A Prospective Longitudinal Single-Arm Study of Low-Energy Radiofrequency (RF) Applied to the Vaginal Introitus to Improve Vaginal Laxity and Sexual Satisfaction in Female Patients: Interim Results at Three-Months

Conducted by:

Yuki Sekiguchi, MD, PhD **Yukari Utsugizawa, MD, PhD**	**Yokohama Motomachi** **Women's Clinic LUNA Group** **Hyakudan-kan 5F 3-115 Motomachi, Naka-ku** **Yokohama, Japan 231-0861**

BACKGROUND: *Decreased sensation and decreased sexual satisfaction associated with introital laxity induced by stretching of the vaginal tissue during childbirth has the potential to negatively impact overall sexual function and quality of life in millions of women. Vaginal laxity may occur after the first delivery and be made worse with multiparity, delivery of a large fetus, or application of forceps. The Viveve System (Viveve, Inc., Palo Alto, CA USA) offers a simple alternative to surgery utilizing non-ablative radiofrequency (RF) energy as a non-surgical approach to reduce laxity of the vaginal introitus.*

OBJECTIVE: *To determine the effect of low energy RF on sexual satisfaction and vaginal laxity when treating the female introitus following vaginal birth.*

METHODS: *The Viveve System is a monopolar reverse gradient RF system that uses surface cooling to deliver non-ablative energy (90 J/cm^2) to tighten the submucosal layers of vaginal tissue. Convenience sampling was used to prospectively enroll patients at one Japanese OB/GYN and urogynecology clinic in this single-arm study of patient self-reported outcomes of vaginal laxity and sexual satisfaction. A 7-point and 6-point Likert-type visual analog scale (VAS) was used to measure vaginal laxity and sexual satisfaction, respectively. FSFI and FSDS-R were used to assess any changes in sexual function and sexual health.*

RESULTS: *A closed cohort of 30 pre-menopausal patients with an average age of 42.9 years (range 30-52) was followed out to 3 months post-procedure. Average parity of subjects was 2.2 (range 1-4). The mean improvement in vaginal laxity score three months post-treatment was 1.6 points ($p < 0.001$), with 77% of patients reporting improvement. The mean patient sexual satisfaction score improved 0.8 points three months post-treatment ($p = 0.005$). For the 17-patient cohort whose sexual satisfaction scores declined after childbirth, 77% reported improved sexual satisfaction scores three months post-treatment, with a significant average improvement of 1.5 points ($p < 0.001$) over pre-treatment scores. The only adverse events reported were mild, with one case each of vaginal leukorrhea and lower abdominal discomfort, which both resolved by 10 days after treatment; and one case of vaginitis at 3 months, which was believe to be unrelated to treatment.*

CONCLUSIONS: *These preliminary results indicate that the Viveve System is well tolerated and demonstrates that this non-surgical procedure offers the potential to reduce vaginal laxity and improve sexual satisfaction. This study remains open to follow-up out to six months.*

Decreases in physical sensation and sexual satisfaction associated with introital laxity induced by stretching of the vaginal tissue during childbirth has the potential to negatively impact overall sexual function and quality of life in millions of women (Klein et al, 2005; Griffiths et al, 2006; Safarinejad et al, 2009). Vaginal laxity may occur after the first delivery and be made worse with multiparity, delivery of a large fetus, or instrument-assisted delivery.

Peer-reviewed research (Barrett et al, 2000) and market surveys of women and OB/GYNs support the finding that changes in sexual health post-childbirth are not being discussed between physicians and their patients In a quantitative study conducted by the OB/GYN Alliance and sponsored by Viveve, 84% of the 524 gynecologist respondents said vaginal laxity caused by vaginal childbirth was under-reported by their patients. In an online survey conducted by Q & A Research and sponsored by Viveve, only 20% of the 421 women reporting vaginal laxity had discussed this condition with their physicians, even though 63% of the respondents expressed concern with vaginal laxity. One possible reason these discussions are not being initiated by physicians is the lack of a safe, effective and

evidence-based treatment for vaginal laxity (Millheiser et al, 2011).

While surgery can be performed to tighten the introitus, pain at incision lines, fibrosis, and scarring can lead to dyspareunia for months following the procedure. The procedure can be painful and the sutures may cause dense scarring and adhesion formation. After the surgical procedure, recovery time may be up to seven days before the woman can return to employment and other commitments. Resuming intercourse is not recommended for 6-8 weeks after surgery. For the many women who are not good surgical candidates due to health issues or situational limitations on downtime, or their unwillingness to undergo a surgical procedure to improve sexual satisfaction, there is no other option.

The Viveve System utilizes non-ablative radiofrequency (RF) energy to induce a mild, controlled reaction in the submucosal tissues that stimulates the body to deposit collagen, thereby remodeling the introitus tissue without causing dense scarring. It is being evaluated as a non-surgical method to reduce laxity of the vaginal introitus. The safety of the procedure has been demonstrated in sheep studies showing tissue reaction to the treatment. Non-dense collagen deposition was observed at the six months post-treatment biopsy. Additionally, a non-significant risk (NSR) feasibility study involving 24 human subjects has previously been conducted to assess the safety and performance of the Viveve System. The procedure was performed in a physician's office, was well tolerated, and was completed without need for any local or general anesthesia. The women were able to return to work and their routine activities on the same day of the procedure, and to resume sexual intercourse 7-10 days after the procedure (Millheiser et al, 2011).

The primary objectives of this clinical trial were to provide further evaluation of the safety and tolerability of treatment with the Viveve System, as well as the system's performance. Additionally, changes in vaginal laxity and sexual satisfaction, as assessed by patient self-reports at 1, 3 and 6 months after treatment with the Viveve System, were reported. Preliminary results at 3 months post-treatment are presented in this report.

Materials and Methods

The Viveve System is a monopolar radiofrequency system that uses surface cooling and radiofrequency (RF) energy delivery to provide a non-surgical and non-ablative approach to create heat within the submucosal layers of vaginal tissue while keeping the surface cool. During the procedure, coolant is delivered to the membrane of the Viveve treatment tip. The RF technology creates a reverse thermal gradient, which heats the deeper tissue at a higher temperature while the coolant protects the surface epithelium.

The Viveve System was developed using the same technology and mechanism of action as the 510(k) cleared Thermage ThermaCool^{TM} TC System (K013639, cleared 1/29/02). The Viveve System received CE Mark December 07, 2010 and is indicated for treatment of the vaginal introitus, after vaginal childbirth, to improve sexual function.

The patient population targeted for this study were females, between the age of 21-55 years, who had experienced at least one full term vaginal delivery (>36 completed weeks gestation) and delivered at least 12 months prior to enrollment date. Patients included in the study all had some level of self-reported vaginal laxity (self-rated as a 1, 2 or 3 on the 7-point laxity scale described below).

Three highly-trained physician operators performed all of the procedures. The patient was draped and placed on an examining table in the dorsal lithotomy position. A return pad was attached to the patient and RF generator per the Instruction Manual for the Viveve System. A pelvic examination, including a recto-vaginal examination, was performed by the physician to manually assess the recto-vaginal septum and confirm it was adequately thick for the procedure. The vagina, perineum, and perianal area were cleansed using a non-alcohol based cleanser.

The active treatment tip was programmed to deliver 90 J/cm^2. The tip was applied to the mucosal surface of the vaginal introitus behind the hymenal ring starting at 1 o'clock, moving clockwise circumferentially around the introitus. The target area was treated with RF energy pulses at 0.5 cm overlapping intervals by moving the tip in a clockwise direction. Once a pass reached the 11 o'clock position, the first pass was completed; the next pass was initiated again back at the 1 o'clock position. Treatment to the urethral area was avoided. A total of five passes were completed.

A follow-up phone call was made at three days following the procedure, and all patients were asked to return for a pelvic exam at 10 days after the procedure.

At 1 and 3 months post-treatment, as well as at a patient's pre-treatment visit, patients were assessed by physical exam (including vital signs, vaginal examination, urine pregnancy test), as well as by self-report questionnaires. Questionnaires administered included two Likert-type visual analog scale questionnaires for scoring patient-reported vaginal laxity/tightness and sexual satisfaction. Two standard sexual function questionnaires were also administered, the Female Sexual Function Index (FSFI), and the Female Sexual Distress Scale Revised (FSDS-R). At the time of the pre-treatment assessment, patients were also asked to recall their vaginal laxity and sexual satisfaction scores before their vaginal delivery.

For vaginal laxity scores, patients were asked to rate their vaginal laxity/looseness on a scale ranging from 1-

VLQ 1-7 score tool used to measure Vaginal Laxity

SSQ tool (1-5 scale) used to measure Sexual Satisfaction

7. The vaginal laxity response categories corresponding to the numerical code were: Very Tight [7], Moderately Tight [6], Slightly Tight [5], Neither Tight nor Loose [4], Slightly Loose [3], Moderately Loose [2], Very Loose [1].

For sexual satisfaction scores, patients were asked to score their sexual satisfaction from vaginal intercourse on a scale ranging from 0-5. The sexual satisfaction response categories corresponding to the numerical code were: Excellent [5], Very Good [4], Good [3], Fair [2], Poor [1], None [0].

The Female Sexual Function Index (FSFI) is a brief, multidimensional self-report instrument for assessing key dimensions of sexual function in women (Rosen, et al, 2000). It assesses six domains of sexual functioning (sexual desire, arousal, lubrication, orgasm, satisfaction, pain), but is not a measure of sexual experience, knowledge, attitudes, or interpersonal functioning in women. Possible domain scores range from 0 to 6, and total scores range from 2 to 36, with higher scores representing a higher level of sexual function. The Female Sexual Distress Scale-Revised (FSDS-R) is another validated screening questionnaire, used for measuring sexual related personal distress in women with Female Sexual Dysfunction (FSD). The FSDS-R has a range of scores possible from 0 (no distress) to 52 (maximum distress).

For analysis of vaginal laxity and sexual satisfaction scores, data were normalized by setting each patient's pre-treatment score as a baseline, and reporting changes relative to that time point. For significance analysis, paired Students t-tests were performed to compare scores at different time points relative to pre-treatment.

Results

Enrollment and Procedure

Thirty patients who met the inclusion/exclusion criteria and signed the informed consent were enrolled between January and June, 2011. The average age of the enrolled women was 42.9 years, with the youngest patient 30 and the oldest 52. Average height of the 30 patients was 62.0 ± 2.2 inches (mean ± standard deviation) and the average weight 112 ± 27 pounds. All 30 patients had prior vaginal deliveries with a total of 65 vaginal full-term deliveries among them, which represented a 2.2 vaginal delivery rate per patient. Among the 65 deliveries, 25 (38%) involved an episiotomy or laceration intervention.

All procedures were administered using a total of 100 pulses at 90J/cm^2 and five passes. All procedures were successfully completed without device or patient related issues, and the average treatment time was 26 minutes (range 20-30 minutes).

During the procedure, all subjects felt warmth, whether sporadic or continuous, or coolness. The sensation of pain/discomfort was scored on a visual analog scale from 0-10, with 0 being no pain and 10 intolerable pain. The average pain score reported by these 30 patients was 1.7 (min 0; max 7.7). One patient (3%) had a pain score of 7.7, three patients (10%) reported pain between 4 and 5, three patients (10%) reported pain between 3 and 4, with the remaining 23 patients (77%) reporting a pain level < 3. In all cases, the procedure was continued with no medical intervention required.

Response at 3 and 10 Days Post-Treatment

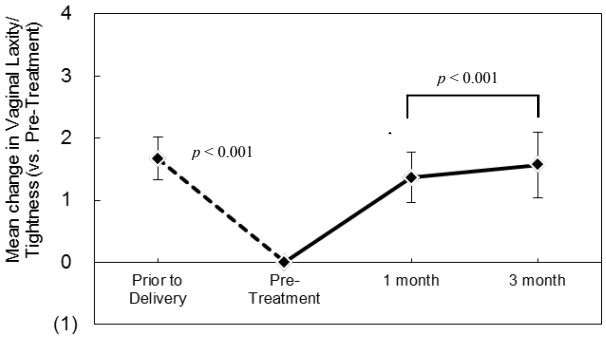
At the three-day evaluation, all subjects reported they had returned to their routine activities even though one patient reported slight abdominal pain and another reported increased vaginal leukorrhea (white discharge). For these two patients, no intervention was required and both conditions were resolved by the 10-day evaluation.

Response at One and Three Months

At one month post-treatment, no adverse events were reported. At three months post-treatment, one patient developed vaginitis, which the clinical physician believes to be unrelated to the treatment with the Viveve System. The patient was treated with prescribed medication and the condition resolved.

Vaginal laxity scores from the Likert-type questionnaires are presented in Figure 1, averaged for all 30 Japan patients. The pre-treatment score was designated the control interval, and each patient's change in laxity at pre-delivery and post-treatment time points was calculated relative to her pre-treatment value. Figure 1 reports those mean changes, with error bars representing mean 95% confidence intervals.

Figure 1: Mean Change in Vaginal Laxity Scores.



At the time of screening, patients were asked to rank their current (pre-treatment) level of vaginal tightness, as well as to recollect their level of vaginal tightness before vaginal delivery. As Figure 1 shows, the mean change in

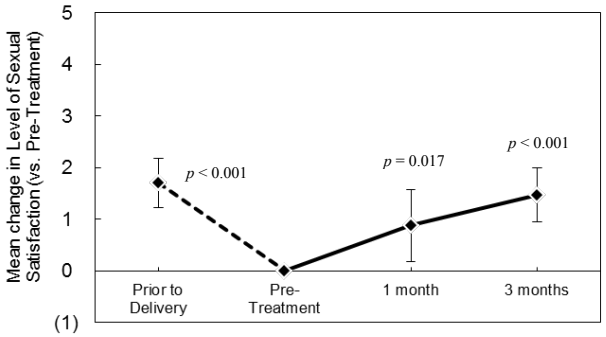
patient-reported vaginal laxity/looseness following childbirth (between prior to delivery and pre-treatment time points) was a decrease of 1.7 points. The mean improvements in vaginal laxity/looseness following treatment were 1.4 and 1.6 points at one and three months post-treatment, respectively. These improvements represented a restoration in the average patient-reported vaginal tightness to near pre-delivery levels, with statistical significance ($p < 0.001$).

Importantly, 77% of the subjects reported some degree of improvement in vaginal laxity/looseness following treatment at three months post-treatment.

Sexual satisfaction scores from the Likert-type questionnaires were also analyzed at one and three months post-treatment. Prior to treatment at the time of screening, patients reported an average sexual satisfaction score of 1.9. This contrasted to their recollection of sexual satisfaction levels before childbirth, which were reported at the time of screening to be an average of 2.7. One month and three months after treatment, average score rose back up to 2.4 and 2.6, respectively ($p = 0.005$ at 3 months post-treatment).

While almost every patient (28/30) in the study reported a decrease in vaginal tightness following childbirth, not every patient enrolled experienced a drop in sexual satisfaction concomitant with that decrease in vaginal laxity. Therefore, the cohort of 17 patients who reported a decrease in sexual satisfaction following childbirth was separated out and analyzed. Figure 2 illustrates the change in mean sexual satisfaction scores over time for these 17 patients, with error bars representing mean 95% confidence intervals. These comparisons again assume the pre-treatment score as the control interval to which to changes are compared.

Figure 2: Mean Change in Sexual Satisfaction Scores for the 17-Patient Cohort with a Drop in Sexual Satisfaction after Childbirth.



As Figure 2 shows, the 17 patients who reported a drop in sexual satisfaction following childbirth reported an average decrease of 1.7 points following delivery (between prior to delivery and pre-treatment). One month post-treatment, the average improvement in sexual satisfaction scores was 0.9. By three months post-treatment, the average improvement in sexual satisfaction score increased to 1.5 points higher than pre-treatment, nearly restoring those patients to pre-childbirth levels. At three months post-treatment, this change was statistically significant ($p < 0.001$).

The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale Revised (FSDS-R) were administered to capture any potential adverse effects on sexual function and sexual health. Table 1 below presents the FSFI six domain average scores and overall score, as well as FSDS-R scores, at time of screening and one and three months after treatment. Scores presented are averages across all patients, with *p*-values calculated using paired Students t-tests to compare each patient's post-treatment scores to that patient's pre-treatment scores.

Table 1: Pre- and Post-Treatment FSFI and FSDS-R Mean Scores

Questionnaire Domain	Pre-Tx (n= 30)	1 month (n = 30)	*p*-value	3 months (n = 30)	*p*-value
FSFI					
Desire	3.3	3.0	0.03	3.1	0.14
Arousal	3.2	3.2	0.89	3.7	0.02
Lubrication	4.5	4.7	0.36	5.0	0.07
Orgasm	3.4	3.8	0.13	4.4	<0.01
Satisfaction	3.6	4.1	0.05	4.5	<0.01
Pain	4.5	5.1	0.09	5.3	0.02
FSFI Overall	**22.4**	**23.9**	**0.19**	**26.0**	**<0.01**
FSDS-R	**15.8**	**9.8**	**<0.01**	**8.9**	**<0.01**

As Table 1 shows, all six FSFI domains except for Desire were trending positively over time; that is, there was an improvement in average one- and three-month scores compared to the screening (pre-treatment) scores. (For each domain, including Pain, improvement is represented by an increase in that domain score.) At one month post-treatment, only the average changes in Desire and Satisfaction scores were found to be marginally significant ($p = 0.03$ and 0.05, respectively). At three months post-treatment, improvements in orgasm, satisfaction and overall scores were found significant ($p < 0.01$), with improvements in arousal and pain marginally significant ($p = 0.02$).

The FSDS-R data indicate that there was an improvement in scores (less sexual distress) from an average score of 15.8 before treatment, to 9.8 and 8.9 at one and three months after treatment. These changes were calculated to be statistically significant at both one and three months post-treatment ($p < 0.01$).

Conclusion

These preliminary results indicate that the VS was well tolerated and demonstrated that this nonsurgical procedure offers the potential to reduce vaginal laxity

and improve sexual satisfaction. This study remains open to follow-up out to six months.

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VIVEVE, INC.®

Corporate Headquarters
450 Sheridan Avenue
Palo Alto, CA 94306
(650) 321-3332 Corporate Office
(650) 326-0114 FAX