

Novel Minimally Invasive Laser Treatment of Urinary Incontinence in Women

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Background and Objective: Urinary incontinence (UI) is a common disorder that affects women of various ages and impacts all aspects of life. Our aim was to evaluate the non-invasive erbium:yttrium-aluminum-garnet (Er:YAG) laser that exploits its thermal effect and has been used in reconstructive and rejuvenation surgery as a potential treatment strategy for stress UI (SUI) and mixed UI (MUI).

Study Design/Materials and Methods: We included 175 women (aged 49.7 ± 10 years) with newly diagnosed SUI (66% of women) and MUI (34%), respectively. Patients were clinically examined and classified by incontinence types (SUI and MUI) and grades (mild, moderate, severe, and very severe) using International Consultation on Incontinence Modular Questionnaire (ICIQ) and assessing Incontinence Severity Index (ISI). Using Er:YAG laser, we performed on average 2.5 ± 0.5 procedures in each woman separated by a 2 month period. At each session, clinical examination was performed, ICIQ and ISI assessed and treatment discomfort measured with visual analog system (VAS) pain scale, and adverse effects and patients' satisfaction were followed. Follow-ups were performed at 2, 6, and 12 months after the treatment.

Results: After the treatment, ISI decreased for 2.6 ± 1.0 points in patients diagnosed with mild UI before the treatment, for 3.6 ± 1.4 points in those with moderate UI, for 5.7 ± 1.8 points in those with severe UI and for 8.4 ± 2.6 in those with very severe UI ($P < 0.001$, paired samples *t*-test). Altogether, in 77% patients diagnosed with SUI, a significant improvement was found after treatment, while only 34% of women with MUI exhibited no UI at one year follow-up. Age did not affect the outcome. No major adverse effects were noticed in either group.

Conclusion: The results of our study, have shown that new non-invasive Er:YAG laser could be regarded as a promising additional treatment strategy for SUI with at least one year lasting positive effects. On the other hand, it does not seem appropriate for treating MUI. *Lasers Surg. Med.* 47:689–697, 2015.

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Key words: Er-Yag laser; gynecology; non-invasive procedure; stress urinary incontinence; mixed urinary incontinence

INTRODUCTION

Female urinary incontinence (UI) is an important health problem, as its prevalence has been estimated to be as high as 40% [1,2]. It affects all aspects of life, including physical, social, economic, and psychological ones and thus seriously impairs the quality of women's life. According to The International Continence Society (ICS) and International Urogynecological Association (IUGA), UI is defined as a condition in which involuntary urine loss occurs. Multiple risk factors for worsening incontinence have been identified including age, parity, vaginal delivery, multiparity, body mass index (BMI), obesity, pelvic trauma, constipation, chronic disease (diabetes), and history of gynaecological and pelvic surgery [1,3,4]. The common cause of UI is pelvic floor dysfunction; regarding the underlying pathophysiological mechanism, UI can be divided into stress UI (SUI), urge UI (UUI), and mixed UI (MUI). SUI is the most prevalent type and is defined as involuntary loss of urine due to sphincter failure during physical activity, coughing, or sneezing, which all cause an increase in abdominal pressure [3,5]. On the other hand, UUI, sometimes also termed overactive bladder syndrome (OAB) encompasses the symptoms of urgency, frequency, and nocturia and is associated with urgency contraction due to detrusor overactivity [3,6]. MUI refers to urine leakage with a combination of SUI and UUI and has a prevalence of 7.5–25% [3,7].

The level of distress depends on the frequency, the amount of leakage, and on the subjective experience of these symptoms. Therefore, patient's report of symptoms is a typical basis for diagnosis, besides from history and clinical examination and exclusion of the underlying causes (e.g., infection, urogenital prolapse). Furthermore,

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symptoms questionnaires are helpful in assessing the subtypes of urinary incontinence [5,8–10]. The International Consultation on Incontinence Modular Questionnaire (ICIQ) aims to promote a more uniform usage of questionnaires: usually, the symptom severity, the frequency of UI episodes and the quality of life are assessed. The ICIQ-short form (ICIQ-SF) has been reported to correlate well to the Patient Global Impression of Improvement (PGI-I) [6]. These questionnaires allow assessment of the treatment effectiveness by comparing pre- and post-treatment scores [5].

There are many approaches for treating UI; the conservative therapy includes lifestyle changes, pelvic floor muscle training (PFMT), bladder training, and electro-magnetic stimulation of the pelvic floor muscles and drugs for UUI from OAB [3,11,12]. A variety of surgical procedures are based on traditional Burch colposuspension and bladder-neck slings and their modifications [2,13–15]. Yet, the incidence of adverse side effects and complications in surgical procedures remains relatively high, ranging from perioperative trauma, injury, hemorrhage, pain, infection, perforation of urethra, vagina or bladder, urinary retention, foreign body reaction to the implant [2,3,7,14,15].

Recently, a novel non-invasive laser therapy based on the thermal action on vaginal mucosa has been introduced. The erbium-doped yttrium-aluminum-garnet (Er:YAG) laser has been successfully used in the field of plastic skin rejuvenation and reconstruction [16–18]. The procedure is based on photothermal treatment of connective tissue: It has been established in animal and human studies that it affects collagen remodelling resulting in tightening of the supportive tissue [19–22].

To the best of our knowledge, no study has so far evaluated the effect of Er:YAG laser treatment on UI in women. Therefore, the aim of our study was to evaluate whether or not the Er:YAG laser treatment improves the symptoms of UI in women. We included women with a diagnosed SUI and MUI, respectively, and performed two to three treatments using Er:YAG laser. The severity of UI was evaluated by clinical examination and the ICIQ-SF standard questionnaire before and after the therapy. We further aimed at evaluating whether age and type of incontinence (SUI vs. MUI) affected the final outcome of the therapy.

METHODS

Study Population

In our prospective, single center, non-randomized, pilot study, conducted in the period from March 2012 to November 2013, we included 175 women with a mean age of 49.7 (± 10) years presented with UI who met the inclusion criteria.

The inclusion criteria were: clinically confirmed UI, normal PAP smear (Papanicolau cytology), negative urine culture, and integrity of the vaginal mucosa (without injuries or bleeding). The exclusion criteria were pregnancy, intake of photosensitive drugs, injuries or vaginal

bleeding, and infection in the treated area as well as an existence of pure UUI.

Patients were further subdivided into two groups according to the type of incontinence: SUI and MUI, respectively.

Authors confirm that the study, was reviewed and approved by the National ethics committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from each patient; no financial incentives were proposed for participating in the study.

The authors confirm that all ongoing and related trials for this intervention are registered.

Assessment of UI

In each patient, medical history was obtained and clinical examination performed; the latter included inspection and evaluation of the incontinence severity. It was assessed by inducing an increase in intraabdominal pressure by coughing maneuver to estimate the degree of leakage in a full and empty bladder. Furthermore, a transvaginal echosonographic examination (Medison, Samsung ultrasound, Korea) was performed to exclude patients with abnormal findings in the urinary and gynecology tract and abnormal appearance of bladder mucosa. Echosonography also enabled an assessment of residual volume in the urinary bladder and the thickness of the bladder wall; based on ours and the experience from other groups [23,24] we excluded patients in whom the bladder thickness was above 5 mm. Muscular strength was measured using perineometrical measurement (PFX Bio-feedback Kegel Exercisers) to assess muscular abnormalities of pelvic floor muscles.

Each woman fulfilled the standard ICIQ-SF. Based on questions one and two to estimate the frequency of UI and the amount of leakage, the severity of incontinence was defined and expressed in terms of incontinence severity index (ISI) and patients were categorized into four grades: Mild, moderate, severe, and very severe UI [8,9]. Besides from standard ICIQ-SF and ISI, patient's personal perception of the degree of UI and disability was obtained. The fifth question is about the quality of life and the sixth to determine the type of incontinence.

The type of incontinence was determined on the basis of clinical examination, echosonography, perineometrical measurement, and the questionnaire.

UI was assessed before and after each treatment; the treatment outcome and the degree of improvement were numerically determined by ICIQ-SF and ISI.

Study Design

All patients were submitted to preoperative evaluation; anamnesis and physical examination (in a restful and straining position, achieved by coughing) were performed as described. After having fulfilled the ICIQ-SF questionnaire, ISI was determined. Patients were informed about the laser procedure and its potential adverse effects. Afterwards, patients received two or three sessions of laser treatment as described below; all interventions were

performed at our outpatients' department. During the intervention, patients were lying in a normal gynecological lithotomy position and received no anaesthesia.

Pain during the treatment was measured at every session with a visual assessment scale (VAS) according to the National Initiative of Pain Control [25]. Follow-ups were performed at 2, 6, and 12 months. At each follow-up, the same outcome measures as before the treatment were assessed (clinical examination, echosonography of the pelvic organs and the urinary bladder, perineometric measurements of the pelvic floor muscles, ICIQ-SF fulfillment, assessment of patients' satisfaction, VAS assessment).

Er:YAG Laser Procedure

We used a 2940 nm Er:YAG laser (SP Spectro, Fotona, Slovenia) set in "smooth mode" (fluence 10.0 J/cm²; four pulses per packet, packet pulse duration is 250 ms; spot size 7 mm; repetition rate 1.6 Hz) which enables non-ablative, thermal-only operation [19,20]. The therapy exploits the photo-thermal effect of a laser beam on mucosa tissue in order to cause its shrinkage without any removal of tissue. To achieve shrinkage of collagen while maintaining its structure without destruction the temperature has to be around 60–65°C [22]. There are three major components of the mechanism of action involved: A photo-thermal effect penetrating up to 0.5 mm inside the vaginal wall and causing the immediate shrinkage of the tissue, which could be as large as 30% of the tissue volume; the mechanical pull of deeper tissue layers following the shrinkage of upper, photo-thermally processed tissue layers; and neo-collagenesis following heat treatment, which generates new collagen fibers that further contribute to the improvement of thickness, elasticity, and firmness of the vaginal wall [20–22].

Laser treatment is performed with a special accessory called G-set, composed of two handpieces (full spot and fractional), two adapters (angular and circular), and a laser speculum (Fig. 1). The laser speculum enables opening of the vaginal canal and serves as a guide for the handpiece adapter, allowing it to easily glide into the vaginal canal without touching it.

Each laser treatment consists of three phases. In the first phase, the full-field handpiece (R11) with a 360°-circular

adapter is used to perform irradiation of the full circumference of the vaginal canal. Applying two passes, around 650 J of laser energy is delivered to the full length of the vaginal wall, causing shrinkage of collagen in mucosa tissue, thus increasing the tightness and firmness of the vaginal wall. In the second phase of the procedure, PS03 handpiece with a 90°-angular adapter is used to deliver fractionated smooth beam perpendicularly to the anterior vaginal wall. Anterior vaginal wall is irradiated with fractionated smooth beam utilizing several longitudinal and adjacent passes. In this phase, of the protocol a total of 250 J of energy is deposited to the vaginal wall causing additional mucosa shrinkage of the targeted anterior wall and consequently lifting of the bladder. After the second phase is completed, the laser speculum is removed from vaginal canal and laser energy is delivered to the mucosa of the vestibule and introitus, by direct irradiation with fractionated smooth beam in three passes. The last phase is performed with the fractional handpiece (PS03) and straight shooting tip. This phase is important to fix urethra in anatomic position and consolidate the ligaments and connective tissue around urethra. It is also used to shrink the introitus of the vaginal canal. Approximately, 100 J of energy is delivered to vaginal mucosa in this third phase. In total, around 1,000 J of energy is deposited to the vaginal mucosa after one completed laser treatment.

After 4–6 weeks, the second laser treatment was performed to complete the laser therapy for SUI. The third procedure was usually performed 6 months after the first procedure.

Statistical Analysis

Statistical evaluations were obtained by using SPSS 17.0 (SPSS Science, Chicago, IL). Descriptive statistics was made with "Frequencies" and "Descriptives" subprograms. For a normal distribution, data were expressed as means and standard deviations (SD). Statistically significant differences were calculated using Crosstabs and χ^2 test, as well as with one way Anova and Bonferroni test as appropriate. Statistical significance level was accepted at 0.05.

RESULTS

General Characteristics of Patients

Demographic characteristics of the patients at the time of the first measurement are presented in Table 1. The distribution of patients regarding the type and grade of incontinence before the beginning of therapy is presented in Table 2. The average ISI before the therapy was 5.7 (SD = 2.1).

General Improvement of UI After Laser Treatment and the Number of Procedures

The improvement of UI with regard to ISI and the number of procedures is presented in Figure 2. On average, 77.6 days (SD = 6.3) elapsed between the first and the second procedure (1st follow-up). Patients were examined



Fig. 1. Scheme of the 2,940 nm Er:YAG laser device.

TABLE 1. Demographic Characteristics of the Patients before the Induction of Therapy

	<i>n</i>	%
Age		
Up to 40 age	30	17
41–45 years	32	18
46–50 years	35	20
51–55 years	32	18
Over 56 years	46	26
BMI*		
Underweight	3	2
Normal range	99	58
Overweight	49	29
Obese	20	12
Number of children		
0	5	3
1	30	17
2	106	61
3	27	15
4	7	4

BMI, Body Mass Index; *n*, Number of Patients.

*For 4 patients no data.

for the second time 174.6 days after the first procedure (SD = 83.4) (2nd follow-up). The last examination was performed 381.3 (SD = 119.2) days after the first procedure (one year after the treatment). While significant differences were found between the first and the second follow up in all groups (regarding the grade of UI), no differences were observed between the second and the last follow up.

Altogether, one procedure was performed in 12 patients (7%), two procedures in 54 (31%), and three procedures in 109 patients (62%). The improvement of the grade of UI at the first, second and last follow-up is presented in Figure 3. At one year follow-up, no woman experienced very severe UI. The patients who exhibited no UI after treatment (108 patients) underwent 2.54 (SD = 0.65) procedures on average. The patients with final mild UI underwent 2.6 (SD = 0.58) procedures (43 patients), and those with moderate UI 2.48 (SD = 0.6) procedures (21 patients).

TABLE 2. The Distribution of Patients Regarding the Type and Grade of Incontinence Before the Beginning of Therapy

	<i>n</i>	%
Type of UI		
SUI	114	65
MUI	61	35
Grade of UI		
Mild	30	17
Moderate	47	27
Severe	89	51
Very severe	9	5

UI, Urinary Incontinence; SUI, Stress Urinary Incontinence; MUI, Mixed Urinary Incontinence; *n*, Number of Patients.

Three patients with final severe UI underwent three (SD = 0.0) procedures. The differences between particular groups regarding the number of the procedures are not statistically significant.

At one-year-follow-up, ISI significantly decreased in all women (Fig. 2). The decrease of ISI regarding the grade of incontinence before the treatment is shown in Figure 4A. Patients with very severe UI diagnosed before therapy experienced the greatest ISI decrease following therapy.

At one-year-follow-up, 108 patients (62%) from both, SUI and MUI groups exhibited no incontinence (Fig. 3). On average, they received 2.54 (SD = 0.65) procedures. 29 patients (16%) whose grade of UI remained unchanged after the treatment received 2.68 (SD = 0.55) procedures. In 38 (22%) patients we noticed worsening of UI (in terms of UII) after the therapy; they received 2.51 (SD = 0.6) procedures. The differences among all three groups regarding the number of procedures are not statistically significant.

Final Outcome Regarding Age

Age did not affect the outcome of UI treatment as we found no significant differences in UI improvement between the groups of different ages ($P = 0.180$, ANOVA with Bonferroni test). The average ISI improvement in the five age groups is presented in Figure 4B.

When dividing patients in the pre- (age < 55 years) and postmenopausal groups (age > 55 years), we also did not find any statistical differences regarding ISI between the two groups. ISI decreased for 4.8 (SD = 2.3) points in the below-55-years-group and for 4.6 (SD = 1.9) points in the above-55-years-group.

Final Outcome Regarding the Type of Incontinence as Diagnosed Before Therapy

At the end (one year follow-up), 108 patients (62.3%) significantly improved incontinence, while nine patients (5.1%) presented with SUI, 53 (30.3%) with UII and 5 (2.3%) with MUI.

The results of the final outcome regarding the type of incontinence (diagnosed before the therapy) are summarized in Figure 5. In patients with SUI as assessed before the treatment UI significantly improved in 77% of the cases (88 patients) while the patients diagnosed with MUI prior to the treatment only improved in 34% of the cases (20 patients). The differences are statistically significant ($P < 0.001$) between the SUI and MUI groups (Fig. 5).

Adverse Effects of Therapy

During the procedure, patients experienced no pain or only mild discomfort. The pain estimated by VAS was on average 0.5 points; the highest score was three on the 0–10 scale. We also observed that at each successive treatment, there was less discomfort in the same patient as compared to the previous procedure. Patients reported no significant side effects after the therapy. In general, they were all satisfied with the procedure and experienced no or only mild discomfort and/or pain during the procedures.

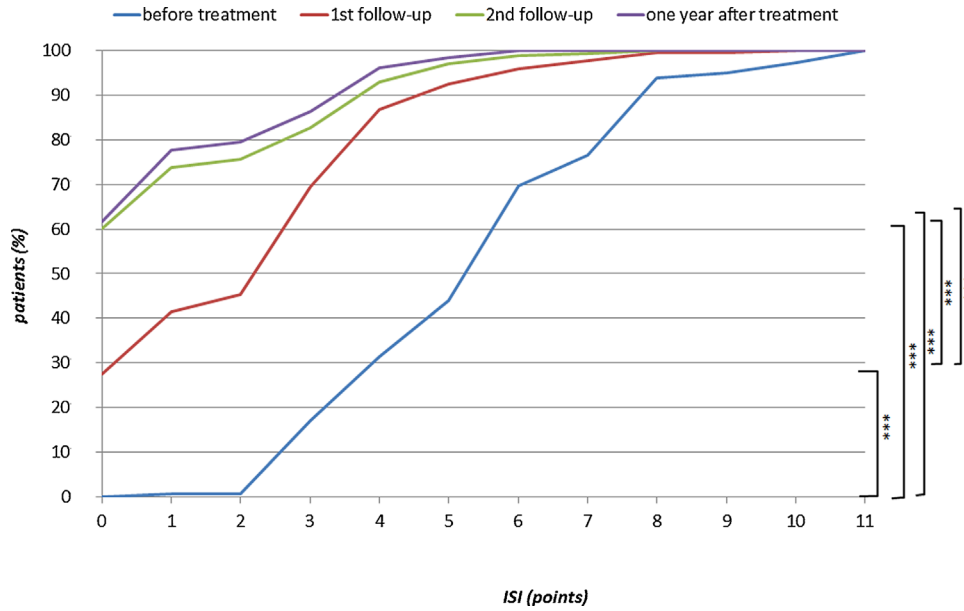


Fig. 2. The effect of the Er:YAG laser therapy on the improvement of incontinence severity index (ISI). The distribution of patients (in %) regarding ISI (expressed in points) before the treatment (blue line), at the first follow-up (2 months after the first procedure, red line), at the second follow-up (6 months after the first procedure, green line) and one year after the laser treatment (violet line) is presented. *** $P < 0.001$, ANOVA with Bonferroni test.

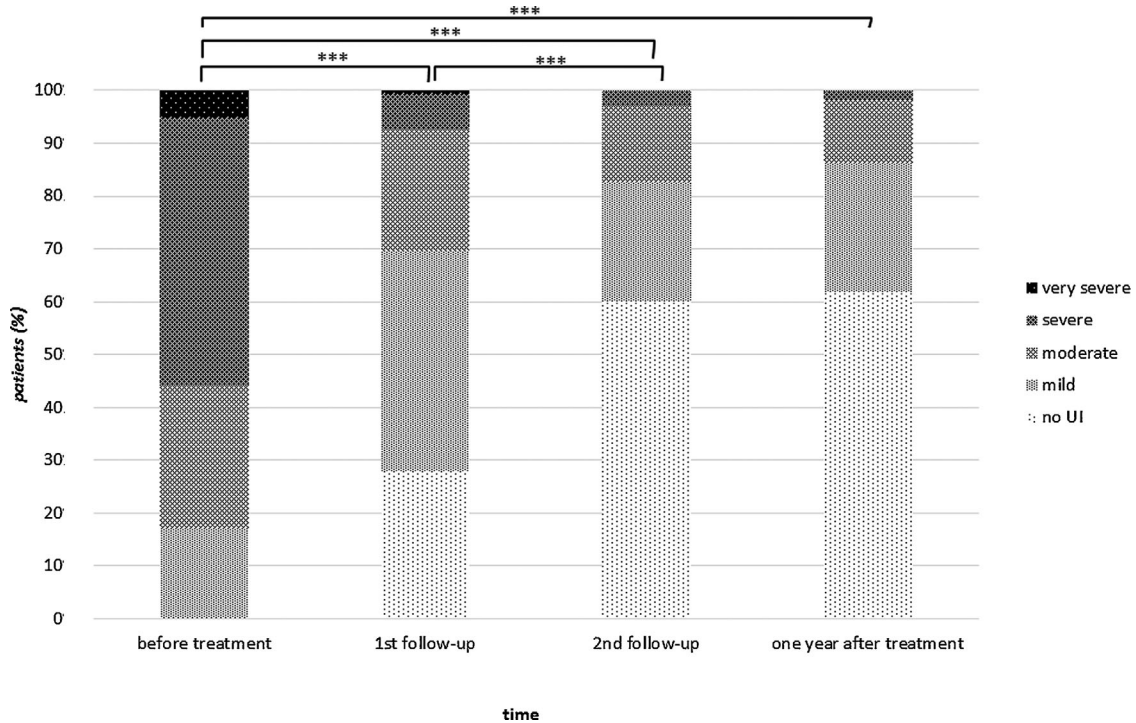


Fig. 3. The effect of Er:YAG laser therapy on the improvement of the grade of urinary incontinence (UI). Plots show the distribution of patients (in %) with regard to the grade of incontinence (mild, moderate, severe, very severe; see legend) before treatment, at the first, second, and last follow up. *** $P < 0.001$, ANOVA with Bonferroni test.

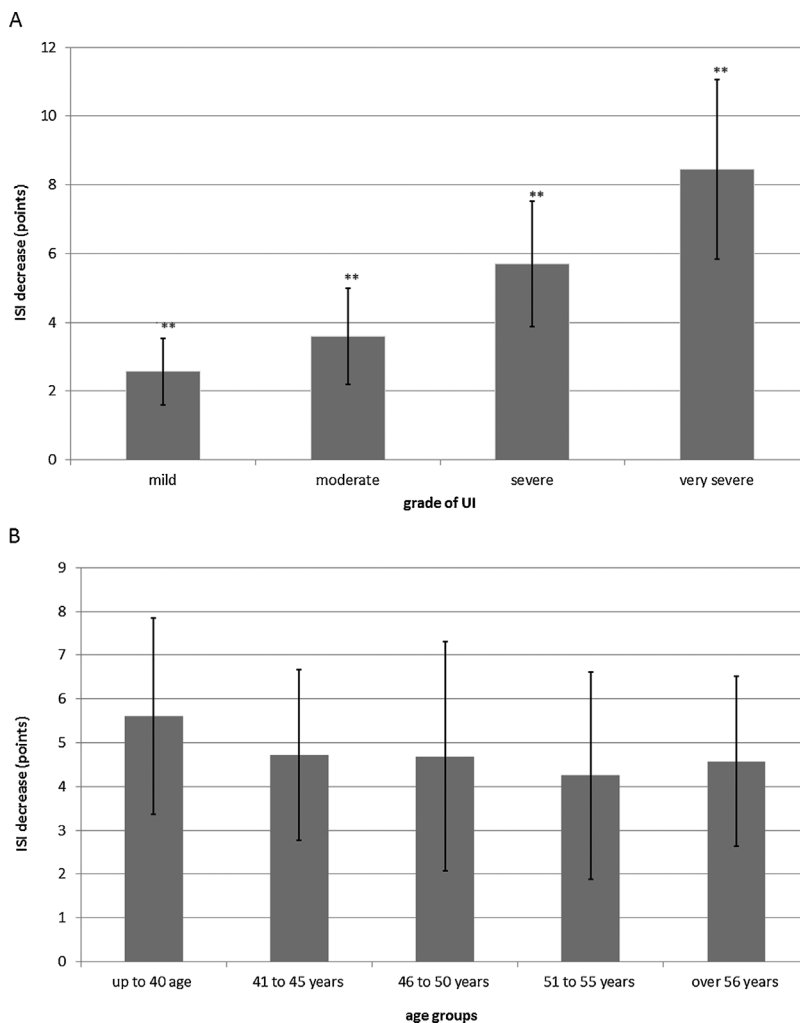


Fig. 4. The incontinence severity index (ISI) decrease following therapy with respect to (A) the grade of urinary incontinence (UI) and (B) to age. ISI decrease one year after the Er:YAG laser treatment is shown with regard to (A) the grade of UI diagnosed before the induction of therapy and (B) in different age groups. Data are presented as means and SD. ** $P < 0.01$, ANOVA with Bonferroni test.

The only noticed side effect was a change of the type of incontinence: After the first procedure, in 11 patients (6.3%) who had SUI before the treatment, transient UUI appeared as a complication. After the second procedure, UUI appeared *de novo* in seven patients (4%) from the SUI group. The final distribution of the type of UI after therapy with regard to initial UI type is presented in Figure 5.

DISCUSSION

The results of our study have shown that minimally invasive, non-surgical and non-ablative laser therapy could successfully be used for the treatment of UI. Two sessions of laser treatment using ER:YAG laser significantly reduced ISI and improved the symptoms of UI in all age groups. Contrary to our hypothesis, age did not influence the final outcome. On the other hand, the outcome was significantly dependent on the type of

incontinence diagnosed before the induction of therapy. While the procedure cured the majority of women with SUI, it was of benefit only in one third of women with MUI.

To the best of our knowledge, this is the first prospective study to explore the use of Er:YAG laser as an alternative therapy for the treatment of UI.

The common mechanism of UI is pelvic floor dysfunction due to loss of its supportive function [3,26,27]. The mechanical stability of the urethra and bladder neck is largely provided by intact pelvic muscles and connective tissue of the pelvis. Thus, the majority of therapeutical approaches aim at strengthening the support of the pelvic floor, either conservatively or surgically. Although, there are reports on the beneficial effects of conservative treatment [11,12], patients have to be very compliant and the final outcome remains questionable. On the other hand, none of the existing surgical approaches is optimal

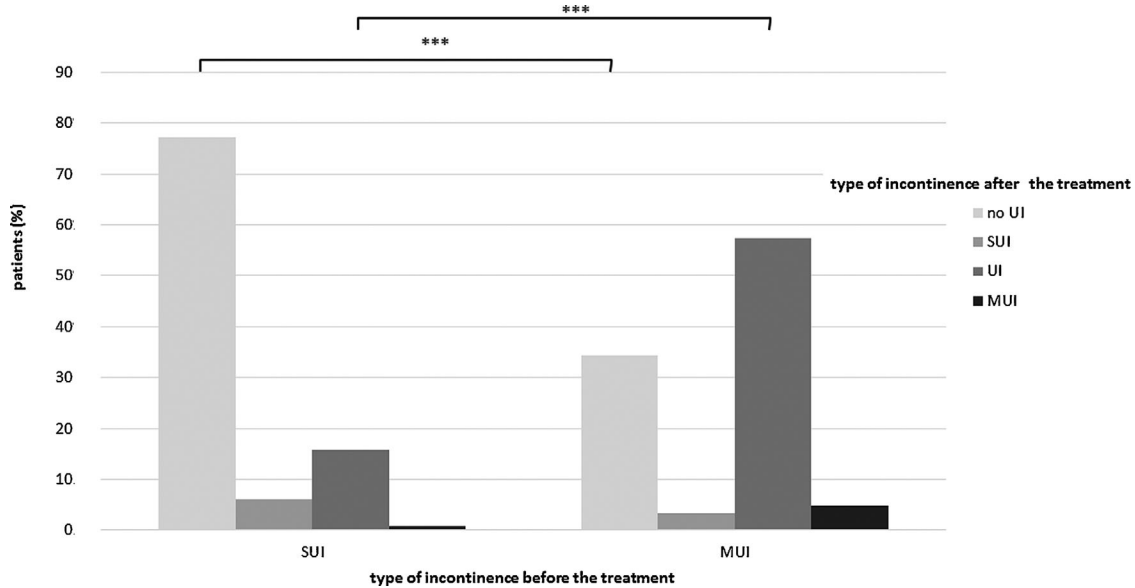


Fig. 5. Final outcome at one year follow-up regarding the type of incontinence as diagnosed before the therapy. The distribution of patients with regard to the final urinary incontinence (UI, expressed in %, see the legend at the right hand) one year after the treatment with Er:YAG laser, from the group of stress UI (SUI) and mixed UI (MUI) diagnosed before induction of therapy.

as they are often associated with complications [2,3,14,15]. Moreover, American Food and Drug Administration (FDA) has amended several warnings and proposed an upgrading in risk qualifications for implantable devices [15]. Indeed, fear for a surgical intervention to treat UI or negative experience with previous surgery were among the reasons why patients included in our study preferentially decided to undergo laser therapy. In this respect, minimally invasive laser intervention could be regarded as an alternative to classical, conservative, and surgical techniques. Laser therapy has so far extensively been investigated and used in dermatology including the treatment of scars and as a rejuvenation procedure [16,17]. The non-ablative therapy exploits the photothermal effect of the laser light. The main advantage of the Er:YAG laser for skin resurfacing is precise ablation with limited residual thermal damage [16,19,20]. In this technique, pulses of lower energy and shorter duration are applied [19]. The process of tissue repair resembles wound healing process: Dermal fibroblasts react to thermal injury with heat-shock response and synthesis of heat shock proteins which induce inflammation and subsequent repair [22]. Photothermal energy may alter the structure of the extracellular matrix (ECM) and the expression levels of the ECM molecules. Furthermore, the energy may affect the dermal metabolism by altering the expression of proteolytic enzymes, cytokines, and growth factors [28]. It has been confirmed that heat caused collagen injury and contraction, and upregulated the gene expression of procollagen type I and procollagen type III in human fibroblasts resembling normal young skin [22]. The newly formed collagen was shown to be arranged in more ordered

fashion, as assessed by the combined TPF-SHG (two-photon excited fluorescence-second-harmonic generation) microscopy [18]. The photothermal effect of Er:YAG laser breaks up intermolecular crosslinks and thereby stabilizes triple-helix-structure of collagen resulting in tissue tightening [19]. Although these studies were preferentially performed in animal and human skin, we may hypothesise that similar mechanisms could apply to the vaginal mucosa and the connective tissue of the pelvic floor. Women with pelvic floor dysfunction have been reported to demonstrate abnormal ECM metabolism in their pelvic support tissues [29]. Wen et al. have found a significantly higher expression of the myofibroblasts' protein, SM-22 α , a potential biomarker for SUI [26]. Moreover, mitofusin-2 (Mfn2) expression changed along with the duration of postmenopause and had a negative association with the expression of procollagens: Mfn2 protein has been suggested to affect the synthesis of procollagen of fibroblasts in postmenopausal women with pelvic floor dysfunction [30]. It is thus obvious that the composition of the pelvic floor supportive structure changes over the years. An appealing approach would be to influence tissue remodelling and mimic the natural composition of a continent pelvic floor. Therefore, we applied the Er:YAG laser into the vaginal canal and treated the connective tissue according to the described protocol. Our results on UI improvement imply the ability of laser photo-thermal effect to act on the vaginal supportive tissue, presumably by altering the organization and composition of its ECM. Based on similar proposals, injectable substances that mimic natural ones and bulge the pelvic floor have been introduced, showing about 50% cure rates success and low complications rates

and morbidity [31]. However, they do not seem to have durability and could need multiple reinjections over time [32]. In this regard, our procedure has yielded better results and the beneficial outcome persisted as far as one year after the last procedure.

Contrary to our hypothesis and reports from the literature, age seemed not to affect the outcome. Although the incidence of pelvic floor disorders increases with age and depends on the level of estrogen [33], the outcome of our laser intervention did not confirm differences between the pre- and postmenopausal women. Reduced synthesis of collagen types I and III is characteristic of chronologically aged skin [34]. Varani et al., proposed that many of age-induced alterations in the composition of aged-skin are a consequence of lower level of mechanical stimulation [34]. In this regard, Er:YAG laser might be suggested as an efficient mechanical stimulus to challenge *de novo* synthesis of collagen. Nevertheless, the speculations should be confirmed by further cyto-histological evaluations.

The percent of women cured after one year in our study, was similar to the results obtained after surgical procedures [3,13,15,35]; yet, compared to surgical outcome the reported side effects were negligible. This undoubtedly is a great advantage of laser therapy. Our patients reported less pain, none of the patients reported inflammation or other side effects. The large majority of patients were satisfied with the procedure and happy with its outcome. The only adverse effect that warrants mentioning was persistent UI or change of SUI into MUI or UUI. Evidence does indicate that women with MUI have greater bother than those with SUI alone [36,37], and are less likely to have success or cure after undergoing surgical management of their SUI [7,36,37]. Accordingly, our study showed significantly worse outcome in women with MUI compared to those with SUI. According to Norton and Brubaker, MUI could merely represent the midpoint on the continuum between SUI and UUI [3].

An interesting finding is that, according to ISI evaluation, the symptoms of UI significantly improved already after two interventions with little additional effect after subsequent ones. We believe that the small and insignificant variation in the reduction of ISI show a proper adaptation of the number of procedures to individual patient's collagen remodeling capacity, which might also be the reason for a non-significant age relevance. Our follow-up in this study, showed that the results of laser treatment could last at least 12 months. As the long term experiences with the same Er:YAG laser modality in aesthetics and dermatology showed that this procedure could safely be repeated many times, we believe that repeating the treatment would also be possible in UI if the symptoms reappeared.

We are aware of the limitations of this pilot study, such as its single center nature, the absence of a control group, relatively small sample size and relatively short term follow-up. In spite of the listed limitations, we believe that our aim to evaluate the potential use of the new minimally invasive laser method in the treatment of UI in women was achieved.

In conclusion, we have shown that minimally invasive Er:YAG laser treatment efficiently improved SUI in the majority of patients and as such could be regarded as a promising new therapy for the treatment of SUI in women. On the other hand, it seems that the therapy is not suited for the treatment of MUI. Apart from non-invasiveness, the main advantage of lasers over surgery is that procedures could be applied ambulatory what is connected also with lower economic burden. Additional studies to optimize the timing and protocols of treatment as well as unrevealing the mechanisms behind are needed.

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REFERENCES

1. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. *BJOG* 2000; 107(12):1460–1470.
2. Castro RA, Arruda RM, Bortolini MAT. Female urinary incontinence: Effective treatment strategies. *Climacteric* 2014;17:1–7.
3. Norton P, Brubaker L. Urinary incontinence in women. *Lancet* 2006;367:57–67.
4. Devore EE, Minassian VA, Grodstein F. Factors associated with persistent urinary incontinence. *Am J Obstet Gynecol* 2013;209(2): 145.e1–e6.
5. Nyström E, Sjöström M, Stenlund H, Samuelsson E. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. *Neurourol Urodyn* 2014;DOI: 10.1002/nau.22657
6. Abrams P, Avery K, Gardener N, Donovan J. The international consultation on incontinence modular questionnaire. *J Urol* 2006;175:1063–1066.
7. Bump RC, Norton PA, Zinner NR, Yalcin I. Mixed urinary incontinence symptoms: Urodynamically severe, incontinence severity, and treatment response. *Obstet Gynecol* 2003;102: 76–83.
8. Sandvik H, Hunskaar S, Seim A, Hermstad R, Vanvik A, Bratt H. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. *J Epidemiol Community Health* 1993;47(6):497–499.
9. Klovning A, Avery K, Sandvik H, Hunskaar S. Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the incontinence severity index. *Neurourol Urodyn* 2009;28:411–415.
10. Minassian VA, Devore E, Hagan K, Grodstein F. Severity of urinary incontinence and effect on quality of life in women, by incontinence type. *Obstet Gynecol* 2013;121(5):1083–1090.
11. Sjöström M, Umefjord G, Stenlund H, Carlbring P, Andersson G, Samuelsson E. Internet-based treatment of stress urinary incontinence: A randomised controlled study with focus on pelvic floor muscle training. *BJU Int* 2013;112(3):362–372.
12. Cavkaytar S, Kokanali MK, Topcu HO, Aksakal OS, Doğanay M. Effect of home-based Kegel exercises on quality of life in women with stress and mixed urinary incontinence. *J Obst Gynaecol* 2015; 35(4):407–410.
13. Meyer F, Hermieu JF, Boyd A, Dominique S, Peyrat L, Haab F, Ravery V. Repeat mid-urethral sling for recurrent female stress urinary incontinence. *Int Urogynecol J* 2013;24: 817–822.
14. Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW. Sling surgery for stress urinary incontinence in women: A systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1): 71.e1–27.

15. Barski D, Gerullis H, Georgas E, Bär A, Lammers B, Ramon A, et al. Coating of mesh grafts for prolapse and urinary incontinence repair with autologous plasma: Exploration stage of a surgical innovation. *BioMed Res Int* 2014;2014:296498. DOI: 10.1155/2014/296498
16. Kunzi-Rapp K, Dierickx CC, Cambier B, Drosner M. Minimally invasive skin rejuvenation with Erbium: YAG laser used in thermal mode. *Lasers Surg Med* 2006;38:899–907.
17. Sadick NS. Update on non-ablative light therapy for rejuvenation: A review. *Lasers Surg Med* 2006;32:120–128.
18. Cicchi R, Kapsokalyvas D, Troiano M, Campolmi P, Morini C, Massi D, Cannarozzo G, Lotti T, Pavone FS. In vivo non-invasive monitoring of collagen remodelling by two-photon microscopy after micro-ablative fractional laser resurfacing. *J Biophotonics* 2014;7:914–925.
19. Majaron B, Srinivas SM, Huang HL, Nelson JS. Deep coagulation of dermal collagen with repetitive Er:YAG laser irradiation. *Lasers Surg Med* 2000;26:215–222.
20. Drnovsek-Olup B, Beltram M, Pizem J. Repetitive Er: YAG laser irradiation of human skin: A histological investigation. *Lasers Surg Med* 2004;35:146–151.
21. Hantash BM, Ubeid AA, Chang H, Kafi R, Bradley Renton B. Bipolar fractional radiofrequency treatment induces neo-elastogenesis and neocollagenesis. *Lasers Surg Med* 2009;41:1–9.
22. Dams SD, de Liefde-van Beest M, Nuijs AM, Oomens CW, Baaijens FP. Pulsed heat shocks enhance procollagen type I and procollagen type III expression in human dermal fibroblasts. *Skin Res Technol* 2010;16(3):354–364.
23. Kuhn A, Genoud S, Robinson D, Herrmann G, Güntherth A, Brandner S, Raio L. Sonographic transvaginal bladder thickness: does the measurement discriminate between urodynamic diagnoses? *Neurourol Urodyn* 2011;30(3):325–328.
24. Oelke M, Khullar V, Wijkstra H. Review on ultrasound measurement of in bladder or detrusor wall thickness in women: Techniques, diagnostic utility, and use in clinical trials. *World J Urol* 2013;31(5):1093–1104.
25. Occhino JA, Trabuco EC, Heisler CA, Klingele CJ, Gebhart JB. Validation of a visual analog scale form of the pelvic organ prolapse/urinary incontinence sexual function questionnaire 12. *Female Pelvic Med Reconstr Surg* 2011;17(5):246–248.
26. Wen Y, Whitin J, Yu T, Cohen H, Polan ML, Chen B. Identification of protein marker in vaginal wall tissues of women with stress urinary incontinence by protein chip array. *J Obstet Gynaecol Res* 2012;38(1):89–96.
27. Zhou L, Lee JH, Wen Y, Constantinou C, Yoshinobu M, Omata S, Chen B. Biomechanical properties and associated collagen composition in vaginal tissue of women with pelvic organ prolapse. *J Urol* 2012;188(3):875–880.
28. Kono A, Oguri A, Yokoo K, Watanabe H. YAG laser treatment causes rapid degeneration and regeneration of collagen fibres in pig skin and facilitates fibroblast growth. *J Plast Surg Hand Surg* 2012;46:308–312.
29. Chen B, Wen Y, Li H, Polan M. Collagen metabolism and turnover in women with stress urinary incontinence and pelvic prolapse. *Int Urogynecol J Pelvic Floor Dysfunct* 2002;13:80–87.
30. Chen H, Lu Y, Qi Y, Bai W, Liao Q. Relationship between the expressions of mitofusin-2 and procollagen in uterosacral ligament fibroblasts of postmenopausal patients with pelvic organ prolapse. *Eur J Obstet Gynecol Reproduct Biol* 2014;174:141–145.
31. Lightner DJ. Review of the available urethral bulking agents. *Curr Opin Urol* 2002;12:333–338.
32. Koelbl H, Saz V, Doerfler D, Haeusler G, Sam C, Hanzal E. Transurethral injection of silicone microimplants for intrinsic urethral sphincter deficiency. *Obstet Gynecol* 1998;92:332–336.
33. Rahn DD, Ward RM, Sanses TV, Carberry C, Mamik MM, Meriwether KV, Olivera CK, Abed H, Balk EM, Murphy M; Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: Systematic review and practice guidelines. *Int Urogynecol J* 2015;26(1):3–13.
34. Varani J, Dame MK, Rittie L, Fligel SEG, Kang S, Fisher GJ, Voorhees JJ. Decreased collagen production in chronologically aged skin: Roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *Am J Pathol* 2006;168(6):1861–1868.
35. Richter HE, Diokno A, Kenton K, Norton P, Albo M, Kraus S, Moalli P, Chai TC, Zimmern P, Litman H, Tennstedt S; Urinary Incontinence Treatment Network. Predictors of treatment failure 24 months after surgery for stress urinary incontinence. *J Urol* 2008;179(3):1024–1030.
36. Dooley Y, Lowenstein L, Kenton K, FitzGerald MP, Brubaker L. Mixed incontinence is more bothersome than pure incontinence subtypes. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19(10):1359–1362.
37. Rickey LM, Huang L, Rahn DD, Hsu Y, Litman HJ, Mueller ER. Risk factors for urgency incontinence in women undergoing stress urinary incontinence surgery. *Adv Urol* 2013;2013:567375. DOI: 10.1155/2013/567375