The Use of the Viveve System to Treat Female Stress Urinary Incontinence: An Interim 6-Month Report

Bruce Allan, PhD, MD, FRCS(C)

Kathryn Husarek, PhD

Stacie Bell, PhD

ABSTRACT

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

Methods: This was a prospective, feasibility study designed to demonstrate that the study treatment meets primary efficacy and safety endpoints. Thirty-seven (37) subjects, meeting all the inclusion and exclusion criteria, were enrolled in the study. The study was divided into two groups; subjects in Group 1 received a single SUI treatment and subjects in Group 2 received two SUI treatments approximately six (6) weeks apart. Follow-up visits are planned for 1, 4, 6, and 12 months post-treatment. At the Screening Visit, and at each timepoint beginning at Month 1, subjects were asked to perform a 1-hour pad weight test and to complete the Urogenital Distress Inventory-6 (UDI-6), Incontinence Impact Questionnaire-7 (IIQ-7), and International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) questionnaires. In addition, subjects completed a 7-day Daily Bladder Voiding Diary and safety assessments.

Results: Preliminary data indicate a remarkable improvement in SUI symptoms and quality of life for subjects, as determined by validated SUI-related patient reported outcomes and the objective 1-hour pad weight test, with a greater than 50% reduction in pad weight for 69% of the subjects at 6 months (data collected to date). The overall response rate is between 75-85%, with all measures considered. Initial review of the bladder voiding diaries suggest that subjects are having fewer urine leaks and are more active in their daily lives. In addition to promising efficacy, the CMRF system was well-tolerated and safe.

Conclusions: The outcome measures evaluated indicate a significant improvement in SUI symptoms and quality of life as evaluated by the objective 1-hour pad weight test and several subjective patient-reported outcome measures. The notable and sustained benefit of the CMRF vaginal treatment to 6-months suggests potential use as a non-surgical approach to treat SUI, offering a much-needed option for millions of women.

Clinical Trial Registration: clinicaltrials.gov Identifier: NCT03066180

BACKGROUND

Urinary incontinence is the involuntary leakage of urine. There are two major types of female urinary incontinence, urge urinary incontinence (UUI) and stress urinary incontinence (SUI). Urge incontinence is defined as the sudden need to void the bladder. Whereas stress incontinence is the loss of urine following a cough, sneeze, or physical activity. Stress incontinence has two major subtypes: intrinsic sphincter deficiency (ISD) and urethral hypermobility. Patients with ISD leak urine because their sphincters do not effectively seal off the inner muscle of the bladder. Urethral hypermobility refers to the urethral shift that occurs when there is an increase in intrabdominal pressure (e.g., cough/sneeze).

SUI affects many women; especially during pregnancy, childbirth, or menopause. More than 55% of women who have delivered a child vaginally will show symptoms of SUI and are twice as likely to suffer from long-term SUI when compared to cesarean delivery [1]. Furthermore, SUI can greatly impact a woman's health and quality of life [2]. Depending on the severity of incontinence, some women may choose to avoid social or religious gatherings [3], physical exercise, travel, and even sex [4, 5].

Currently, limited treatment options exist for women suffering from SUI. Pelvic floor muscle training (PFMT) is generally prescribed as a first step in treatment. Some women may find benefit from these exercises [6], but long-term compliance and sustainability is difficult [7]. At the other end of the treatment spectrum is surgery with mesh or a sling. Although synthetic sling placement has a proven success rate [8], complications of mesh surgery are a common cause of litigation. In addition, surgery often comes with several risks including infection, voiding dysfunction, and anesthetic concerns [9], leading many women to use surgery as a last resort for treatment. The large gap between conservative and highly-invasive treatment options presents an opportunity to provide more effective and less-invasive treatments for women suffering from SUI.

Radiofrequency (RF) energy has a long history of use in mucosal tissue in the pharynx, skin, cornea, and vagina and RF devices have been used to treat a variety of health-related concerns, including SUI [10]. The Viveve System, a cryogen-cooled monopolar radiofrequency device, has a well-documented safety profile and has previously been used to treat sexual dysfunction [11, 12]. The patented device delivers monopolar RF with cryogen cooling to protect the upper surface mucosa while at the same time enabling energy (heat) to reach the deeper tissue layers. Recently, a pilot study using the Viveve System to treat women with SUI reported a >90% improvement from baseline in SUI symptoms and quality of life (pilot study data). Following those impressive results, another study was conducted to further evaluate the use of the Viveve System to treat SUI.

MATERIALS AND METHODS

Study Design and Research Subjects

This feasibility study is a single site, randomized, unblinded trial that is currently ongoing.

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 1-hour pad weight test (1-50 g leakage) [13]. Women were excluded from the trial who: were currently pregnant or discontinued breast feeding fewer than 6 months prior to enrollment; had an abnormal pelvic exam; had clinically-significant pelvic organ prolapse; were morbidly obese; had a history of genital fistula or a thin recto-vaginal septum; had a previous energy-based device treatment in the genitourinary area; and/or were taking any new medication that affects urination.

Group Assignment and Intervention

Subjects meeting the inclusion and exclusion criteria were randomized 1:1 to receive either 1 or 2 treatments. Both groups were treated with 90 Joules/cm^2. Randomized subjects received one or two treatments of 220 pulses. If a subject was assigned to Group 2 (2 SUI treatments), the treatment protocol was repeated 6 weeks following the initial treatment.

Follow-Up Visits

The standardized 1-hour pad weight test [14], a 7-day bladder voiding diary and validated patient reported outcome measures [Urogenital Distress Inventory-6 (UDI-6) [15], Incontinence Impact Questionnaire-Short Form (IIQ-7) [15], and International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) [16, 17]] were administered at the screening visit and at months 1, 4, and 6 months post-treatment. These will also be completed at the final visit at 12 months. Adverse events and concomitant medications were collected at each of the follow-up visits.

Objective 1-hour Pad Weight Test

The 1-hour pad weight test is a standardized series of tests (walking, coughing, climbing stairs, etc.) that the subject completes following ingestion of a set amount (500 mL) of sodium-free liquid. Subjects are asked to wear pre-weighed pads during the assessments. The pad is weighed again at the completion of the series of tests to determine the amount of leakage.

Subjective Patient Reported Outcomes

The questionnaires used to evaluate the status of the subject's SUI were UDI-6, IIQ-7, and ICIQ-UI-SF. These questionnaires have been used in several SUI clinical trials

and have been validated for this use [15, 16]. Scoring was done as per the respective questionnaire guidelines.

Table 1. Baseline Subject Characteristics				
	Group 1		Group 2	
No. of Subjects	16		13	
Demographic Data	**Mean**	**SD**	**Mean**	**SD**
Age	42.9	4.0	46.5	9.2
Age Categories	**N**	**%**	**N**	**%**
<35 years	1	6.3%	1	7.7%
35-39 years	4	25.0%	2	15.3%
40-44 years	4	25.0%	3	23.1%
≥45 years	7	43.7%	7	53.9%
Clinical Data	**Mean**	**SD**	**Mean**	**SD**
BMI	25.1	4.6	25.9	4.7
BMI Categories	**N**	**%**	**N**	**%**
BMI <20	3	18.8%	0	0%
BMI 20-24	5	31.2%	5	38.5%
BMI 25-29	5	31.2%	6	46.1%
BMI ≥30	3	18.8%	2	15.4%
Maternal History	**Mean**	**SD**	**Mean**	**SD**
No. of pregnancies	2.0	1.3	2.3	0.9
No. of full-term deliveries	1.7	1.0	2.3	0.8
No. of vaginal deliveries	1.5	1.1	2.0	1.1

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

7-Day Bladder Voiding Diary

A site-developed 7-day bladder voiding diary was provided to subjects for completion. The voiding diary included questions about leakage and daily activities.

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. Documentation and data management were conducted in a manner that aligns with local ethics review board guidelines.

Table 2. % of Subjects with >50% Reduction in Mean Pad Weight and Mean Leakage Volume					
Group	**Baseline Pad Weight**	**Subjects with a >50% Reduction in Pad Weight from Baseline** *Mean pad weight leakage volume (g)*			**Cure Rate (≤1 g leak)**
		1 mo	**4 mos**	**6 mos**	**6 mos**
All Subjects (N=29)	6.17 g	**55%** 2.14 g	**76%** 1.31 g	**69%** 1.69 g	66%
Group 1 (N=16)	4.81 g	**56%** 2.19 g	**69%** 1.19 g	**69%** 1.81 g	69%
Group 2 (N=13)	7.85 g	**54%** 2.08 g	**85%** 1.46 g	**69%** 1.54 g	62%

Table 2. Mean pad weight data at 1, 4, and 6-month follow-up visits. Percentage of subjects considered cured at 6 months.

RESULTS

Participants

Between June and November 2017, 37 subjects were included in the study. Twenty-one (21) and 14 subjects were randomized to receive one or two treatments, respectively; two (2) subjects dropped out of the study prior to treatment. Twenty-nine (29) subjects completed the baseline and 6-month follow-up visit. Table 1 shows the baseline characteristics for all subjects.

1-hour Pad Weight

Mean 1-hour pad weight values are presented in Table 2. Baseline values differ between treatment groups; however, the 6-month pad weight leakage volumes are similar and the percentage of subjects with >50% reduction in pad weight is identical at 69%. The cure rate, defined here as ≤1 g of leakage and per FDA guidelines [18], is also comparable between groups. Overall mean change from baseline showed a decrease of 4.48 g for all subjects.

Patient Reported Outcomes

Clinically-meaningful decreases in subject's SUI symptoms and quality of life were noted on two measures (UDI-6 and ICIQ-UI-SF) as early as 1-month post-treatment [15, 16] (Figure 1). By 6-months post-treatment, all SUI-related subjective measures for both treatment groups show sustained improvement in mean composite scores. Group 1 reported greater mean composite scores than Group 2 at all measured timepoints for UDI-6 and IIQ-7.

7-Day Bladder Voiding Diary

Subjects report a decrease in leakage episodes as soon as 1-month post-treatment (Table 3). By 6 months, almost 80% of subjects report less leakage episodes compared to baseline, with most reporting a 50% or greater reduction from baseline. Additionally, some subjects report an ability to resume strenuous physical exercise (e.g. rock climbing) post-treatment.

Safety

No unanticipated or serious adverse events (SAEs) have been reported in the trial to date.

DISCUSSION

This early feasibility study highlights the promising efficacy and safety of the use of the Viveve System for the treatment of SUI. The results show continued benefit out to 6-months post-treatment for both treatment groups. While the objective, pad-weight data is similar between treatment groups, the subjective, SUI-related patient-reported outcome measures show slight differences in the mean composite scores, with Group 2 reporting decreased scores 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 1 or 2 treatments. Additionally, an analysis of 130 clinical trials showed a significant placebo effect in studies with continuous subjective outcomes, however little to no placebo effect for objective measures [19]. A larger number of subjects, or a longer follow-up period, may be necessary to determine if one or two treatments deliver greater benefits to women. Of note, this study will continue out to 12 months to assess safety and efficacy.

Figure 1. SUI-related Patient Reported Outcomes

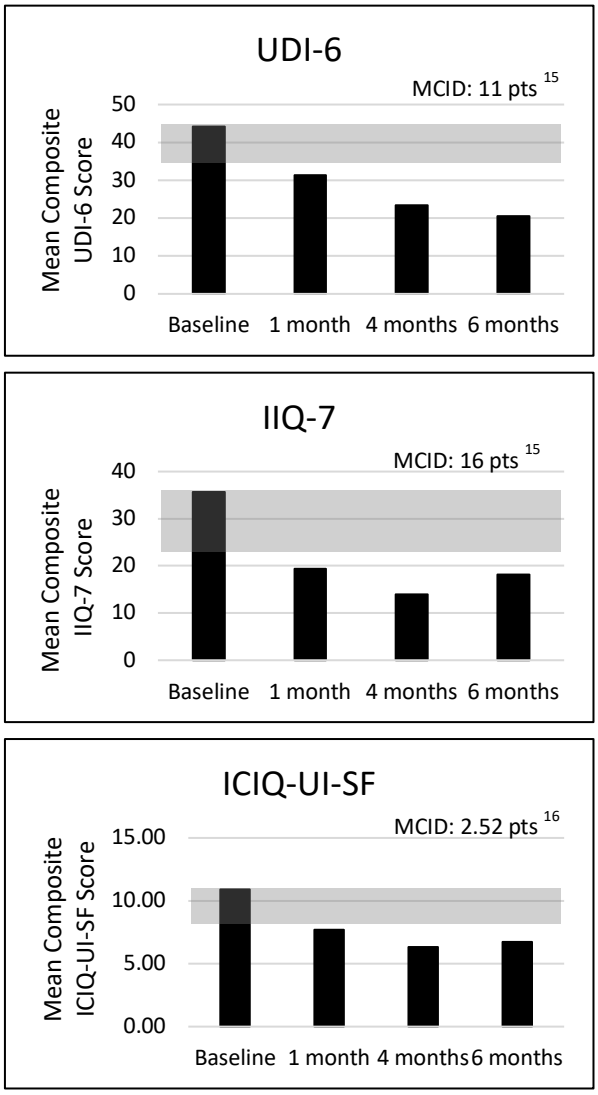

Figure 1. Mean composite scores for SUI-related patient reported outcomes. The gray bar in each graph denotes a published minimal clinical important difference (MCID) from the literature.

Although other RF devices are currently claiming to help treat SUI, no other studies with a non-ablative, monopolar radiofrequency device demonstrate a decrease in SUI symptoms as evaluated by objective measures (1-hour pad test and voiding diary) sustained out to 6-months post-treatment [10, 20-24]. This early feasibility study also includes validated SUI-related subjective questionnaires (UDI-6, IIQ-7, ICIQ-UI-SF) as study endpoints with results that go out to 6 months, with >70% response rate (reduction from baseline). Additionally, an earlier pilot study demonstrated the efficacy of the Viveve System for the treatment of SUI out to 12 months, with >90% response rate (reduction from baseline using validated SUI questionnaires) (pilot study data).

The Viveve System only requires one treatment to obtain these impressive results. Other RF devices require multiple (3+) sessions, typically at 1-month intervals. This causes increased time and monetary cost to the patient and increases the potential for a decrease in treatment compliance. In addition, based upon the Viveve System's proposed mechanism of action, which includes fibroblast activation and restoration of collagen in the lamina propria tissue layer [25], and is known about collagen restoration (collagen ref), repeating RF treatments sooner than 6 weeks may actually disrupt the natural collagen restoration process.

It should also be noted that the Viveve System has a well-established safety profile. To date, thousands of women have been treated globally for sexual dysfunction with only mild adverse events reported [11, 26, 27]. In the previously published, large scale, randomized controlled clinical trial using the Viveve System, the active and sham groups reported similar numbers of adverse events [12]. Additionally, recent ovine studies have shown evidence of cellular responses related to clinical outcomes and no thermal damage to the vaginal tissue following multiple pulses in the same area (Viveve internal data).

Table 3. Number of Incontinence Episodes per Day

Group	Baseline Mean # Daily Incontinence Episodes	Number of Incontinence Episodes/Day *% of subjects with >50% reduction from baseline in incontinence episodes/day*		
		1 mo	4 mos	6 mos*
All Subjects (N=29)	2.0	**1.2** 48%	**1.2** 69%	**1.0** 64%
Group 1 (N=16)	1.5	**0.7** 50%	**1.1** 75%	**0.7** 60%
Group 2 (N=13)	2.7	**1.7** 46%	**1.3** 62%	**1.3** 69%

Table 2. Mean number of incontinence episodes at 1, 4, and 6-month follow-up visits. *N=28 at 6-month timepoint.

CONCLUSIONS

While this paper summarizes data from an early feasibility study, the results include the first 6-month objective outcome data for radiofrequency treatment for SUI. The Viveve treatment shows promise as a viable option for patients searching for minimally-invasive non-surgical treatments. Initial experience merits a larger scale study to investigate this treatment for SUI.

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