.

The VHI additive instrument ranged with scores from 1-25; it is a composite score of 5 questions, each of which was assessed via a 1 (abnormal) to 5 (normal) scale. Thus, the higher the value of the score, the better the patient's assessment is of improvement after the treatment. Measurements were taken at baseline, 3-months, and 6- months. The omnibus test was statistically significant $F(2, 36) = 19.83$, $p < 0.001$. Scores increased from baseline to 3-months, then stayed flat at 6-months, which indicates that symptoms maintained their improved status from 3 to 6-months. The following table (Table 1) presents the three-time period means and corresponding pairwise comparison p-values.

Table 1: Repeated Measure ANOVA Pairwise Comparison Results (Three Measurements)

Item	BL Mean	3M Mean	6M Mean	BL-3M p	BL-6M p	3M-6M p
MESA SI	19.00	10.05	11.11	0.00	0.00	0.30
MESA UI	10.00	3.25	4.37	0.00	0.00	0.16
iQoL	44.21	75.23	67.16	0.00	0.00	0.27
VHI	16.00	21.84	22.58	0.00	0.00	0.33

Repeated Measures ANOVA Results (Outcomes with Four Measurements)

The following clinical evaluation baseline and post-treatment results are shown in Tables 2 and 3; The cough stress final weight scores ranged from 0-39, with lower values indicating less urine, and higher values indicating more urine captured in the pad. Measurements were taken at baseline, 1-month, 3-months, and 6-months. The omnibus test was statistically significant $F(3, 54) = 15.96$, $p < 0.001$. Scores decreased from baseline to 1-month, then stayed flat at 3-months and 6-months, which indicates that symptoms maintained their improved status from 1 to 6-months.

The UDI-6 additive scale ranged with scores ranging from 0-39 depending on the measurement; the additive scale was anchored by 1 = a little bit, and 3 = greatly. Thus, lower

values indicate symptom improvement, with the cutoff value of 33.3 being considered the top of the normal range Measurements were taken at baseline, 1-month, 3-months, and 6-months. The omnibus test was statistically significant $F(3, 54) = 26.81$, $p < 0.001$. Scores decreased from baseline to 1-month, then stayed flat at 3-months, then began to rise again at 6-months, which indicates that symptoms maintained their improved status from 1 to 3-months, but then began to increase again at 6-months. Regardless, the 6-month mean (26.76) was below the cutoff range of 33.3; thus, the increase from 3- to 6-months, while statistically significant, is clinically negligible.

Table 2: Repeated Measure ANOVA Means (Four Measurements)

Item	BL Mean	1M Mean	3M Mean	6M Mean
Cough Stress	13.05	4.32	3.84	2,79
UDI-6	43.85	18.20	21.05	26.76
Pee Frequency	55.07	44.33	45.00	47.87
Pee Quantity	448.07	416.0	388.60	343.07

Table 3: Repeated Measure ANOVA Pairwise Comparison p-Values (Four Measurements)

Item	BL-1M	BL-3M	BL-6M	1M-3M	1M-6M	3M-6M
Cough Stress	0.001	< 0.001	< .0.001	0.72	0.25	0.78
UDI-6	< .0.001	< 0.001	< 0.001	0.24	0.02	0.03
Pee Frequency	0.009	0.02	0.04	0.81	0.06	0.22
Pee Quantity	0.39	0.12	0.05	0.23	0.17	0.28

Histological Results

Histological biopsies of the vaginal mucosa at 3-months post-treatment demonstrate an increase in elastic fibers density compared to the baseline biopsy. Both superficial and deep elastic fibers are seen. The biopsies also find no damage to the submucosal collagen layer and no scar tissue formation in post-treatment, verifying no adverse effect of the fractional RF treatment.

Figure 2 shows biopsies performed prior to treatment and at 3-months post treatment stained with elastic and Ki-67 stains.

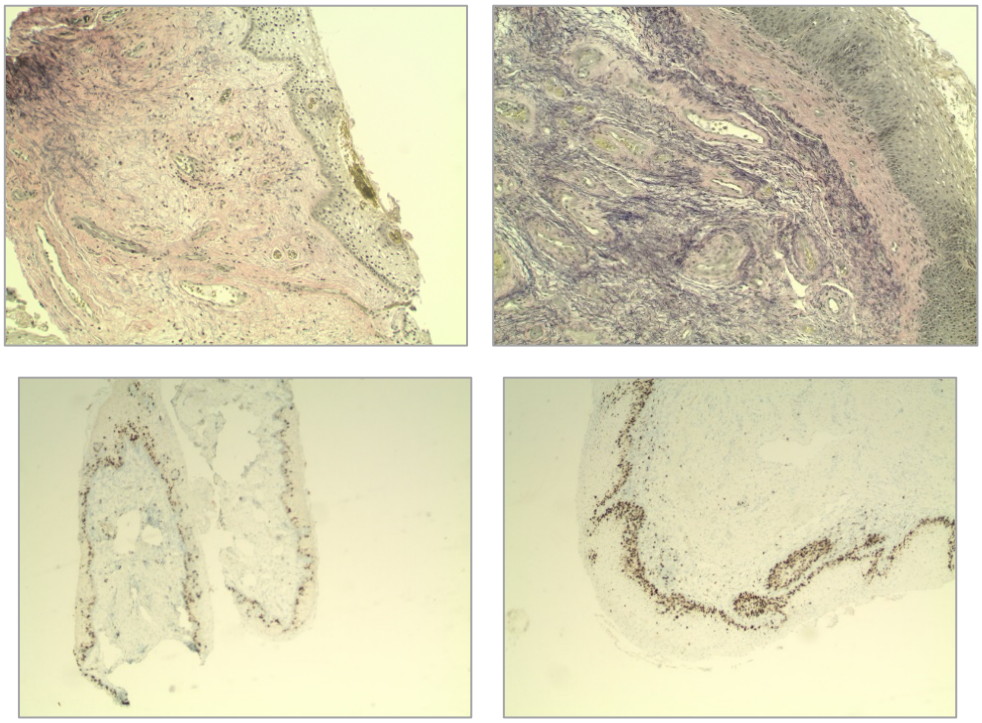

Figure 2. Histological section of skin biopsies before (Left) and 3-months following fractional treatment (Right) demonstrating increase in elastic fibers density. Up - Elastic x10, bottom – Ki-67x4.

Discussion

In summary, nine of the 13 outcomes measured from baseline to 6-months post-treatment improved statistically. That is, patient scores of MESA SI, MESA UI, iQoL, VHI, cough stress, and UDI-6, all improved from baseline to the various post-treatment periods, with most improving at the second measurement and staying improved at the third or fourth measurement compared to baseline. Also, data from voiding diaries noted a significant reduction in urinary frequency with a significant increase in functional bladder capacity. For the single-measure metrics, intravaginal pain and UDI change were better compared to a hypothesized value or cutoff value, whereas MESA UI Change and MESA SI Change were

marginally significantly better over their respective cutoff values. Subject satisfaction did not change from 3 to 6-month measurements, indicating that subjects were as satisfied with the treatment 3-months post-treatment to 6-months post-treatment, and were generally highly satisfied, as evidenced by the high mean values at both periods. In all, there is significant evidence to suggest that the Morpheus8V System for symptoms of SUI and vulvovaginal atrophy was highly efficacious. Further studies need to be performed with longer follow up to determine durability of success and whether additional treatments would be required.

Conclusion

This is the first study to report on the use of RF microneedling in the vaginal canal. Preliminary data would seem to indicate that such an intervention can result in improvement of vaginal atrophy which would be consistent with the data available on fractional CO2 laser treatments. Also, in addition through a different mechanism of improving connective tissue and support of the anterior vaginal wall stress and stress predominant mixed incontinence seem to improve. This procedure had a high patient satisfaction and improvement in quality of life. Fractional RF appears to hold potential to treat, in-office, two very common conditions that millions of women suffer from.

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