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# First assessment of short-term efficacy of Er:YAG laser treatment on stress urinary incontinence in women: prospective cohort study

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Key words: STRESS URINARY INCONTINENCE, ER:YAG LASER, QUALITY OF LIFE

## ABSTRACT

**Objectives** This is the first assessment of efficacy and safety of the Er:YAG laser in the treatment of stress urinary incontinence. The aim of this study was to assess the short-term outcome of a non-invasive laser treatment for mild-to-severe stages of this condition and to check its applicability in different body mass index and age groups.

**Methods** A prospective cohort, single-center study at the Ob/Gyn Clinic, Zagreb, Croatia recruited a consecutive sample of 73 female patients suffering from stress urinary incontinence. The procedure was performed with a 2940-nm Er:YAG laser (XS Dynamis, Fotona, Slovenia) designed to achieve heating up of vaginal mucosa to around 60°C, 500–700 µm in depth.

**Results** The score in the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form was reduced to a median of 46% (95% confidence interval 33–67%;  $p < 0.001$ ). The reduction was significantly higher in women with normal body mass index (67%) than in overweight women (25%), as well as in women younger than 39 years (100%) compared with those older than 60 years (8%) ( $p < 0.001$ ). No serious adverse events were noticed.

**Conclusion** This study of Er:YAG laser therapy in women has demonstrated a clinically relevant, short-term improvement of stress urinary incontinence, with minimal adverse events of a transient nature.

## INTRODUCTION

The etiology of stress urinary incontinence (SUI) is not completely understood, although identifiable risk factors for the condition include congenital status, pregnancy, childbirth, menopause, cognitive impairment, obesity, and advanced age<sup>1</sup>. The estimation of global prevalence for urinary incontinence (UI) in women reaches about 35% in some European countries and about 50% in the US<sup>2,3</sup>.

The endopelvic fascia and other connective tissues are rich in collagen, which makes up to 80% of its protein content. However, collagenesis not only diminishes in the course of

the aging process but is also significantly affected by the destruction of collagen fibrils due to childbirth trauma<sup>4</sup>. At the same time, the paraurethral tissues of incontinent women have shown collagen and ultrastructural changes which may contribute to the weakening of support at the bladder neck<sup>5</sup>. A recent review showed that the menopause has little if any impact on the risk of UI in general, when confounding factors (age or weight) are taken into account<sup>6</sup>.

Although the initial treatment for SUI should include non-surgical therapies, surgical procedures are more likely to cure SUI but are associated with more adverse events<sup>7,8</sup>. Previous data have shown that the rate of SUI surgery in the US is

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increasing, with a near doubling of rates between 1979 and 1997, and the same trend continuing to 2009<sup>9</sup>. Less invasive operative mesh techniques are relatively effective, but are not immune to complications such as bleeding, bladder perforation, urethral injury, infection, and the retention requiring mesh resection<sup>10</sup>. In patients for whom the risks of anesthesia and surgery are too high, a minimally invasive approach is recommended and further research is needed in terms of more compliant, less invasive and low-cost methods for the treatment of SUI and pelvic floor dysfunction<sup>11</sup>.

The technical advantages of medical laser technology have been amply justified and its medical effects – biochemical, ablative and photothermal – are well-established facts. Laser-generated thermal energy, particularly in a moist environment, not only effectively improves collagen structure, but also stimulates neocollagenesis<sup>12</sup>. An increase in temperature breaks up intermolecular cross-links and stabilizes the collagen triple-helix structure, thus resulting in the shortening of collagen fibers. In order to achieve a shrinkage of the collagen protein without destroying its fibrillar structure and stimulation of neocollagenesis, the temperature must vary between 60°C and 65°C<sup>13</sup>.

Thus far, experimental and clinical studies have reported significant successes in the treatment of various disorders and conditions based on collagen damage. Most references come from the fields of dermatology and esthetic medicine. Facial ptosis, uvular and soft-palate relaxation in snoring disorders, and ligament trauma in orthopedics are only some of the conditions where the application of laser-generated thermal impulses has been scientifically confirmed as highly successful<sup>14–16</sup>. The precise mechanisms underlining the normalization of some vaginal properties is not yet completely clear but collagen remodelling and increased vascularization have been documented by histology following laser application<sup>17</sup>.

Following current trends in the treatment of SUI, the aim of this study was to assess the outcome of a non-invasive laser treatment for mild-to-severe stages of this condition and to check its applicability in different body mass index and age groups.

## MATERIALS AND METHODS

This prospective cohort study included a consecutive sample of 73 patients suffering from SUI. Following a pilot study involving 22 women, a sample size calculation was performed before the study. Assuming 80% power, to detect a mean 3.0 point difference in the score on the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) compared to baseline<sup>18</sup> with a standard deviation of 6.0 points, for an  $\alpha$  value set to 0.05 and two-sided Wilcoxon test, a sample size of 36 was required. A 30% uplift for loss to follow-up was included, making the final required sample size to be 52 women.

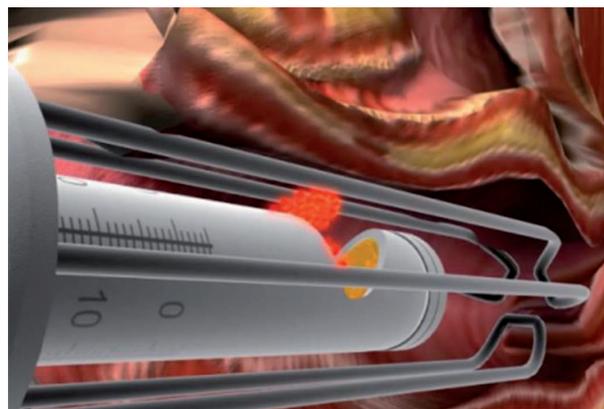
The inclusion criteria for entering the study were: history of vaginal delivery; SUI; normal cell cytology; negative urine culture; a vaginal canal, introitus and vestibule free of injuries and bleeding.

The exclusion criteria were: severe prolapse and damage of the rectovaginal fascia; patients with urge incontinence; patients with severe neurological conditions associated with incontinence (multiple sclerosis, spinal cord injury, stroke, Parkinson's disease); neurogenic bladder; insulin-dependent diabetes mellitus; actual urinary tract infection; hematuria; age  $\leq 18$  and  $> 70$  years; pregnancy; less than 24 weeks after vaginal delivery; body mass index (BMI)  $> 35$  kg/m<sup>2</sup>; intake of photosensitive drugs; injury or/and active infection in the treatment area; and undiagnosed vaginal bleeding.

The study was approved by the Ethics Committee of the University of Rijeka School of Medicine in Rijeka, Croatia.

The procedure was performed with a 2940-nm Er:YAG laser (XS Dynamis, Fotona, Slovenia), using a special modality, SMOOTH mode, which delivers laser energy in a non-ablative, thermal-only technique based on the manufacturer's proprietary pulsing sequence designed to achieve heating of vaginal mucosa to around 60°C, achieving depth to 500–700  $\mu$ m (Figure 1). The patients were placed in the lithotomy position and laser probes, consisting of laser speculum and a specially designed laser delivery system, were introduced into the vaginal canal. In a three-step protocol, the laser irradiation was applied to the anterior vaginal wall, the whole circumference of the vaginal canal and vestibule area. To each area, several passes were applied until 2500–3000 J, depending on the length of the canal. Cumulative laser energy was deposited within approximately 10 min. During the laser intervention, patient discomfort and treatment tolerability, as well as potential adverse events, were monitored. No anesthesia was used before or during the session. During the initial postoperative period of 14 days after intervention, patients were instructed to avoid increased intra-abdominal pressure as well as sexual intercourse. The first follow-up appointments were at 1 month, and the second follow-up was at 2–6 months after the intervention.

The degree of incontinence and its impact on quality of life were assessed with the ICIQ-UI SF, where a maximum score of 21 represents permanent incontinence. The questionnaire allows for the assessment of the prevalence, frequency, and perceived cause of UI and its impact on everyday life. The results of the ICIQ-UI SF may be divided into the following



**Figure 1** Er:YAG fractional non-ablative laser treatment of the anterior vaginal wall

four categories of severity: mild (1–5), moderate (6–12), severe (13–18) and very severe (19–21)<sup>19</sup>. The level of statistical significance was set to  $p < 0.05$  and all confidence intervals were given at the 95% level. In all instances, two-tailed tests of statistical significance were used. Distributions were described by medians and interquartile ranges as the Shapiro–Wilk test had indicated statistically significant deviations from the normal distributions of almost all quantitative variables. The absolute and relative differences between medians at baseline and at second follow-up measurement were given. Confidence intervals of the median of differences were calculated by bootstrapping. Statistical significance of the difference between median outcomes values at the first and second follow-up measurements was calculated by the Friedman test with Monte Carlo statistical significance based on 10 000 sampled tables.

Baseline comparabilities of those that remained in the study and those that were lost to follow-up were analyzed with regard to age, parity, average, and the last birth weight, body mass index, percentage of menopausal patients, perineometry results, residual urine and PISQ-12 score (Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire).

Sensitivity analysis was done under the worst case and unrealistic assumption that all outcome values for those that were lost to follow-up would be the same throughout the study as at baseline, indicating no treatment effect. For sensitivity analysis, missing values at follow-up were replaced by

baseline values. Correlation of raw age data and ICIQ-UI SF score was analyzed by Spearman rank correlation. Association of the four age groups with the ICIQ-UI SF score was assessed by the Jonckheere–Terpstra test. Data analysis used the R language<sup>20</sup>.

## RESULTS

A total of 73 women were included in the study. Their median (interquartile range; IQR) age was 47 (41–54) years with the median (IQR) body mass index of 23 (21–25) kg/m<sup>2</sup> (Table 1). At the second follow-up, 2–6 months after the intervention, 45 (62%) remained in the study, and 28 (38%) were lost to follow-up. Those lost to follow-up had similar baseline characteristics to those who remained in the study (Table 1).

No major adverse events throughout the course of laser treatment and the follow-up period were noticed or reported. The patients eventually signaled sensation of warmth or pricking or irritation during treatment and seldom reported vaginal discharge in the next few days after the procedure. A visual analog scale (VAS) level of 2 was achieved by 5% of participants, and 95% had a score of 0. Slight vulvar edema, which was infrequently noticed, disappeared within 48 h after the treatment. One case of *de novo* urgency was reported. The symptoms vanished spontaneously after 8 days.

**Table 1** Patients' characteristic at baseline, and baseline characteristics of those who remained in the study and those who were lost to follow-up at second follow-up, 2–6 months after the intervention. Data are presented as medians (interquartile ranges) or  $n$  (%)

	Baseline ( $n = 73$ )	At second follow-up	
		Remained ( $n = 45, 62\%$ )	Lost ( $n = 28, 38\%$ )
Age (years)	47 (41–54)	45 (40–52)	49 (41–57)
Parity	2 (2–3)	2 (2–3)	2 (2–3)
Average birth weight (kg)	3.5 (3.1–3.8)	3.5 (3.0–3.7)	3.5 (3.2–3.9)
The last birth weight (kg)	3.5 (3.0–3.8)	3.5 (3.0–3.8)	3.5 (3.2–3.9)
Body mass index (kg/m <sup>2</sup> )	23 (21–25)	23 (21–28)	23 (20–25)
normal ( $\leq 24.9$ )	50 (68.5%)	30 (66.7%)	20 (71.4%)
overweight (25.0–29.9)	16 (21.9%)	10 (22.2%)	6 (21.4%)
obese ( $\geq 30.0$ )	7 (9.6%)	5 (11.1%)	2 (7.1%)
total	73 (100.0%)	45 (100.0%)	28 (100.0%)
<i>Menopause status</i>			
Premenopausal	51 (69.9%)	31 (68.9%)	20 (71.4%)
Postmenopausal	22 (30.1%)	14 (31.1%)	8 (28.6%)
Total	73 (100.0%)	45 (100.0%)	28 (100.0%)
<i>Perineometry</i>			
Average (mmHg)	5.3 (4.0–7.0)	5.8 (4.3–12.1)	5.0 (4.0–5.9)
Duration (s)	8.5 (5.0–14.8)	8.5 (4.8–16.5)	8.1 (5.1–14.4)
Residual volume (ml)	3.0 (0.9–9.3)	3.1 (1.0–7.6)	3.0 (0.5–9.5)
ICIQ-UI	12.0 (6.0–16.0)	12.0 (6.0–15.5)	11.5 (5.3–17.8)
PISQ-12	34.5 (29.0–37.8)	34.0 (28.8–39.0)	35.0 (28.8–37.3)

ICIQ-UI, Consultation on Incontinence Questionnaire-Urinary Incontinence; PISQ-12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire

We found statistically significant differences between baseline and 2–6 months after the intervention (Table 2). Sensitivity analysis, done under the worst case and the unrealistic assumption that all outcome values for those that were lost to follow-up would be the same throughout the study as at baseline, indicating no treatment effect, nevertheless revealed statistically significant and clinically relevant differences after the intervention (Table 2).

At the first follow-up measurement, 1 month after the intervention, the number of those with an ICIQ-UI score = 0 increased from zero to 17/52 (42.3%). At the second follow-up measurement, 2–6 months after the intervention, 18/47 (38.3%) had an ICIQ-UI score = 0 (Figure 2). From baseline to the second follow-up, a total of 34/47 (72.3%) of participants experienced improvement, 11/47 (23.4%) experienced no change in the ICIQ-UI score, and two participants (4.3%) experienced worsening of symptoms.

In a pre-specified *post-hoc* sub-group analysis, we noticed statistically significant differences between different BMI levels and a lowering of the ICIQ-UI SF score (Table 2). The decrease in the normal BMI group was statistically significantly stronger (Mann–Whitney test,  $U = 99.0$ ;  $Z = -2.65$ ;  $p = 0.008$ ). From baseline to the second follow-up, SUI changed from moderate, severe or very severe to mild in 38.3% of women in the normal BMI group, and in 12.5% of women in the overweight group.

Age was associated with a relative decrease of ICIQ-UI SF score (Spearman rank correlation coefficient,  $\rho = -0.55$ ;  $p < 0.001$ ). The difference between age groups was statistically significant (Jonckheere–Terpstra test, standardized  $J-T = -3.45$ ;  $p < 0.001$ ) (Table 2).

## DISCUSSION

This study has indicated clinically relevant short-term improvement of SUI using the thermal effect of the Er:YAG laser. All side-effects were minimal and of a transient nature.

Since laser treatment of SUI is a novel method, very few studies have thus far described laser therapies for female pelvic floor disorders. Gaspar and colleagues<sup>21</sup> found significant improvement in vaginal rejuvenation in terms of resting muscle tone using a fractional CO<sub>2</sub> laser. Their patients underwent several interventions (platelet-rich plasma applied locally in the vaginal mucosa, pelvic exercise by perineometer biofeedback control and laser intervention), so it is not clear what impact the laser treatment produced on the primary outcome *per se*. In contrast, our study showed the short-term results of a unique intervention with Er:YAG laser on the improvement of SUI and quality of life.

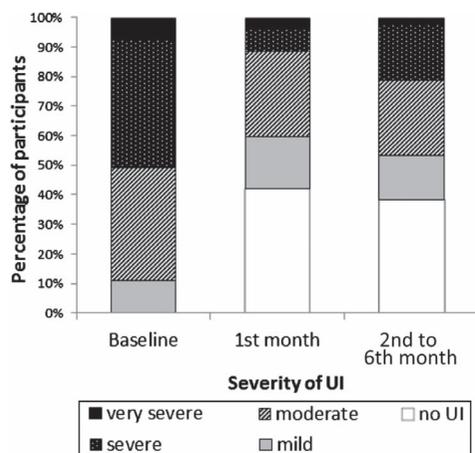
Findings from several studies, discussing impact of age on less invasive surgery for SUI, suggest that younger women have better improvement in UI symptom relief with less retreatment, i.e. subjective and objective cure rates were significantly lower in older patient groups<sup>22,23</sup>. On the other hand, BMI was diversely associated with the outcomes in some studies assessing less invasive surgical approaches for SUI<sup>24,25</sup>. Using the same tool for quality-of-life assessment as we did, an Italian group found a significant difference between obese women and normal BMI examinees in terms of lower mean  $\pm$  SD improvement in obese women when compared with their normal counterparts following less invasive surgery for SUI<sup>26</sup>.

Results from the current study support the expectation of better outcomes in non-obese and younger patients. Thus,

**Table 2** ICIQ-UI score differences from baseline before the intervention, at first and at second follow-up at 2–6 months; ICIQ-UI sensitivity analysis was done under the assumption that the second follow-up values for all those that were lost for follow-up were the same as at baseline, indicating no effect. Data are presented as medians (interquartile ranges) if not stated otherwise

	Baseline (n = 73)	Follow-up		p	Rd	Ad	95% CI
		1st month (n = 52)	2–6 months (n = 47)				
ICIQ-UI	12.0 (6.0–16.0)	4.0 (0.0–10.8)	4.0 (0.0–11.0)	<0.001	46%	–5.5	33–67%
ICIQ-UI sensitivity analysis	12.0 (6.0–16.0)	7.0 (0.0–15.0)	7.0 (0.0–13.0)	<0.001	43%	–5.0	36–72%
<i>ICIQ-UI by BMI</i>							
Normal	10.5 (5.8–15.3)	0 (0–7.0)	0 (0–8.0)	0.008	67%	–6.0	44–100%
Overweight	14.0 (7.0–17.0)	9 (4.0–13.0)	11.5 (4.3–14.0)		25%	–4.0	0–46%
<i>ICIQ-UI by age</i>							
≤ 39 years	8.0 (3.8–10.0)	0 (0–4.0)	0 (0–0)	<0.001	100%	–6.5	81–100%
40–49 years	13.0 (6.8–16.0)	1.5 (0–8.0)	7.3 (0–13.4)		46%	–5.0	25–67%
50–59 years	14.0 (6.0–18.0)	11.0 (4.0–12.0)	9.0 (4.0–13.0)		35%	–5.5	4–64%
≥ 60 years	13.0 (3.8–17.3)	9.0 (2.0–12.5)	11.0 (3.0–16.0)		8%	–0	–20–33%

ICIQ-UI, Consultation on Incontinence Questionnaire-Urinary Incontinence; BMI, body mass index; p, two-tail Monte Carlo statistical significance, Friedman test for ICIQ-UI change in total sample and in sensitivity analysis, Mann–Whitney U test for difference between BMI groups, Jonckheere–Terpstra test for difference between age groups; Rd, median relative difference between baseline and at 2–6-month follow-up; Ad, median absolute difference between baseline and 2–6-month follow-up; 95% CI, 95% confidence interval of the median difference between baseline and at 2–6-month follow-up



**Figure 2** Klovning's categories of ICIQ-UI SF score severity. ICIQ-UI, Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form; UI, urinary incontinence

early detection of low grades of SUI in younger and normal-weight women may partly form a practical approach leading to earlier consultation and treatment.

This study has several shortcomings. It was performed on a non-probability, consecutive sample of patients. Although this may jeopardize the sample representativeness, there is no rational ground to assume whether the sampling bias had an effect in favor or against our hypothesis. The non-existence of a control group may have prevented us from noticing a placebo effect and therefore made us overestimate the intervention effect. This is a serious limitation and we have respected it during the interpretation of results. *Post-hoc* analysis of BMI and age subgroups should be less vulnerable to this source of error. Future studies with proper control groups are needed. This study had a high lost-to-follow-up rate of 38% of initial participants. We have addressed this potential source of bias by documenting the baseline comparability of those respondents who remained and those who were lost to follow-up, and by sensitivity analysis where we have assumed no treatment effect for all that were lost to follow-up yet achieving statistically significant and clinically relevant differences after treatment. We monitored only the short-term outcomes so our results should not be generalized to longer time periods. Our second follow-up had varied duration for different respondents. Distribution of follow-

up visits was relatively uniform throughout the 2–6-month period. Consequently, sample sizes at each month (2nd, 3rd, 4th, 5th, 6th) varied from  $n = 8$  to  $n = 12$ . The standard error of a particular month's samples was too large to use them for any inference. On this particular sample level, we have not noticed differences in median ICIQ-UI scores. From the 2nd to the 6th month, they varied from 3.5 to 4.5, with no statistically significant correlation between time (month) and ICIQ-UI score. According to the differences between the first month of follow-up, and our second follow-up (2–6 months after the treatment), we think that this source of bias increased and did not lower the internal validity of our conclusion.

In conclusion, we believe that this first assessment of Er:YAG laser treatment has indicated that it may result in a clinically relevant short-term improvement of SUI with minimal adverse events of a transient nature. It may be particularly effective in women with normal BMI and in younger women. Considering that the menopause has an irrelevant impact on the risk of UI in general<sup>6</sup>, our efforts should transfer to convenient, less invasive interventions during the reproductive phase of life, in order to prevent postmenopausal UI and its impact on quality of life.

Future studies are needed to confirm whether Er:YAG laser therapy should become another minimally invasive, safe and effective option for treating women with SUI symptoms. Future research should also include measures of the change in sexual gratification.

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*Conflict of interest* The authors report no conflict of interest. The authors alone were responsible for the content and writing of this paper.

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