

Evaluation of the Safety and Efficacy of Hybrid Fractional 2940 nm and 1470 nm Lasers for Treatment of Vaginal Tissue: Pilot Study

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INTRODUCTION

Vaginal delivery is the most common form of childbirth but it has been associated with increased risk of developing pelvic floor disorders later in life, such as urinary incontinence (UI) ¹. Urinary incontinence is the involuntary leakage of urine, and about 50% of women with UI report symptoms of stress urinary incontinence (SUI), a form of UI that is synchronous with sneezing, coughing, exercise, or other physical activity ². After delivery, collagen and elastin synthesis help repair trauma to pelvic floor tissues; however, newer tissue is weaker due to defects in the reparative processes ¹. Additionally, as a woman's body ages, decline in estrogen levels cause the vaginal mucosa to become thinner and dry, while collagen in the lamina propria is gradually lost ³. The declining condition of the vagina frequently leads to symptoms, such as dryness, decreased feelings of friction, loss of sexual satisfaction during sexual intercourse by women and their partners, or dyspareunia ³.

The Er:YAG (erbium-doped yttrium aluminum garnet) laser emits infrared light with a wavelength of 2940 nm, and this ablative wavelength is strongly absorbed in water. The 1470 nm wavelength is a non-ablative wavelength used for coagulation. Fractional delivery of both 2940 nm and 1470 nm lasers is a well-established method of skin rejuvenation that causes collagen

remodeling while leaving surrounding healthy tissue intact and unaffected in order to decrease healing time. Similarities between the epidermis of skin and vaginal mucosa may suggest that the clinical results seen with skin rejuvenation can be translated to vaginal tissue. This study was designed to evaluate the safety and efficacy of hybrid fractional ablative 2940 nm and non-ablative 1470 nm lasers for treatment of vaginal tissue in premenopausal women.

MATERIALS AND METHODS

Subjects

Healthy premenopausal women between the ages of 25 to 50 were enrolled in the open label study of four months duration. Inclusion criteria included having a history of at least one vaginal delivery at least six months prior to enrollment, self-reported vaginal laxity, and regular sexual activity with a monogamous heterosexual partner. The following exclusion criteria were adopted: previous pelvic floor reconstructive surgery, having more than Grade I prolapse using the Baden-Walker Halfway Scoring System in any vaginal compartment, pregnant or lactating, not using a medically approved method of contraception, use of vaginal topical estrogen within one month prior to enrollment, acute or recurrent urinary tract infections, active sexually transmitted diseases, use

¹ Memon HU, Handa VL. *Vaginal childbirth and pelvic floor disorders*. Women's Health (London, England). 2013; 9(3):10.2217/whe.13.17. doi:10.2217/whe.13.17.

² Reynolds WS, Dmochowski RR, Penson DF. *Epidemiology of stress urinary incontinence in women*. Curr Urol Rep. 2011 Oct; 12(5):370-6.

³ Castelo-Branco C, Canelo, MJ, Villero J, Nohales F, Julia MD. *Management of post-menopausal vaginal atrophy and atrophic vaginitis*. Maturitas. 2005; 52 Suppl 1:S46-52.

of vaginal topical antibiotics or antifungal agents within one week prior to enrollment, any medical condition that would interfere with wound healing, known collagen disorder, known vascular disease, scleroderma, history of immunosuppression, history of bleeding disorder, significant concurrent illness such as diabetes, use of medications known to affect sexual function, and clinically significant anxiety, depression, or psychosexual disorder⁴.

Laser System

The laser system used was the JOULE™ (Sciton, Inc, Palo Alto, CA, USA), which delivers hybrid fractional 2940 nm and 1470 nm wavelengths through the diVa™ vaginal handpiece. The system is tunable to deliver between 100 to 800 µm of 2940 nm laser at 0, 7, or 14% density and between 200 to 700 µm of 1470 nm laser at densities that vary depending on depth. Treatment can be delivered 360-degrees around the vaginal canal or targeted to specific regions using the 180-degrees or 90-degrees treatment angles.

Vaginal Manometer

The vaginal manometer used was the InTone™ (InControl Medical, Brookfield, WI, USA), which has a pressure sensor built into the insertion unit to measure pressure exerted by the vagina with relaxed pelvic floor muscles in pound per square inch (psi). The number of inflation pumps until 2.0 psi was recorded at each study visit to assess resting vaginal tone.

METHODS

After subject screening using the inclusion/exclusion criteria, informed consent, medical history, and OB/GYN history were obtained. At each study visit, subjects completed a Female Sexual Function Index (FSFI) questionnaire, International Consultation on Incontinence Short Form (ICIQ SF) questionnaire, and a self-reported laxity rating on a 7-point scale with higher

numbers corresponding to greater vaginal laxity. Then, subjects provided a urine sample for pregnancy test and urinalysis before undergoing pelvic examination and assessment of pelvic support graded on the Baden-Walker scoring system, physician-reported laxity rating on a 4-point scale, vaginal pH test, and InTone measurement before receiving laser treatment.

A protocol of three laser treatments performed at 4 – 6 week intervals was adopted and used⁵. Treatment discomfort was assessed using the Numeric Pain Rating Scale (NPRS) during insertion of the diVa device and during treatment. Diaries were dispensed and patients instructed as to their completion. Follow-up (FU) examination occurred one month after all three treatments were completed. FSFI and ICIQ SF scores and self-reported laxity ratings were collected at one month and eight months after treatment completion for final evaluation. Patient sexual partners provided vaginal laxity ratings on the same 7-point scale before each study visit. Biopsies were collected from two volunteers during the first study visit before laser treatment and at one month FU. Tissue samples were assessed by two pathologists blinded as to which slides had the before and after sample.

Safety was assessed in terms of adverse events. Efficacy criteria were assessed by:

1. Change from baseline in FSFI scores. This index allows for scoring of desire, arousal, lubrication, orgasm, satisfaction, and pain during intercourse (dyspareunia); but only lubrication, orgasm, and pain domains were assessed⁶.
2. Change from baseline in ICIQ SF scores. This questionnaire is a subjective 4-item measure of severity of stress urinary incontinence and quality of life⁷. Change from baseline in vaginal pH.
3. Change from baseline in vaginal pH.

⁴ Persu C, Chapple C, Cauni V, Gutue S, Geavlete P. *Pelvic Organ Prolapse Quantification System (POP-Q)* – a new era in pelvic prolapse staging. *Journal of Medicine and Life*. 2011;4(1):75-81.

⁵ Salvatore S, Nappi RE, Zerbinati N, Calligaro A, Ferrero S, Origoni M, Candiani M and Leone Roberti Maggiore U. *A 12-week treatment with fractional CO2 laser for vulvovaginal atrophy: a pilot study*. *Climacteric*. 2014; 17:363-369.

⁶ Rosen R, et al. *The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function*. *Journal of Sex and Marital Therapy*. 200; 26(2): 191-208.

⁷ Raad J. *Rehab Measures: International Consultation on Incontinence Questionnaire – Short Form*. Rehabilitation Measures Database Web site. <http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1020> Published Aug. 2, 2012. Updated Dec. 4, 2013. Accessed May 31, 2016.

4. Change from baseline in number of InTone inflation pumps until 2.0 psi is reached.
5. Change from baseline in partner-reported vaginal laxity rating.
6. Change from baseline in subject-reported vaginal laxity rating.
7. Change from baseline in physician-reported vaginal laxity rating.
8. Change from baseline in histology.

RESULTS

Twenty women were enrolled, 2 withdrew, and 18 were analyzed. Mean age was 41 ± 4.3 years and the majority were Caucasian.

Safety

There were no complications during the study or since the study was completed. Mean treatment discomfort was 0 during insertion of the device and an average of 3 out of 10 during laser treatment.

Efficacy Measures

Comparison of the mean efficacy measures over the study duration, *Table 1*, showed improvement in FSFI scores; lubrication, orgasm, and pain during intercourse sub-scores; and ICIQ SF scores. Vaginal pH, InTone inflation pumps, subject-reported laxity ratings, partner-reported laxity ratings, and physician-reported laxity ratings decreased over time.

Table 1. Mean Efficacy Measures Over Study Duration (n = 18)

Study Visit	1	2	3	4 (1 mo FU)	5 (8 mo FU)
FSFI Scores Mean \pm SD	19.0 ± 5.2^a	24.8 ± 4.0^a	25.8 ± 5.5^a	26.2 ± 4.9^a	28.0 ± 4.8^a
Lubrication Sub-Score Mean \pm SD	3.4 ± 1.2^a	4.7 ± 1.2^a	5.2 ± 1.2^a	5.0 ± 1.4^a	5.4 ± 1.0^a
Orgasm Sub-Score Mean \pm SD	3.2 ± 1.4^a	4.4 ± 1.3^a	4.2 ± 1.7^a	4.5 ± 1.6^a	4.9 ± 1.4^a
Pain Sub-Score Mean \pm SD	4.5 ± 1.0^a	5.3 ± 0.7^a	5.7 ± 0.4^a	5.7 ± 0.4^a	5.7 ± 0.7^a
ICIQ SF Score Mean \pm SD	5.2 ± 4.6^b	4.9 ± 5.1^b	3.5 ± 4.4^b	2.6 ± 4.7^b	3.3 ± 4.7^b
Vaginal pH Mean \pm SD	4.8 ± 0.6	4.9 ± 0.2	4.6 ± 0.5	4.7 ± 0.5	-
Inflation Pumps Mean \pm SD	9.8 ± 1.6	8.9 ± 2.3	8.5 ± 1.6	9.1 ± 1.7	-
Subject-Reported Laxity Rating Mean \pm SD	3.7 ± 0.9	2.9 ± 1.3	3.1 ± 0.9	2.4 ± 1.4	2.3 ± 1.4
Partner-Reported Laxity Rating Mean \pm SD	3.2 ± 1.0	2.3 ± 1.1	2.1 ± 1.0	2.1 ± 1.1	-
Physician-Reported Laxity Rating Mean \pm SD	1.8 ± 0.5	1.7 ± 0.6	2.0 ± 0.6	1.4 ± 0.5	-

^a n = 11; subjects with sexual dysfunction at enrollment (FSFI scores ≤ 26.55)

^b n = 12; subjects with urinary incontinence at enrollment (ICIQ SF scores > 0)

A FSFI score of less than or equal to 26.55 is classified as female sexual dysfunction (FSD)⁶. Initially, 11 subjects were classified with FSD ($n = 11$), but at one month FU there were only 5 subjects ($n = 5$) and at the eight month FU there were only 3 subjects ($n = 3$) still classified with FSD. In other words, 73% of all subjects diagnosed with FSD were resolved with clear indication of improvement even eight months after treatment. Overall, of the subjects with FSD, there was a 38% increase in mean FSFI score by one month FU and 47% increase by eight month FU. The increase in mean sub-scores for the lubrication and orgasm domains indicate subjects saw improvement in the ability to become naturally lubricated and achieve orgasm during intercourse. Increase in pain sub-scores indicates an improvement in comfort, or decrease in pain, experienced during intercourse.

Only 12 subjects had symptoms of SUI at the onset of the study. The average ICIQ SF scores decreased by 50% at the one month FU, indicating a decrease in severity of SUI. With

further delineation, of the subjects with slight/mild incontinence ($n = 9$) or moderate incontinence ($n = 1$), eight ($n = 8$) reported complete resolution of incontinence (80%) at one month FU and five ($n = 5$) still had complete resolution at eight month FU. The mean vaginal pH values decreased slightly but were all within the normal range.

HISTOLOGICAL ASSESSMENT

Mean epithelial thickness was determined by obtaining 10 measurements from each sample slide. Histological assessment showed evidence of an increase from a mean of $320 \pm 26 \mu\text{m}$ to $434 \pm 38 \mu\text{m}$, *Figure 1*. At higher magnification, there was a change from loose, haphazard collagen before treatment to denser collagen with horizontal streaming after treatment, *Figures 2, 3*. Fibroblasts were greater in number and more activated after treatment with larger nuclei and open chromatin. Vascularity was more notable with endothelial enlargement in the superficial lamina propria and small vessels appeared more stented open, suggesting increased blood flow to the tissues.

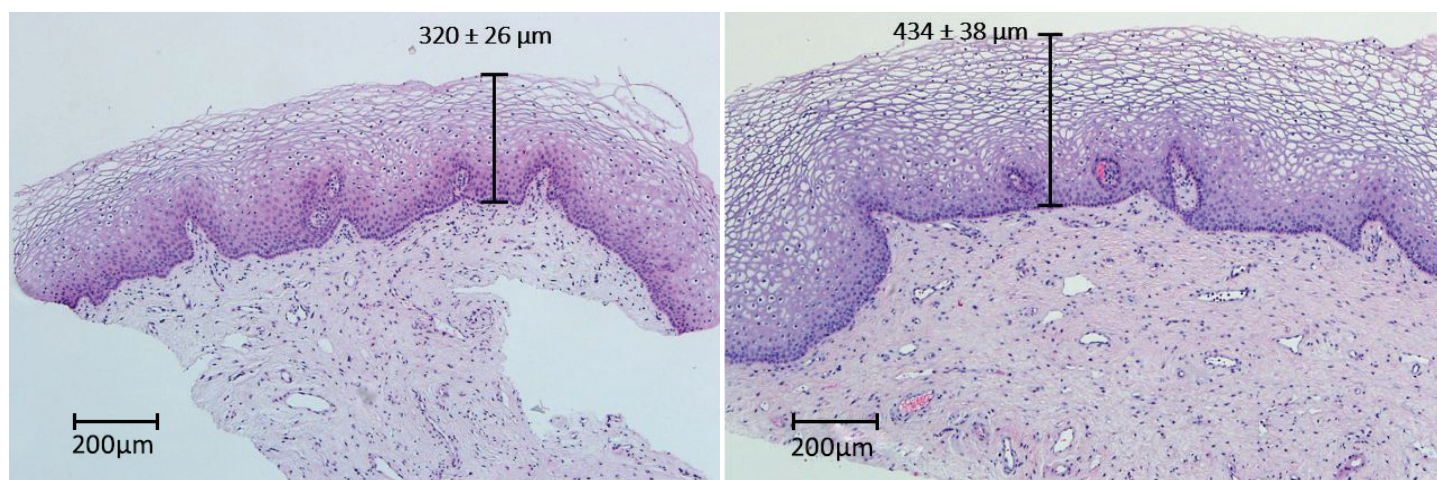


Figure 1. Hematoxylin and Eosin (H&E) stained vaginal mucosa at baseline before laser (left) compared to one month after treatment (right) showed increase in epithelial thickness.

⁶ Rosen R, et al. *The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function*. Journal of Sex and Marital Therapy. 2000; 26(2): 191-208.

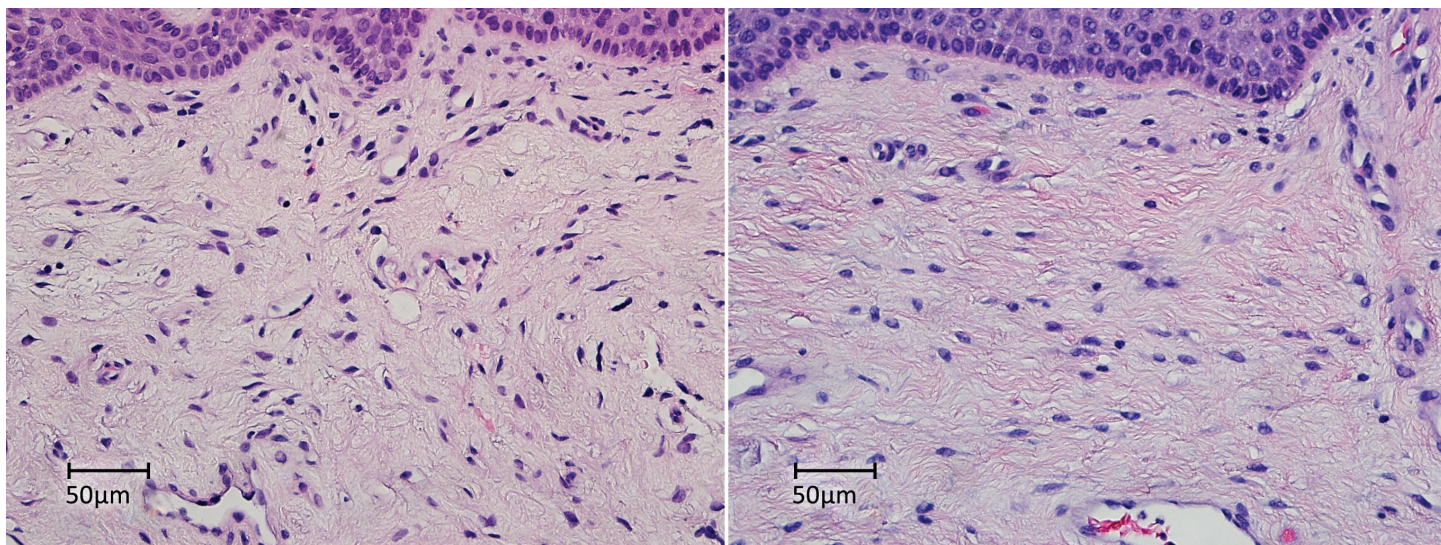


Figure 2. H&E stained lamina propria at baseline before laser (left) compared to one month after treatment (right) showed increased density of collagen with horizontal streaming.

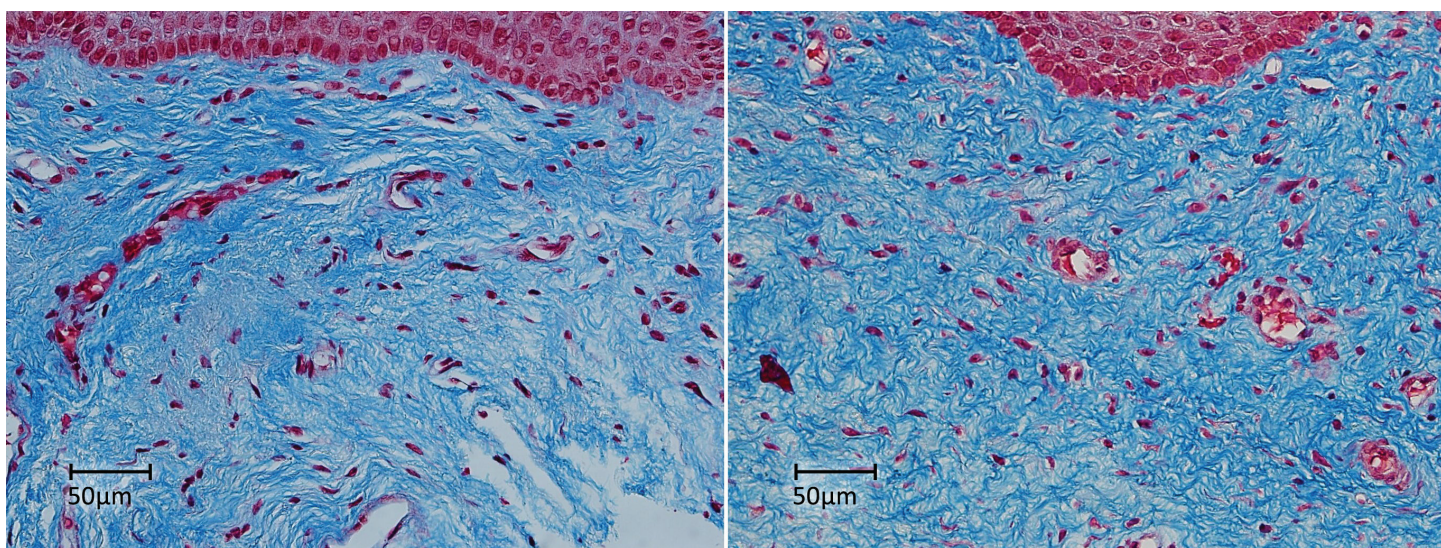


Figure 3. Masson's trichrome stained lamina propria at baseline before laser (left) compared to one month after treatment (right) showed increased density of collagen, active fibroblasts, and vascularity.

SUBJECT SATISFACTION WITH TREATMENT

Satisfaction with treatment results was subjectively evaluated by the subjects at follow-up, *Figure 4*. Eighty-eight percent of the subjects rated their level of satisfaction to be moderate, high, or very high. Only two patients had low satisfaction.

Subject Satisfaction with Treatment Results

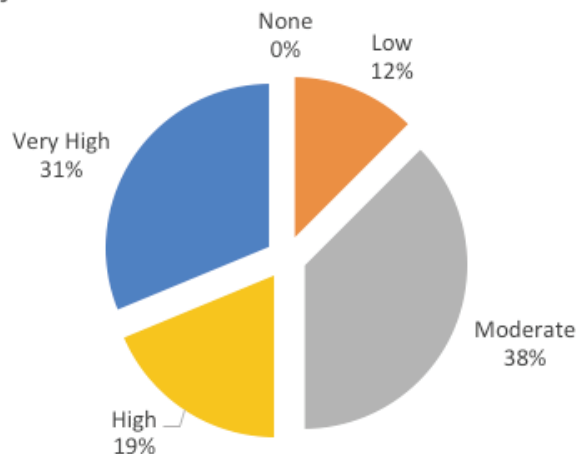


Figure 4. Subjective subject satisfaction with treatment results.

DISCUSSION

Assessment of the microscopic changes in histology is key in understanding the mechanisms of action behind the clinical evidence, specifically the improvement in FSFI scores with regard to lubrication and pain. Thickening of the epithelial layer increases cell redundancy and allows for more layers of glycogen-filled cells, which provide lubrication and decrease pain with intercourse. Increased vascularity in the connective tissue layer would bring more blood flow to the tissues, also improving lubrication and sensitivity.

Increases in collagen and elastin in the lamina propria surrounding the vaginal mucosa would ultimately lead to increased vaginal canal tightening and improved elasticity. This was suggested by a decrease in the number of inflation pumps needed to reach 2.0 psi and decreases in vaginal laxity scores as measured by the clinicians, patients and their sexual partners. As vaginal laxity decreases and elasticity increases, there is more physical contact, friction and sensation during intravaginal intercourse.

Thus, there were improvements in the ability to reach orgasm and in overall sexual function.

The ablated microchannels located beneath the urethra and bladder neck essentially fill with collagen during the healing process. Collagen provides support for the urethra. With increased vascularity in the tissues, a thicker vaginal epithelium and new collagen formation all beneath the urethra, it follows that patients would experience an improvement in urinary control.

Both the 2940 nm and 1470 nm wavelengths were selected due to their high absorption in water, the main chromophore in human mucosal tissue. Unlike the CO₂ (carbon dioxide) laser, which is not as highly absorbed in water as Er:YAG and is known to leave a layer of necrosed tissue surrounding an ablated microchannel, the combination of both 2940 nm and 1470 nm allows creation of a very controlled column of ablation surrounded by a tunable layer of coagulation. Fractional delivery is meant to decrease the length of time before re-epithelization of the mucosa.

Currently, short-term follow-up limits the understanding of the duration of the clinical effects of the treatment. Histological assessment confirmed that neocollagenesis was active at the one month follow-up after the completion of three treatments. In dermatology, collagen remodeling is still present in skin three months after fractional resurfacing, which may translate to long-term effects in vaginal tissues⁸.

CONCLUSION

This study showed that three hybrid fractional 2940 nm and 1470 nm laser treatments spaced four weeks apart are safe and effective for treatment of premenopausal vaginal tissue. Treatment induced the clinical effects of improved vaginal tone, decreased stress urinary incontinence, decreased vaginal laxity, and improved sexual function; specifically, with regard to improved lubrication, enhanced ability to reach orgasm, and decrease in pain with intercourse. No adverse events were reported. Further studies are needed to evaluate efficacy in postmenopausal patients and to optimize treatment protocols.

⁸Longo C, Galimberti M, De Pace, B, Pellacani G, Bencini PL. *Laser skin rejuvenation: epidermal changes and collagen remodeling evaluated by in vivo confocal microscopy*. *Lasers Med Sci*. 2013 May; 28(3):769-76.

DISCLAIMER

Sciton is the manufacturer of the diVa device and has a financial interest in the diVa device. Some or all uses of the diVa device described in this information have not been cleared by the FDA to treat or improve: female sexual dysfunction, female sexual arousal disorder, female orgasmic disorder, hypoactive sexual desire disorder, vaginal dryness, ability to orgasm, pain during intercourse, vaginal laxity, or stress urinary incontinence.

The clinical trials were funded by Sciton.