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Non-ablative Er:YAG laser therapy effect on stress urinary incontinence related to quality of life and sexual function: A randomized controlled trial

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ABSTRACT

Objective: Stress urinary incontinence (SUI) is a common complaint in women after childbirth. It affects their quality of life and sexual satisfaction and is one of the major reasons for gynaecological surgery. There is a need for effective non-invasive treatment alternatives. The aim of this study was to evaluate the efficacy and safety of non-ablative Er:YAG laser therapy in the treatment of SUI and improvement of sexual gratification in parous women.

Study design: 114 premenopausal parous women with SUI were randomized in two groups of 57 women; a laser intervention group and sham group. Both groups were treated according to the IncontiLase® clinical treatment protocol for SUI with non-ablative thermal-only Er:YAG laser, except that there was no energy output when treating the sham group. Patients were blinded to the allocation. At baseline and 3 months after treatment patients were clinically examined, answered questionnaires for SUI severity and sexual function assessment and their pelvic floor muscle (PFM) function was assessed with perineometry. Validated International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) was used as the primary outcome measure. The Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire short form (PISQ-12) and The Female Sexual Function Index (FSFI) were used to assess the sexual function. Patients were monitored for discomfort and side-effects during treatment and follow-up period.

Results: 3 months after treatment the ICIQ-UI SF ($p < 0.001$), PISQ-12 ($p = 0.014$) and FSFI ($p = 0.025$) scores were significantly more improved in the laser group than in the sham control group. All perineometry variables improved in the laser group after treatment; duration and maximum pressure had statistically significantly better improvement than the sham group, whereas average pressure did not. 21% of laser treated patients were dry (ICIQ-UI SF = 0) at follow up compared to only 4% of the sham control patients. No serious adverse effects were observed or reported. The treatment was well tolerated by patients.

Conclusions: The non-ablative Er:YAG laser therapy improves the impact of SUI symptoms on quality of life and sexual function in premenopausal parous women significantly better than placebo. It provides a promising minimally-invasive safe treatment alternative for SUI.

Introduction

Female stress urinary incontinence (SUI) is a significant public health problem, with estimated prevalence rates of 4–35% of adult women [1,2]. SUI is attributed to anatomical defects in the structures that support the bladder and urethra. Consequently, the urethra is not closed off properly during exertion, resulting in leakage [2]. Age, pregnancy, labor, and vaginal delivery are significant risk factors. Urinary incontinence (UI) has been found to reduce both social interactions and physical activities and is associated with poor self-rated health, impaired emotional and psychological well-being and impaired sexual relationships [2].

Conservative management of SUI consists of pelvic floor muscle training (PFMT) which requires a high level of patient compliance

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as long term regular and correct performance of exercises is necessary to achieve results [2]. A variety of effective surgical procedures are available, but they are linked to a significant downtime and complication rate [3,4]. Time to normal activity is 2–5 weeks after mid-urethral sling procedures; perioperative complications occur in around 12% of patients, major vascular/visceral injury in 0.4–2%, bladder perforation in 0.6%–4.9%, postoperative voiding dysfunction 3.8–7.2%, de novo urgency in around 8%, vaginal tape erosion in around 2%, and repeat incontinence surgery within 1 year in 1.9–3.1% of patients [4]. There is a need for effective non-surgical options with good patient acceptance.

Altered collagen/elastin in the vaginal connective tissue may result in loose origins or insertions of the striated muscles involved in the pelvic floor closure mechanisms, preventing their isometric contraction, and therefore efficient functioning of the closure, causing stress incontinence [5]. Collagen content is diminished in incontinent women [6,7]. Temporarily increasing the temperature of collagen induces collagen shrinkage [8,9] and initiates neocollagenesis [10,11], leading to the contraction and shrinkage of the irradiated bulk tissue and an overall improvement of its tightness and elasticity. This prompted the idea that laser-mediated heating of the pelvic floor tissue could improve the support structures, ensure that the tension developed by the active contraction of the pelvic floor muscles (PFM) is smoothly transmitted, and represent an effective non-surgical method for treating female UI and other disorders resulting from diminished pelvic floor support [12].

Several pilot studies have been published testing this concept [11,13–16]. Histological study of vaginal wall biopsies before and after non-ablative Er:YAG laser SUI treatment showed signs of neocollagenesis, elastogenesis, neoangiogenesis, reduction of epithelial degeneration and atrophy, and an increase of the fibroblast population after laser treatment [11]. SUI was successfully improved with non-ablative vaginal Er:YAG laser treatment with concomitant improvement in sexual satisfaction [13–16]. However, these pilot studies lacked a control group.

The aim of this study is to evaluate the efficacy of non-ablative vaginal Er:YAG laser therapy for treatment of SUI by comparing it with a sham laser treatment in a patient-blinded randomized controlled trial.

Materials and methods

The study protocol was approved by the National Medical Ethics Committee of Republic of Slovenia (No.152/08/12) and registered at ClinicalTrials.gov (#NCT03296241). The study was conducted in accordance with the protocol.

Power analysis was based on the proportion of patients expected to be dry (ICIQ-UI SF score = 0) after treatment in each group. Based on the expected cure rate in the sham group of 5% and the laser group of 30% 3 months after treatment, we calculated that we would need 54 patients per group to give 90% power to detect the difference with a chi-square test at two-sided $\alpha = 0.05$. No pilot sham-controlled studies of vaginal laser treatment were available so estimates of the cure rates were based on our preliminary experience and controlled PFMT trials [2]. 6 additional patients were recruited to account for uncertainties in effect size estimation and loss during follow up.

From August 2012 to May 2013 female patients presenting at the Division of Gynecology and Obstetrics, University Medical Centre Ljubljana, Slovenia, with a complaint of UI were screened for inclusion in the study (Fig. 1). Premenopausal (age range 35–65 years), sexually active women with at least one vaginal delivery and a diagnosis of SUI who signed informed consent were included in this study. Clinical examination, a cough test (stress test), a Q-tip test, and urodynamic analysis were conducted during initial consultation. Exclusion criteria were pelvic organ prolapse (POP) greater than stage I (according to POP-Q classification), inability to perform correct pelvic floor muscle (PFM) contraction, urgency or mixed UI, infection, and previous gynecologic surgery or irradiation. Correct PFM contraction was assessed with a one finger vaginal palpation by trained and certified physiotherapists specialized in rehabilitation of pelvic floor defects.

114 patients were included in the study and randomized (1:1) by random drawing of sealed envelopes into one of the two groups; laser or sham group. Patients and the personnel conducting

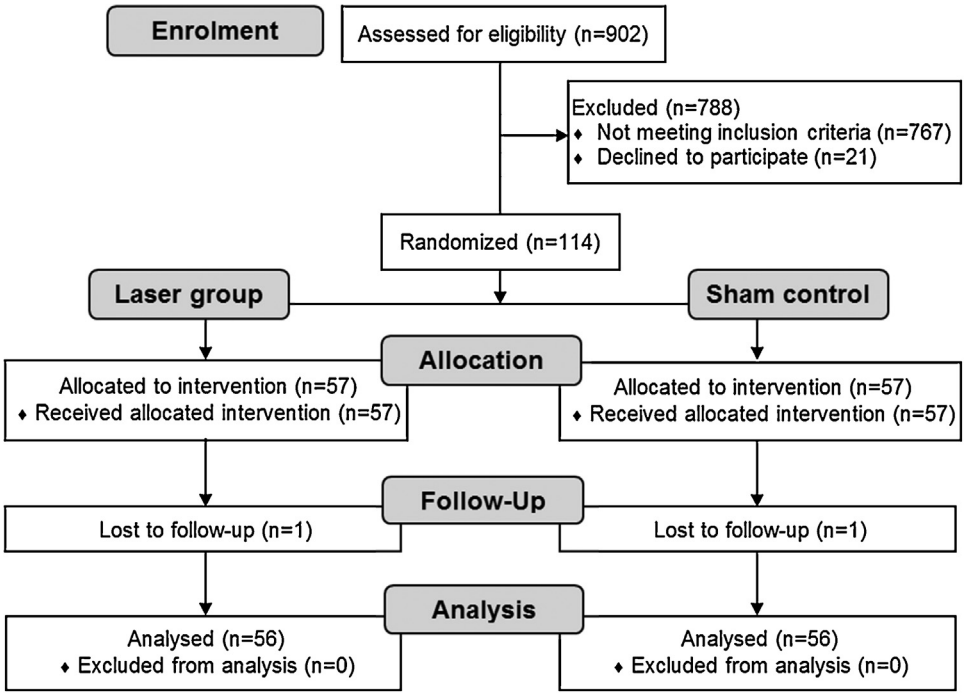

Fig. 1. CONSORT flow diagram of the progress of patients through the phases of this randomized controlled trial.

outcome measurements were blinded to the allocation. The gynecologist preforming the treatment could not be blinded.

All patients of both groups were submitted to a single session with non-ablative 2940 nm Er:YAG laser (XS Dynamis, Fotona, Slovenia). Laser group was treated according to the manufacturer's IncontiLase® protocol described below; receiving therapeutic laser irradiation dosage with 10 J/cm^2 fluence, 7 mm spot size, and non-ablative thermal SMOOTH® pulses. The sham group was treated with the same procedure but with zero intensity settings, without receiving therapeutic irradiation. All patients were asked to rate the tolerability of treatment on a five-point scale (1-poor, 2-fair, 3-good, 4-very good, 5-excellent).

A wire speculum was introduced into the vaginal canal enabling handpiece insertion without touching the vaginal wall. The introitus was anesthetized with lidocaine spray. First, the PS03 pixelated handpiece with an angular adapter was used to irradiate the anterior vaginal wall. Four laser pulses were deposited at every 5 mm along the total length of the vagina in five passes. Second, the R11 full beam handpiece with a circular adaptor was used to irradiate the whole vaginal canal in three passes. Finally, the speculum was removed and the mucosa of the vestibule and the introitus was irradiated with the PS03 with a straight adapter. The aim of the procedure was to thoroughly heat these areas and thus induce collagen shrinkage and neocollagenesis.

Outcome assessment at baseline and 3 months after treatment included clinical examination, perineometry, and 3 questionnaires. A validated Slovenian translation of the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) [17,18] was used as a brief and robust method to assess the degree of SUI and its impact on quality of life, and served as the primary outcome measure. The ICIQ-UI SF score is divided into the following severity categories [19]: slight (1–5), moderate (6–12), severe (13–18) and very severe (19–21). These categories were used to group patients based on baseline SUI severity for post-hoc subgroup analysis.

Sexual function was assessed with two validated questionnaires. The Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire with 12 questions (PISQ-12) is a condition specific questionnaire focused on sexual function in women with POP and/or UI [20,21]. The PISQ-12 has a maximal score of 48, the mean score in a population of sexually active women without bothersome POP or UI was 40 [20]. The Female Sexual Function Index (FSFI) is a generalized questionnaire utilized to assess sexual function in women in a general population. The FSFI consists of a 19-item survey assessing six domains of female sexual dysfunction (FSD). Scores range from 2 to 36, with a total score of 26 or less suggestive of FSD and individual domain scores of less than 3.6 abnormal [22].

Perineometry was conducted with Myomed 632 perineometer (Enraf Nonius, Delft, The Netherlands), which shows good test-retest intra-rater reliability [23]. The measurement protocol was previously described [23]. The women were tested in supine position with the knees bent and legs slightly apart. The participants were asked to perform eight PFM contractions with a holding period of 10 s with 10 s rest between each contraction. The variables measured were maximal and average contraction pressure in hPa and mean muscle endurance (stamina) in seconds. The participants were not taught, encouraged or discouraged to perform PFMT during the study period. The resulting potential confounding is accounted for by comparing the results in the laser group against the sham control group.

The R package "PROscorer" *fsfi* function [24] was used to calculate the 6 subscale scores and the FSFI Total score for all patients. Strong evidence suggests that FSFI may not be a valid measure of sexual function in women with little or no recent sexual activity [25], and the *fsfi* function also calculates whether respondents have been sufficiently sexually active for the FSFI to be a valid assessment of their sexual function. This evaluation is based on the fact that 15 of the 19 FSFI items have a response option of "no sexual activity" or "did not attempt intercourse", which corresponds to an item score of 0. A respondent is considered sufficiently sexually active for the FSFI to be a valid assessment of their sexual function when the number of items with responses of 0 or NA out of these 15 items is less than or equal to 7. Missing responses are included in this count because respondents with no relevant sexual activity often skip these items. See [25] for more details on how the cutoff was chosen. 54/56 patients in the laser group and 52/56 patients in the sham group were sufficiently sexually active at both assessment times according to the above criteria and are included in the analysis of FSFI scores.

The outcome measures were compared between the laser and sham control groups with ANCOVA with baseline value as a covariate ($\alpha = 0.05$). ANCOVA was also used to compare the two baseline-SUI-severity subgroups within the laser group. Age, BMI and parity were additionally used as covariates in sensitivity analysis. The effect size and its 95% confidence interval (CI) were calculated for all outcome measures. The percent of patients that were dry at follow up was compared between groups with a Chi-Square test. Statistical package IBM SPSS Statistics v. 21 was used for all calculations.

Results

112/114 patients concluded the study (Fig. 1). Demographic characteristics and baseline values of the outcome measures are presented in Table 1. The mean duration of the laser procedure was 20 min. Patients reported minimal treatment discomfort mostly described as a sensation of warmth. In the laser group 80% of patients (45/56) rated the tolerability of treatment as good or better than good on a 5-point scale. In the sham group 91% of patients (51/56) rated the tolerability as good or better than good. Increased amount of vaginal discharge lasting up to 3 weeks was reported by 49/56 patients in the laser group and 6/56 in the sham control group. 2/56 patients in the laser group reported de novo urgency which resolved a few days after treatment. 1/56 patients in the laser group complained of increased vaginal dryness after treatment. No other adverse effects were reported and there was no pathology on follow-up local gynaecological examination.

Table 1
Characteristics of laser and sham control treatment groups at baseline.

	Laser group		Sham group	
	Mean	SD	Mean	SD
Demographic characteristics:				
Age	39.95	6.36	41.84	5.67
BMI	23.54	3.66	23.73	3.60
Parity:	2.05	0.84	2.29	0.82
1 (n, %)	13	23.2%	9	16.1%
2	29	51.8%	26	46.4%
3	11	19.6%	17	30.4%
4	3	5.4%	4	7.1%
Baseline values of outcome measures:				
ICIQ-UI SF	12.00	4.24	12.41	3.35
Slight SUI (ICIQ-UI SF 1–5) (n, %)	5	8.9%	3	5.4%
Moderate SUI (ICIQ-UI SF 6–12)	22	39.3%	17	30.4%
Severe SUI (ICIQ-UI SF 13–18)	29	51.8%	36	64.3%
PISQ-12	32.93	6.48	33.63	5.29
FSFI	25.76	4.89	26.46	3.68
Perineometer measurements:				
Muscle stamina (s)	8.02	2.77	7.00	3.21
Maximal contraction pressure (hPa)	34.34	19.18	30.50	14.70
Average contraction pressure (hPa)	20.93	13.01	18.00	10.42

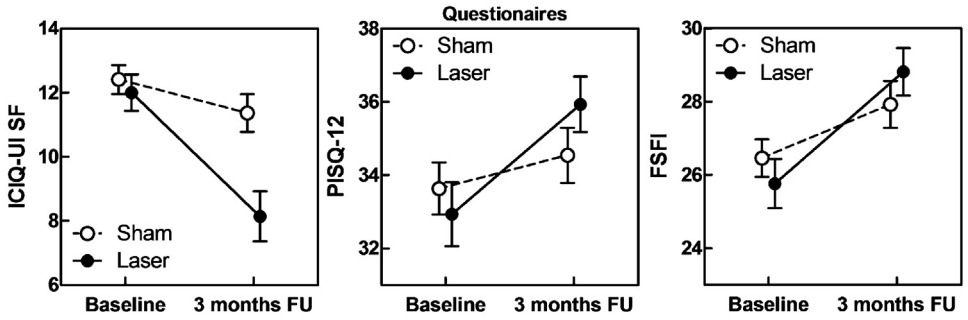

Fig. 2. ICIQ-UI SF sum score (left), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) sum score (centre), and Female Sexual Function Index (FSFI) sum score (right) in the laser and sham control groups at baseline and 3 months after treatment (mean ± SE, n = 56 in each group except FSFI where n = 54 in laser group and n = 52 in sham group). Score range: ICIQ-UI SF: 0 (best) – 21 (worst); PISQ-12: 0 (worst) – 48 (best); FSFI: 2 (worst) – 36 (best).

Laser treatment improved SUI (according to the ICIQ-UI SF score) and sexual function (as evaluated with PISQ-12 and FSFI questionnaires) significantly better than sham (Fig. 2, Table 2). 21.4% (12/56) of laser group patients were dry 3 months after treatment according to ICIQ-UI SF (score = 0), whereas only 3.6% (2/56) of sham control patients were dry (Chi-Square test: $\chi^2 = 7.6$, p = 0.006; Risk Ratio (RR) = 6.00, 95%CI: 1.41–25.59). Covariates age, BMI, and parity had no significant effect on the outcome.

Comparing patients with slight-moderate and severe SUI at baseline the absolute decrease in ICIQ-UI SF score after laser treatment was the same in both subgroups (effect size mild-moderate vs. severe −0.204; 95%CI: −2.629 to 2.220, p = 0.866) but fewer severe-SUI patients achieved dryness after treatment. 11/27 patients in the slight-moderate subgroup were dry after laser treatment and only 1/29 in the severe subgroup. The effect of laser treatment above that of sham was significant in the slight-moderate severity subgroup (Table 2). In the subgroup with severe SUI an effect above that of sham could not be demonstrated (Table 2).

All PFM variables showed significant improvement in the laser group but not in the sham control group (Table 2, Fig. 3). Laser group had somewhat better baseline perineometric values than the sham group (Table 1) but this could only have obscured the effect of laser treatment and not inflate it as laser group patients with lower baseline values actually achieved greater improvement (Spearman's correlation: n = 56, r = −0.416, p = 0.05).

Discussion

The results of this randomized trial show significant superiority of a single session of the non-ablative vaginal Er:YAG laser treatment over sham control in the improvement of SUI (ICIQ-UI SF score), sexual function (PISQ-12 and FSFI score), and perineometry values.

The Er:YAG treatment procedure is easy to learn and does not require specialized surgical skill. The treatment is well tolerated, there is no bleeding, anesthesia or a hospital stay are not required. Patients are advised to avoid increased intra-abdominal pressure and sexual intercourse for 3 days after vaginal Er:YAG treatment [14]. No serious adverse events were reported in this or previous studies of laser SUI treatment [13–16]. Vaginal Er:YAG laser thus offers a minimally invasive alternative for patients with mild to moderate SUI who do not wish to undergo an invasive procedure or have contraindications to surgery.

A single treatment session was applied in this study, resulting in 21.4% of laser group patients reporting subjective cure (ICIQ-UI SF score = 0). A similar rate of subjective cure (21.9%) was reported by Tien et al. [16] who also performed a single session of Er:YAG treatment. Work published after our study was concluded shows that a two-session treatment may be more effective [15]. Significant improvement in the grade of UI was found between the first and the second session, but not between the second and the third [15]. In a study on 175 women with SUI or mixed incontinence the percentage of patients without incontinence after one treatment session was comparable to the results of this study, while it increased to 60% after the second session and remained at the same level until the last, 12 month follow-up [15]. A recent study on 42 patients with mild to severe SUI treated with two non-ablative Er:YAG sessions with 21–28 days interval between sessions reported 38% of all patients had no SUI symptoms at 3–6 moths follow-up [14].

Most of the patients who were dry after treatment in this study had slight to moderate SUI at baseline. Patients with severe SUI at baseline had the same absolute decrease in ICIQ-UI SF score but did

Table 2
Effect size. Change from baseline in laser and sham control groups. p value from paired *t*-test. Effect size of laser vs. sham control group (difference in means and 95% confidence interval) and p value from ANCOVA. ICIQ-UI SF score is the main outcome measure.

Outcome measure	Laser			Sham			Laser vs. Sham		
	Change (95% CI)		p	Change (95% CI)		p	Effect size (95% CI)		p
ICIQ-UI SF	−3.86	(−5.06 to −2.66)	**<0.001**	−1.05	(−2.01 to −0.09)	**0.032**	−2.86	(−4.34 to −1.35)	**<0.001**
≤12[a]	−3.96	(−5.37 −2.56)	**<0.001**	−0.45	(−2.08 1.18)	0.481	−3.66	(−5.78 to −1.55)	**0.001**
>12[b]	−3.76	(−5.38 −2.13)	**<0.001**	−1.39	(−2.85 0.69)	**0.042**	−1.93	(−4.20 to 0.34)	0.094
PISQ-12	3.00	(1.81–4.19)	**<0.001**	0.89	(−0.27 to 2.06)	0.129	1.87	(0.38–3.37)	**0.014**
FSFI[*]	3.06	(1.96–4.16)	**<0.001**	1.35	(0.48–2.22)	**0.003**	1.52	(0.19–2.86)	**0.025**
Duration	1.04	(0.50–1.57)	**<0.001**	0.45	(−0.15 to 1.05)	0.141	0.98	(0.30–1.66)	**0.005**
Max p	5.60	(2.25–8.95)	**0.001**	1.89	(−1.74 to 5.51)	0.302	4.68	(0.01–9.35)	**0.050**
Average p	4.24	(1.72–6.75)	**0.001**	1.64	(−0.60 to 3.89)	0.148	3.03	(−0.28 to 6.35)	0.072

p values indicating significance are in bold.
[a] Subgroup with slight to moderate SUI at baseline according to the ICIQ-UI SF score (n = 27 in the laser group and n = 20 in the sham group).
[b] Subgroup with severe SUI at baseline according to the ICIQ-UI SF score (n = 29 in the laser group and n = 36 in the sham group).
[*] Only the subset of patients who were sufficiently sexually active at both assessment times for FSFI results to be a valid measure of sexual function were analyzed (n = 54 in the laser group and n = 52 in the sham group).

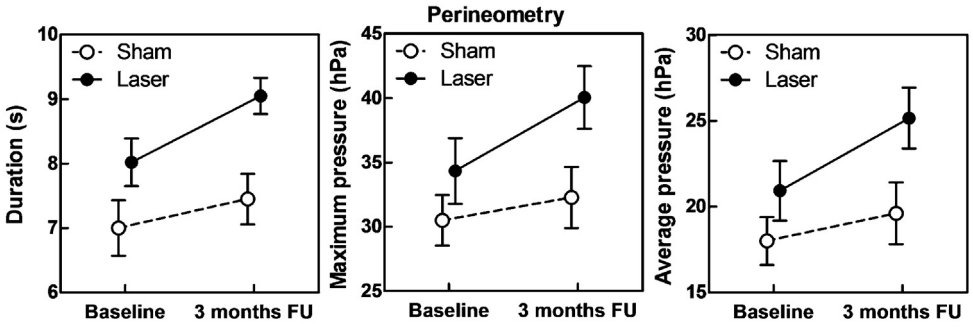

Fig. 3. Perineometry: duration (s) of contraction (left), maximal (centre) and average (right) pelvic floor muscle contraction pressure (hPa) in the laser and sham control groups at baseline and 3 months after treatment (mean ± SE, n = 56 in each group).

not achieve subjective cure after a single session. They might have benefited from additional sessions as subjective cure rate after a two-session treatment was similar between severe (35.3%) and moderate (30%) SUI patients [14]. When multiple treatment sessions are initially performed, the effects last longer [26].

Ablative lasers are sometimes used for vaginal treatment. There are several studies of CO_2 laser treatment for genitourinary syndrome of menopause [27], including some that had noted improvement in ICIQ-UI SF after treatment as a secondary outcome measure [28]. However, only a single uncontrolled study has focused specifically on the use of ablative fractional laser for treatment of SUI [29]. Patients with mild SUI were treated with four initial monthly sessions and subsequent yearly maintenance sessions. The treatment reportedly had good tolerability and no side effects [29]. Nevertheless, such multiple ablative vaginal treatments raise concerns regarding the possibility of vaginal scarring and infection, which can be reduced with use of a non-ablative treatment.

Improvements in PFM stamina and maximum pressure in the laser group were significantly better than in the sham group. A significant improvement in perineometry values above baseline has been reported previously after Er:YAG treatment of vaginal relaxation syndrome [30] and SUI [13]. Effect of the laser on the muscle itself is highly unlikely. Only the upper 500–700 μm of the vaginal wall are affected by the laser [11]. However, pelvic floor muscles and ligaments that are involved in the closure mechanism (e.g. the pubococcygeus muscle and the pubourethral ligament) have connective tissue components that insert into the connective tissue of the vagina [5]. The heat-induced improvement of the connective tissue may help ensure that the tension developed by the active contraction of the muscle is smoothly transmitted, resulting in improved perineometry values after treatment. A combination of PFMT and laser treatment should be evaluated in the future, as targeting both the connective tissue and pelvic floor musculature could potentially improve the results above those of either therapy used alone. The educative effect of biofeedback perineometry used as an evaluation tool at baseline probably accounts for small improvements in the sham group at follow-up assessment, emphasizing the value of a proper control.

Some placebo-effect was evident in all the functional measures. This observation confirms previous findings that indicate a marked placebo effect on UI (8% cured in the placebo arms) [31] and sexual function [32]. The magnitude of the placebo effect estimated in this sham-controlled study will be useful for putting into perspective the results of uncontrolled or active-controlled studies.

This study has some limitations. First is the lack of objective outcome measures. In a recent non-controlled study objective cure rate (a 20-min pad test pad weight <1 g) 6 months after non-ablative Er:YAG treatment of SUI was higher than the subjective cure rate; 39% vs. 22% [16]. The discrepancy between the pad test and questionnaires may be caused by the fact that the short term pad tests are not correlated with patients' daily activities and have poor to moderate sensitivity [33]. On the other hand, validated quality of life questionnaires are standardized, take the patients daily activities into account and are meaningful to patients [33].

This study had a relatively short follow up time (3 months). However, in a majority of studies of other non-surgical treatment alternatives [2,31] effects were registered immediately at the end of treatment with little data as to how long effects last after the treatment is discontinued. Several uncontrolled studies of vaginal Er:YAG treatment with longer-term follow up (12–36 months) have recently demonstrated no long-term side effects [15,26]. Treatment effects of a three-sessions laser treatment with monthly intervals last about 12 months after which time the effect begins to fade, but can be restored and maintained by "maintenance sessions" performed once every 6 months [34].

In conclusion, non-ablative Er:YAG laser treatment for SUI is a fast, simple, and well tolerated procedure which effectively improves incontinence related quality of life and sexual function. It is a promising minimally-invasive treatment option for SUI, which, after further optimization, could reduce the need for surgery.

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