A 12-month feasibility study to investigate the effectiveness of cryogen-cooled monopolar radiofrequency treatment for female stress urinary incontinence

Bruce B. Allan, PhD, MD, FRCS(C)[1]; Stacie Bell, PhD[2]; Kathryn Husarek, PhD[2]

[1]Allan Centre, Calgary, AB, Canada; [2]Viveve Inc., United States

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Abstract

Introduction: The purpose of this early feasibility study was to evaluate the safety and efficacy of a non-ablative, cryogen-cooled, monopolar radiofrequency (CMRF) treatment for female stress urinary incontinence (SUI).

Methods: Subjects meeting all the inclusion and exclusion criteria were enrolled and randomized into two groups. Subjects in group 1 received one CMRF treatment and subjects in group 2 received two CMRF treatments six weeks apart. Followup visits were performed at one, four, six, and 12 months post-treatment. At each study visit, subjects performed an objective, standardized one-hour pad weight test and completed several patient-reported outcome measures, a seven-day bladder voiding diary, and safety assessments.

Results: Data indicate an improvement in SUI symptoms and quality of life for subjects, as determined by validated SUI-related patient-reported outcomes and the objective one-hour pad weight test, with a >50% reduction in pad weight from baseline for 52% of the subjects at 12 months. In addition to efficacy, the CMRF treatment was well-tolerated and safe.

Conclusions: The outcome measures evaluated indicate an improvement in SUI symptoms and quality of life. The sustained benefit of the CMRF vaginal treatment at 12 months suggests potential use as an office-based, non-surgical approach to treat mild to moderate SUI.

Introduction

According to the International Continence Society, urinary incontinence is defined as the involuntary loss of urine. The two major types of female urinary incontinence are urge urinary incontinence (UUI) and stress urinary incontinence (SUI). SUI is the involuntary loss of urine with effort, force, or physical exertion, including exercise or on sneezing or coughing. SUI is the most prevalent type of UI in women[1] but in reality, many women have a mixed presentation.

SUI is a common affliction in women. According to the American Urogynecologic Society (AUGS), SUI affects one in three women over 45 years old.[2] Pregnancy, childbirth, obesity, and menopause are all common contributors of SUI.[3] More than half of women who have had a vaginal childbirth will show symptoms of SUI and are more likely to develop long-term SUI when compared to cesarean delivery.[4] Furthermore, SUI has significant impacts on a woman's health and quality of life.[5] Some women may choose to avoid social gatherings, physical exercise, travel, and sexual intercourse depending on the severity of incontinence.[6,7]

Although various treatments exist for women suffering from SUI, the current options have limitations. Conservative treatment options include: "watching and waiting" to see if SUI worsens, diet/exercise changes,[1] and pelvic floor muscle-training (PFMT). Some women may find benefit from these therapies[8], but long-term compliance and sustainability are difficult.[9] While pharmacological intervention[10] or injectable bulking agents[11, 12] offer additional semi-conservative treatment options, they may pose efficacy or safety issues[13] and usually do not offer a permanent solution. Current surgical options exist (e.g., mesh or sling placement) with proven success rates,[14] however, complications of mesh surgery can and have occurred, negatively impacting patients. Due to these negative impacts, some countries, including the U.K.,[15] New Zealand,[16] and Australia,[17] have banned the use of surgical mesh to treat SUI. The gap between conservative and highly invasive, surgical treatment options presents an opportunity to provide more effective and non-surgical treatments for women suffering from mild to moderate SUI. In an effort to provide new treatment options, office-based procedures with energy-based devices, such as laser and radiofrequency devices, for treating women's intimate health issues (e.g., SUI, vaginal atrophy/genitourinary syndrome of menopause [GSM], vaginal laxity) are occurring more frequently.[18-21] Radiofrequency (RF) energy has previously been used to treat

various epithelial tissues, including pharynx, skin, cornea, and vagina, for a variety of patient conditions, including SUI.[22] Earlier RF devices that were FDA cleared to treat SUI used transvaginal surgery or transurethral probes with hooks in the bladder to deliver the RF energy.[23,24] However, due to patient safety concerns, these RF devices are no longer commercially available.[23-25]

In contrast, another monopolar radiofrequency device with cryogen-cooling (CMRF) has a well-documented safety profile and has previously been used to effectively treat vaginal laxity and sexual dysfunction.[26,27] The device delivers monopolar RF energy vaginally through an external probe deep into the lamina propria layer of vaginal tissue while using cryogen cooling to protect the upper mucosal layer. Recently, a small 10-patient pilot study using CMRF to treat women with SUI reported a >90% improvement from baseline in SUI symptoms and quality of life as reported by SUI-related questionnaires after 12 months of treatment. Following those positive subjective results, this larger, investigator-initiated, early feasibility study was conducted to gather the first long-term, objective data on the use of CMRF to treat female SUI.

Methods

Study design and research subjects

This feasibility study was a single-site, randomized, unblinded trial. Women presenting to the center with SUI were invited to participate in study screening. Following written informed consent, women completed study screening procedures that included the collection of demographic data and medical/obstetric history, and completion of the standardized one-hour pad weight test (PWT) put forth by the International Continence Society.[28] The one-hour PWT is a standardized series of activities (walking, coughing, climbing stairs, etc.) that the subject completes following ingestion of 500 mL of sodium-free liquid. Subjects were asked to wear pre-weighed pads during the assessment. The pad was weighed again at the completion of the test to determine the amount of leakage. The primary outcome of the study was the improvement in urinary incontinence as measured by the one-hour PWT, with a 30% reduction from baseline indicating a clinically meaningful improvement. However, a more commonly used endpoint is a >50% reduction in the one-hour PWT,[29,30] therefore, that is how the data is presented.

Subjects also completed several validated SUI patient-reported outcome measures (Urogenital Distress Inventory-6 [UDI-6],[31] Incontinence Impact Questionnaire-Short Form [IIQ-7],[31] and International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence-Short Form [ICIQ-UI-SF][32]). Additionally, a site-developed seven-day bladder voiding diary, which included questions regarding leakage and daily activities, was also sent home with the subject for completion prior to randomization.

The trial included females (≥18 years of age) with a normal pelvic exam who were diagnosed with mild to moderate SUI as defined by the one-hour PWT (1–50 g leakage).[28] Women were excluded from the trial who: were currently pregnant, had given birth <6 months prior or discontinued breastfeeding <6 months prior to enrollment; had a condition/illness that might confound the results of urinary incontinence assessment (including an abnormal pelvic exam, greater than stage II pelvic organ prolapse, or were morbidly obese); had a history of genital fistula or a thin recto-vaginal septum (≤2 cm); had a previous energy-based device treatment in the genitourinary area; and/or were taking any new medication that affects urination.

Subjects returned to the center for followup visits at one, four, six, and 12 months post-treatment. The one-hour PWT, seven-day bladder voiding diary, and subjective questionnaires (UDI-6, IIQ-7, and ICIQ-UI-SF) were completed at each followup visit. Adverse events and concomitant medications were collected at each of the followup visits. Any subjects who did not complete the study and were lost to followup were excluded from the analysis in future timepoints.

Randomization and intervention

Subjects meeting the inclusion and exclusion criteria were randomized to receive either one or two CMRF treatments using a random number generator; odd numbers were placed into group 1 and received one CMRF treatment and even numbers were placed into group 2 and received two CMRF treatments. If a subject was assigned to group 2, the second treatment occurred six weeks following the initial treatment. Two treatment groups and the six-week timing between the treatments were chosen based on previous studies with other energy-based devices for SUI that require repeat treatments 4–6 weeks apart.[18]

This technology and its use in women with vaginal laxity and sexual disfunction consists of 110 pulses of 90 J/cm^2 at the introitus of the vaginal canal.[33,34] The Viveve system protocol for sexual function was modified to provide additional energy to the tissue beyond the introitus for support of the urethra to improve SUI. One treatment consisted of a total of 220 pulses of 90 J/cm^2. The treatment area was divided into quadrants of the vaginal introitus with the area directly beneath the urethra excluded. Each quadrant was treated with five consecutive passes of five locations of pulses for a total of 25 pulses per quadrant. The remaining 20 pulses are distributed equally in quadrants one and four. As this is a minimally invasive, office-based procedure, no anesthesia is necessary during or after the treatment.

Ethics

Ethical/institutional review board approval was obtained from the Health Research Ethics Board of Alberta and the study was done in compliance with Good Clinical Practices and International Conference on Harmonization (ICH) guidelines. Health Canada clearance was also obtained by Dr. Allan for this investigator-initiated study. Documentation and data management were conducted in a manner that aligns with local ethics review board guidelines.

Results

Participants

Between June and November 2017, 37 subjects were enrolled in the study. Twenty-one and 14 subjects were randomized to receive one or two treatments, respectively; two subjects dropped out of the study prior to treatment. Twenty-five subjects completed the 12-month followup visit (Fig. 1). Table 1 shows the baseline characteristics for the randomized subjects. Group 2 was older (with a mean age of 46.1 years) than group 1 (mean age of 41.0 years). Group 2 also had a slightly higher body mass index (BMI) at baseline than group 1 (24.5 vs. 26.0).

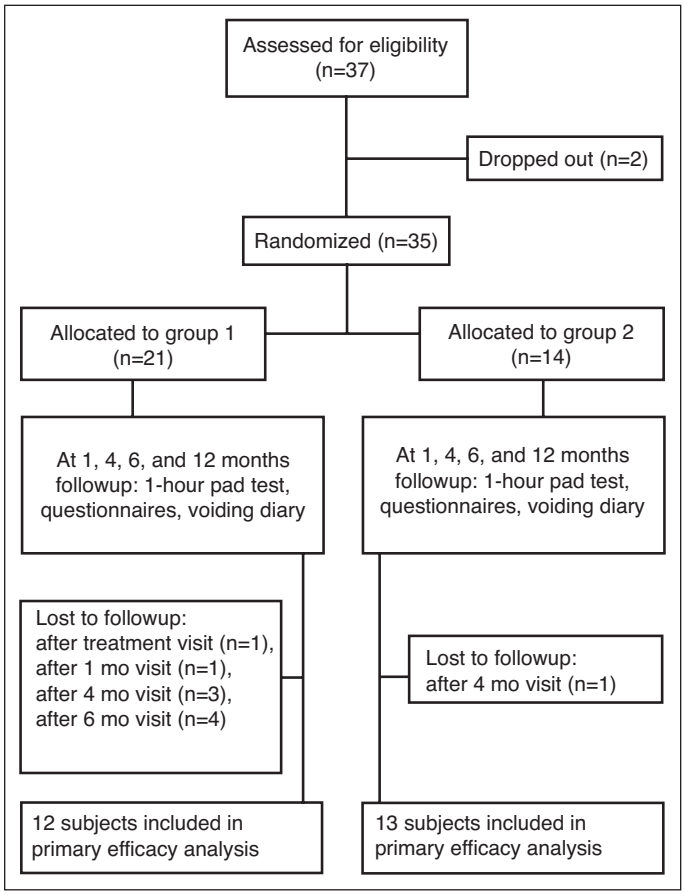

Fig.1. Patient disposition.

One-hour pad weight

Mean leakage volumes based on the one-hour PWT are presented in Table 2. The mean leakage volume at baseline was mild for both groups, although some women (n=10) with moderate incontinence, defined as >10–50 g of leakage on the one-hour PWT, were included in the trial. Baseline values did not differ greatly between treatment groups. The 12-month pad weight leakage volume was greater in group 2 than group 1; however, the percentage of subjects with >50% reduction in pad weight was similar, 54% and 50%, respectively. The cure rate, defined here as ≤1 g of leakage on the one-hour PWT, varied between treatment groups at 12 months (75% for group 1 and 54% for group 2), as did mean change from baseline (CFB). Group 1 had a mean CFB of -1.75 g, while group 2 had a mean CFB of -4.31 g.

Three post-menopausal women were randomized into the study; all were in group 2. Two of the three women were dry at 12 months based on the one-hour PWT. To date, the previous clinical trials using this CMRF technology only enrolled pre-menopausal women,[26,27] and the success of the CMRF treatment on these two post-menopausal women warrants further investigation and clinical studies,

Table 1. Baseline demographics, clinical characteristics, and maternal history for trial subjects

	Group 1		Group 2	
No. of subjects	21		14	
Demographic data	**Mean**	**SD**	**Mean**	**SD**
Age	41.0	4.6	46.1	9.2
Age categories	n	%	n	%
<35 years	3	14.3%	2	14.3%
35–39 years	5	23.8%	1	7.1%
40–44 years	6	28.5%	4	28.5%
≥45 years	7	33.3%	7	50.0%
Clinical data	**Mean**	**SD**	**Mean**	**SD**
BMI	24.5	4.4	26.0	4.5
BMI categories	**n**	**%**	**n**	**%**
BMI 18.5–24.9	13	61.9%	6	42.9%
BMI 25–29.9	5	23.8%	6	42.9%
BMI ≥30	3	14.3%	2	14.3%
Maternal history	**Mean**	**SD**	**Mean**	**SD**
No. of pregnancies	2.0	1.2	2.3	0.8
No. of full-term deliveries	1.7	1.0	2.3	0.7
No. of vaginal deliveries	1.5	1.0	2.0	1.0
Race	**n**	**%**	**n**	**%**
White	20	95.2%	14	100%
Asian	1	4.8%	0	0.0%

BMI: body mass index; SD: standard deviation.

Table 2. Mean leakage volume on the 1-hour PWT at 1-, 4-, 6-, and 12-month followup visits

	Baseline			Month 1			Month 4			Month 6			Month 12		
Group	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
All subjects	35	7.29	7.5	34	2.15	2.4	33	1.27	1.8	29	1.69	2.5	25	3.20	4.6
Group 1	21	7.24	8.1	20	2.25	2.6	19	1.11	1.6	16	1.81	3.0	12	2.83	4.6
Group 2	14	7.36	6.8	14	2.00	2.1	14	1.50	2.1	13	1.54	1.8	13	3.54	4.8

PWT: pad weight test; SD: standard deviation.

especially since aging and menopause are contributing factors to incontinence.[3]

Seven-day bladder voiding diary

Subjects reported a decrease in incontinence episodes (IEs) per day as soon as one month post-treatment (Table 3). Although baseline IEs varied between the groups by almost a whole episode per day, at 12 months, both groups averaged ≤1 episode per day. Overall, over half (64%) of randomized subjects reported less leakage episodes compared to baseline, with most (63.5%) reporting a >50% reduction from baseline. Additionally, some subjects reported an ability to resume strenuous physical exercise (e.g., rock-climbing) after treatment.

Patient-reported outcomes

Although group 1 had slightly higher baseline scores, there was not a significant difference between the groups at baseline. Clinically meaningful score decreases, defined as 11 points for UDI-6 and 2.52 points for ICIQ-UI-SF, in subject's SUI symptoms and improvement in quality of life were noted on two measures (UDI-6 and ICIQ-UI-SF) as early as one month post-treatment[31,32] (Figs. 2A, 2C). IIQ-7 scores did not reach the minimal clinically important difference (MCID), defined as a 16-point reduction, until four months post-treatment (Fig. 2B). Only UDI-6 scores met the MCID at all timepoints for both groups (Fig. 2A). Although the mean composite score was decreased from baseline at 12 months, both IIQ-7 and ICIQ-UI-SF mean composite scores did not meet the MCID for group 1 at the 12-month timepoint (Figs. 2B, 2C). Alternatively, group 2 did meet the MCID for all measurements at 12 months post-treatment (Figs. 2A, 2C).

Safety

No unanticipated or serious adverse events (SAEs) were reported in the trial. One patient reported two urinary tract infections (UTIs). The first UTI occurred between the treatment visit and one-month followup, and the second occurred between the six-month and 12-month visits. For both UTIs, the subject was treated with one week of antibiotics. The investigator assessed the UTIs as unrelated to treatment.

Discussion

This feasibility study highlights the promising efficacy and safety of a CMRF procedure for the treatment of SUI. The 12-month data are a continuation on the previously published 6-month data indicating positive results of the CMRF procedure for SUI.[35] While the results show continued benefit out to 12 months post-treatment for all subjects, there is a slight decrease in efficacy from six months. Additionally, even though there were minor differences reported between the treatment groups, the small number of subjects makes it difficult to determine any significant differences between them.

Although the percentage of women with a >50% reduction from baseline in leakage volume at 12 months is similar between groups (50% for group 1 and 54% for group 2), the actual mean leakage volume from the one-hour PWT differed between groups. The lower leakage volume reported from the one-hour PWT in group 1 at 12 months could be due to a greater amount of subject dropout at 12 months. Interestingly, of the nine women who dropped out of group 1 before the end of the trial, eight had improvement from baseline on the one-hour PWT at their last measured visit, and five of the nine had no leakage at all (0 g of leakage on the one-hour PWT). In addition, when the leakage volumes at the last measured visit are considered, group 1 has a mean CFB of -4.81 g (vs.

Table 3. Mean number of incontinence episodes at 1-, 4-, 6-, and 12-month followup visits

	Baseline			Month 1			Month 4			Month 6			Month 12		
Group	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
All subjects	35	2.2	2.4	34	1.3	1.9	32	1.3	2.1	28	1.0	1.9	25	0.8	0.8
Group 1	21	1.9	2.1	20	1.1	1.5	18*	1.2	2.1	15*	0.7	1.0	12	1.0	1.1
Group 2	14	2.7	2.8	14	1.7	2.4	14	1.3	2.3	13	1.3	2.5	13	0.6	0.5

*Subject completed study visit but did not complete voiding diary. SD: standard deviation.

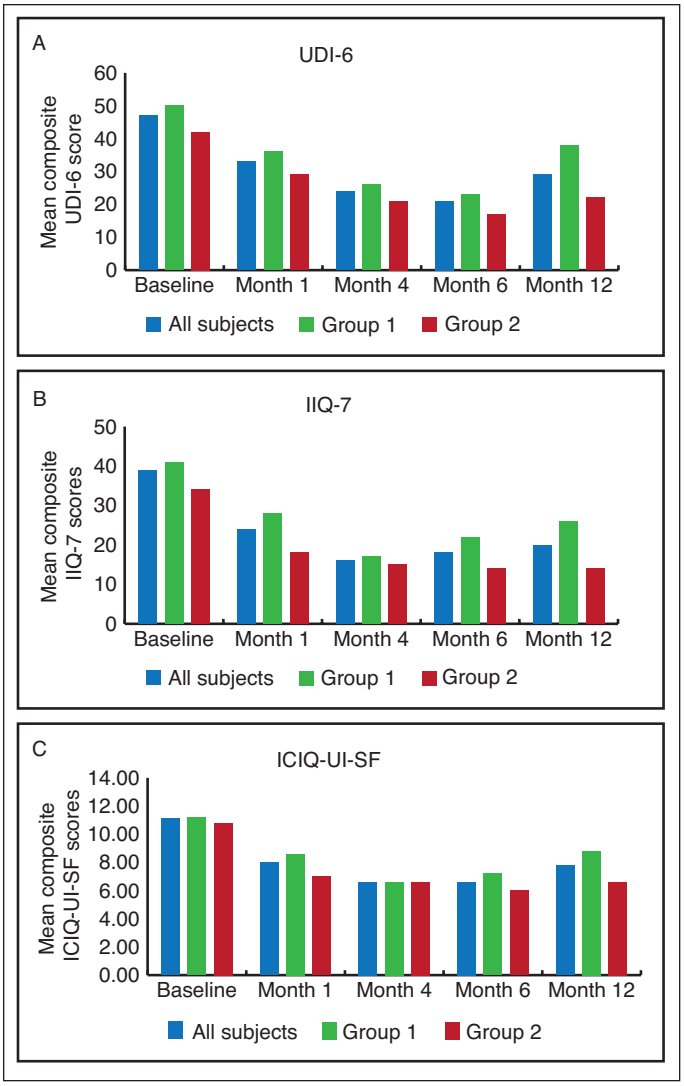

Fig. 2. Mean composite scores for stress urinary incontinence (SUI)-related patient-reported outcomes. ICIQ-UI-SF: International Consultation of Incontinence Questionnaire – Short Form; IIQ: Incontinence Impact Questionnaire; UDI: Urinary Distress Inventory.

-1.75 g for the subjects who completed the 12-month visit). Therefore, the population of subjects who were lost to followup could be selective based on their positive outcomes at their last measured visit. Of note, four of the nine dropouts from group 1 were considered to have moderate SUI (>10–50 g of leakage) at baseline and three of these women had no leakage at their last measured timepoint.

Another difference between the groups is the average number of IEs at baseline and 12 months. While group 1 reported lower baseline IEs (1.9 vs. 2.7, respectively), group 2 had a bigger change from baseline. This difference could due to the unblinded nature of the study. Alternatively, group 2 had a larger BMI than group 1 at baseline, possibly indicating a more sedentary lifestyle, which could lead to less leakage episodes.

Additionally, many subjects met the MCID scores for the subjective SUI-related patient-reported outcome measures at 12 months. However, there are slight differences in the mean composite scores between groups, with group 2 reporting decreased scores (over group 1) at almost all timepoints. This could be due to a lower baseline value for group 2 or also because this was an unblinded study, so subjects knew whether they received one or two CMRF treatments. Analysis of over 100 clinical trials showed a significant placebo effect in studies with continuous subjective outcomes, however, little or no placebo effect for objective measures.[36] Furthermore, based upon what is known about collagen restoration and the CMRF system's proposed mechanism of action, including fibroblast activation and restoration of connective tissue of the lamina propria, a second CMRF treatment done at a later timepoint (e.g., six months vs. six weeks) may provide additional treatment benefits to women. A larger number of subjects, another study including a sham treatment group, a longer followup period, and/or a longer time between treatments may be necessary to determine the differences between one or two treatments and the optimal timing.

Although there are data to indicate that other energy-based devices are providing benefit for SUI, no other clinical trials with a monopolar radiofrequency device have demonstrated a decrease in SUI symptoms as evaluated by objective measures (one-hour pad test and voiding diary) or a sustained benefit out to 12 months post-treatment.[22,37-40] Additionally, it should be noted the CMRF system has a well-documented safety profile. Thousands of women have been treated globally for sexual dysfunction and data from these clinical trials reported only mild adverse events.[26,33,34] Furthermore, recent ovine studies have confirmed tissue temperatures that would result in cellular responses related to the observed clinical outcomes with no thermal damage to the vaginal tissue following multiple pulses in the same area (Viveve internal data).

Conclusions

While this paper summarizes data from an investigator-initiated feasibility study, the results include the first 12-month objective outcome data for a vaginal CMRF procedure for the treatment of SUI. In this trial, there was no benefit to a second CMRF treatment at six weeks. However, this CMRF procedure shows promise as another option for patients searching for more effective and non-surgical treatments for SUI. This preliminary study merits a larger scale, randomized, blinded, and sham-controlled clinical trial to investigate this procedure for the treatment of SUI. Additional studies to investigate optimal timing between procedures are also warranted.

Competing interests: Dr. Allan has received study support from Viveve for an investigator-sponsored research program and has been a consultant for Viveve, Inc. Dr. Bell was an employee of Viveve, Inc. at the time of the study. Dr. Husarek is currently an employee of Viveve, Inc.

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This paper has been peer-reviewed

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Correspondence: Dr. Bruce B. Allan, Allan Centre, Calgary, AB, Canada; drallan@allancentre.com