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Erbium:YAG laser treatment of female stress urinary incontinence: midterm data

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Abstract

Introduction and hypothesis

Stress urinary incontinence (SUI) can be treated by intravaginal laser therapy. We wanted to find out how incontinence severity at baseline and the number of laser interventions affect success rate, and whether the effect of laser therapy was obvious 6 months and 2 years after the last laser intervention.

Methods

Thirty-two women with SUI I, 16 with SUI II and 11 with SUI III were treated with an Erbium:YAG laser following the IncontiLase® protocol. Therapy included 5 laser sessions with a 1 month interval between sessions. Objective (1h-pad test) and subjective data (ICIQ-UI SF, PISQ-12) were assessed at baseline, after two and 4 laser sessions and 6 months and 2 years after the 5th laser session.

Results

Objective cure/improve rates for mild SUI I were 69%, 78%, 91% and 78% after 2, 4 and 5 laser sessions at the 6-month and 2-year follow-ups. Subjective cure rates (ICIQ-UI SF) were 53%, 69%, 72% and 66%, and sexual function (PISQ-12) also improved. For SUI II, objective cure/improve rates were 31%, 63%, 69% and 50%. Subjective cure rate was 13% at the 2-year follow-up. For SUI III, only one patient had an objective improvement after 2 and 4 laser sessions.

Conclusions

Intravaginal laser therapy led to cure/improvement for SUI I and SUI II, but at present, cannot be recommended for severe SUI III. Outcome was better after 4-5 laser sessions than after 2 laser sessions. Follow-up data 6 months and 2 years after laser intervention showed sustainability of the treatment.

Keywords

Erbium:YAG laser; ICIQ-UI SF; intravaginal laser therapy; non-ablative; 1-h pad test; stress urinary incontinence

Brief summary

Intravaginal laser therapy can cure/improve mild to moderate stress urinary incontinence. Three to four laser treatments are effective for up to two years.

INTRODUCTION

Anatomical causes for stress urinary incontinence (SUI) are an insufficient support of urethra and bladder or an impairment of the urethral sphincter and a reduction of urethral closure pressure [1]. Causes for insufficient urethral support may be a loss of pelvic muscle strength due to a damage of pelvic floor innervation after vaginal delivery, an alteration of the mucosa due to the menopausal decrease of estrogen, or an altered composition of the connective tissue and supporting ligaments due to a decreased and insufficient collagen production [2].

SUI should initially be treated by non-surgical management, such as weight reduction, hormonal substitution, physiotherapy, pelvic floor exercise or the use of pessaries [3]. If these treatments do not lead to an improvement within three to six months, an operative intervention is indicated. For the past two decades, tension-free suburethral slings (TVT) were the gold standard for the operative treatment of SUI [3]. Tape insertion is recommended for moderate to severe cases of SUI, preferentially for women after the childbearing age. The trans- or periurethral injection of bulking agents can be an alternative, less invasive treatment option, especially suited for elderly, multi morbid patients [4], or for recurrent SUI after midurethral sling failure [5].

So far, however, there are limited treatment alternatives for younger, active women between pregnancies with a disturbing incontinence, for example during physical exercises. Can the new, minimally invasive intravaginal laser therapy be an option for this patient group?

Currently, three different laser techniques are available for treating SUI: the microablative fractional carbon dioxide (CO_2) laser (10,600 nm) [6], the dual-phase Erbium:YAG laser (2,940

nm) combining fractional cold ablation and thermal ablation [7], and the non-ablative Erbium:YAG laser (2,940 nm) with SMOOTH mode technology [8]. In all three cases, the laser therapy induces neocollagenesis, thickens and strengthens the anterior vaginal wall, that leads to an improved support of bladder and urethra and consequently, to continence.

Randomized controlled trials directly comparing the three laser treatments for SUI are not published. The wavelength of the Erbium:YAG laser, but not of the CO_2 laser matches the absorption peak of water, the major constituent of soft tissue [8]. Therefore, the CO_2 laser penetrates deeper into the tissue [9]. The fractional ablation leads to coagulation and tissue necrosis and a wound healing response with fibroblast stimulation and neocollagenesis [6, 9]. This process is accompanied by pain and a prolonged recovery phase [9]. The dual-phase Erbium:YAG laser therapy is more gentle and less invasive. The cold fractional ablative mode creates small canals into the superficial layer of the vaginal epithelium leaving intact tissue capable of regeneration in between, while the subsequent thermal mode reaches the lamina propria of the vaginal epithelium, irritates collagen fibers and stimulates neocollagenesis. This thermal tissue effect leads to a controlled layer by layer ablation with rapid wound healing without coagulation and tissue necrosis [7].

Most studies on laser treatment of SUI investigated the non-ablative SMOOTH mode technology of the Erbium:YAG laser [8, 10-13]. Special software settings make this treatment even less invasive. Seven consecutive SMOOTH mode pulses of 250 msec, each consisting of six micro pulses with a non-ablative fluence, leave the vaginal epithelium intact. The laser energy is delivered in pulses to a depth of 500-700 μm and the tissue supporting the urethra is heated to

temperatures up to 60°C [8]. This leads to a heat-induced denaturation of dermal collagen, and consequently, to collagen remodeling and new collagen formation [14]. Histologically, also an increase of the epithelial thickness, a higher number of capillaries and an increased volume density of the capillaries was observed [15].

Studies on laser therapy for SUI mostly reported successful outcome. However, individual study results, even when applying the SMOOTH mode technology, cannot be compared due to different laser settings, different numbers of treatment sessions, different patient inclusion and exclusion criteria and different definition of success [16]. Only one randomized controlled trial is available showing subjective superiority of the non-ablative laser over sham treatment at the 3-month follow-up [13]. Published data were often limited by a statistical bias, methodological flaws, and lack of a control group or comparison with other clinically proven treatment modalities [16]. Further limitations are small patient numbers, the absence of dose finding by empirically using 1 or 2 successive laser sessions, only a subjective therapy outcome, short follow-up observation periods between 1 month and maximally 12 months, or no consideration of initial incontinence severity grades. Therefore, international experts unanimously agree that more trials are necessary [16-19].

In this study, we focused on dose finding and a longer follow-up period of the Erbium:YAG therapy with SMOOTH mode technology by comparing outcome after two, 4 and 5 laser sessions and by following therapy outcome for up to two years. We wanted to evaluate both, subjective and objective outcomes and to find out how incontinence severity at baseline affects

success rate. Stringent criteria, similar to previous studies on sling insertions, were used to rate therapy success [20].

MATERIALS AND METHODS

Fifty-nine women with SUI were included at a tertiary urogynecological center. The study was approved by the local ethics committee and patients gave written informed consent. Preoperative SUI and mixed urinary incontinence (MUI; 14/59) were determined as previously described [5, 20, 21]. Patient characteristics, parity and delivery mode, previous operations, grade of prolapse, and presence of intrinsic sphincter deficiency (ISD; 6/59), defined as the urodynamic maximal urethral closure pressure of ≤20 cm H_2O [22], were evaluated at baseline. Severity of SUI was graded by the Stamey's incontinence scoring system, i.e. SUI 0 = no incontinence, SUI I = incontinence with coughing or straining, SUI II = incontinence with change in position and walking, SUI III = total incontinence at all times [23] (Table 1).

Patients were treated with an Erbium:YAG laser (FotonaSmooth XS®; 2940 nm; Fotona, Ljubljana, Slovenia) in the SMOOTH mode following the IncontiLase protocol [24]. If requested, a lidocaine/prilocaine combination cream (Emla®) was applied. The laser protocol included 3 steps: 1) intravaginal laser pulses with a directed angular, patterned laser beam (PS03-GAc, 7 mm, 6 J/cm^2, 1.6 Hz, 7 pulses, 6 passes), 2) intravaginal laser pulses with a circular full laser beam (R11-GCc, 7 mm, 3 J/cm^2, 1.6 Hz, 7 pulses, 2 passes) and 3) laser pulses of vestibule and introitus with a straight, patterned laser (PS03, 7 mm, 10 J/cm2, 1.6 Hz, 2-3 pulses, 2-3 passes). All patients received 5 laser sessions, one at baseline, and one after 1, 2, 3 and 4 months.

Objective (1h-pad test) [25] and subjective ICIQ-UI SF [26, 27] and PISQ-12 [28, 29] data and complications were assessed at baseline, 1 month after the 2nd and the 4th laser session, and 6 months and 2 years after the 5th laser session, i.e. at 0, 2, 4, 10 and 28 months after baseline

(Figure 1). ICIQ-UI SF evaluates subjective incontinence symptoms and quality of life (sum scores: 0= no problems to 21= severe problems) and PISQ-12 assesses 12 subjective symptoms of pelvic organ prolapse, urinary incontinence and sexual function (score: 0= severe problems to 48= no problems or maximum satisfaction). Patients were classed as "cured" based on ≤2 g urine on the 1h-pad test or an ICIQ-UI SF score ≤5. Patients were classed as "improved" when having a 1h-pad weight reduction >50%, and classed as "not-cured" when having a pad weight reduction ≤50% or an ICIQ-UI SF score >5 [11, 20, 27].

Descriptive statistics were used for baseline characteristics, outcome variables and complication rates. Differences among SUI grades were tested with the F-test for normally distributed continuous variables, with the Kruskal-Wallis test for not-normally distributed continuous variables, with Poisson regression for count data and with the Fisher-test for categorical variables. Results were considered to be significant at level $\alpha<0.05$. Statistical analysis and graphic representations of the data were generated using R 3.2.2 for Windows 7.

RESULTS

At time of inclusion, 32 patients had SUI I (54%), 16 had SUI II (27%) and 11 had SUI III (19%). Patient characteristics were shown in Table 1. At baseline, significant differences between groups were only found for BMI (body mass index) and ISD, both being highest in SUI III (Table 1). Patients only had prolapse stages I and II and presence of prolapse was not significantly different between incontinence groups. One hour pad weights, ICIQ-UI SF and PISQ-12 scores were significantly different between SUI groups. Only one patient with SUI III had a previous incontinence surgery with a sling (Table 1).

For SUI I, objective cured/improved rates were 69% (22/32), 78% (25/32), 91% (29/32) or 78% (25/32) 1 month after the 2nd, 1 month after the 4th, or 6 months and 2 years after the 5th laser session, respectively (Figure 2). For SUI II, cured/improved rates were 31% (5/16), 63% (10/16), 69% (11/16) and 50% (8/16), and for SUI III, cured/improved rates were 9% (1/11), 9% (1/11), 0% (0/11) and 0% (0/7) at the same time points (Figure 2). For SUI I, median urine loss decreased from 7 g to 3 g after 2 laser sessions, and stayed at 2 g after 4 or 5 laser sessions (Table 2). Similarly for SUI II, the strongest decrease was found after 2 laser sessions, but 4 or 5 laser sessions led to a further improvement (Table 2). Outcome was equally positive 6 months or 2 years after laser intervention. The laser therapy only had a minor effect on SUI III (Table 2). The four SUI III patients with the highest urine loss at baseline (pad weights ≥50 g), among them the patient with recurrent incontinence dropped out after the 6 month follow-up visit, possibly, because they opted for another incontinence therapy.

For SUI I, subjective cure rates (ICIQ-UI SF) were 53% (17/32), 69% (22/32), 72% (23/32) or 66% (21/32) 1 month after the 2nd, 1 month after the 4th, or 6 months and 2 years after the 5th laser session, respectively (Figure 3). Thirteen percent (2/16) SUI II patients were cured at the 2-years follow-up. Other than that, subjective cure was not found for any SUI II or SUI III patient at any visit (Figure 3). The median ICIQ-UI SF score improved after 2 laser sessions, from 10 to 5 for SUI I and from 15 to 10 for SUI II, and remained at this level, also after 4 or 5 laser sessions (Table 3). Laser treatment did not affect the ICIQ-UI SF score of SUI III (Table 3).

The PISQ-12 score improved from 20 at baseline to 31 at the 6-month follow-up visit for SUI I, from 14 to 24 for SUI II, and from 12 to 15 for SUI III (Table 4).

Complications of laser therapy were minor. For most cases, topical anesthetic cream was not even necessary. Only six patients reported weak pain (11%, 6/57) during or after laser therapy. The pain was transient and restricted to the first few days after laser application. One patient (1/57; 2%) had a vaginal discharge. Data were not available for two patients.

DISCUSSION

Laser therapy has become increasingly popular, primarily in dermatology and cosmetics, but more and more also in aesthetic gynecology and urogynecology. In 2018, the US Food and Drug Administration (FDA) has issued a warning that energy-based medical devices have not been cleared or approved to perform vaginal "rejuvenation," cosmetic vaginal procedures, or non-surgical vaginal procedures. Consequently, leading researchers in the field of urogynecology stated that a strict training of gynecology professionals and robust clinical trials are necessary to demonstrate the long-term complication profile, safety, and efficacy of nonsurgical and surgical lasers [17, 30].

In this study, we evaluated objective and subjective outcome of intravaginal Erbium:YAG laser therapy with SMOOTH mode technology to treat SUI. Objective therapy success depended on initial incontinence severity. At the 6-months post-laser visit, initial pad weights of 5-10 g had a cure rate of 67% (20/30), an improvement rate of 27% (8/30) and a failure rate of 7% (2/30); 11-20 g urine loss resulted in 7% (1/15) cure, 73% (11/15) improvement and 20% (3/15) failure; 21-86 g loss led to a failure rate of 100% (14/14). Similarly, also subjective success depended on initial severity. An ICIQ-UI SF score of 6-10 at baseline resulted in 79% (19/24) success and 21% (5/24) failure; a score of 11-21 resulted in 11% (4/35) success and 89% (31/35) failure. Therefore, laser therapy should only be recommended for patients with a urine loss ≤20 g or an ICIQ-UI SF score ≤10.

A strength of this trial is the evaluation of both, objective and subjective outcome. To investigate an association of objective and subjective improvement, we compared improvement in the pad

test with the results of the ICIQ-UI SF question addressing the quality of life ("Overall, how much does leaking urine interfere with your everyday life?"). At the 6-month follow-up visit, only 10 of the 18 objectively improved patients (56%) also indicated subjective improvement (reduction of VAS score >50% compared to baseline), while the therapy subjectively failed for the remaining 8 patients (reduction of VAS score ≤50% compared to baseline). The fact that objective outcome was better than subjective outcome may reflect that the laser therapy could not meet the patients' very high expectations. Therefore, rational outcomes and expectations should be discussed before offering laser therapy for SUI.

Patients with mild to moderate SUI are good candidates for laser therapy. However, classification of SUI grades is defined by different criteria in literature. According to the subjective criteria by Klovning [27], none of our patients would fall into SUI category I defined by an ICIQ-UI SF score of 1-5. Conversely, according to objective criteria by the International Continence Society [25], 8 of our SUI III patients (Stamey grading [23]) would fall into SUI category II defined by a 1h-pad weight of 11-50 g. These discrepancies show the difficulty to choose the right assessment criteria for successful laser therapy.

In this study, we made a dose finding and evaluated short and midterm follow-up data (Figures 2 and 3). Already 2 laser sessions showed a major cure/improvement, but success was even higher after 4 sessions, while outcome after 5 sessions was similar to 4 sessions. Therefore, 3 to 4 laser sessions at intervals of 1 month seem ideal for most effective laser therapy. Outcomes at the 6

month and 2 year follow-up visits were similar, indicating that laser treatment is sustainable and does not need to be repeated within 2 years after laser therapy.

Limitations of this study are the relatively small case number, the lack of a placebo group, no direct comparison with an alternative treatment group, and the absence of urodynamics. However, two large European, randomized, single blinded, sham-controlled multicenter studies in which we also participate are expected to overcome some of these limitations. A search on the ClinicalTrials.gov database revealed that even more data will be available in the future.

We recommend intravaginal laser therapy for younger women between childbirths with a disturbing incontinence, for example during sports activity. In addition, the therapy is minimally invasive, has few and only minor complications and may be a valuable option for women being afraid of incontinence surgery or having had bad experiences with a previous surgery. Further advantages of laser treatment are the absence of synthetic material and the ambulatory setting.

Mild to moderate SUI can successfully be treated by an Erbium:YAG laser with non-ablative SMOOTH mode technology. Three to 4 laser sessions at intervals of 1 month are ideal and the therapy is effective for up to two years post treatment. Besides the incontinence severity grade, medical history and predisposition, but also personal preferences determine whether SUI should be treated by suburethral slings, bulking agents or laser therapy. According to this study, laser therapy is an ideal option for women between pregnancies who seek a fast, ambulatory, minimally invasive intervention free of synthetic material.

Conflict of Interest: The authors declare that they have no conflict of interest.

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FIGURE LEGENDS

Figure 1

Study plan. Time points of laser treatments (black marks) and objective and subjective symptom assessments (red marks) are shown. BL: baseline; M: month

Figure 2

1-h pad test. Objective cure rates [%] are shown for patients with initial SUI I, SUI II or SUI III at the following time points: 1 month after 2 laser sessions (2 M), 1 month after 4 laser sessions (4 M) and 6 months and 2 years after the 5^{th} laser session (10 M and 28 M). M: month; color code: green = cured (pad weight ≤2 g), orange = improved (pad weight reduction of >50% compared to baseline), red = not-cured (pad weight reduction of ≤50 % compared to baseline)

Figure 3

ICIQ-UI SF score. Subjective cure rates [%] are shown for patients with initial SUI I, SUI II or SUI III at the following time points: 1 month after 2 laser sessions (2 M), 1 month after 4 laser sessions (4 M) and 6 months and 2 years after the 5^{th} laser session (10 M and 28 M). M: month; color code: green = cured (ICIQ-UI SF ≤5), red = not-cured (ICIQ-UI SF >5).

Table 1. Baseline patient characteristics

Patient characteristics	N=59	SUI I (N=32)	SUI II (N=16)	SUI III (N=11)	p-value
Age, mean (SD)	49 (11)	48 (13)	48 (7)	51 (12)	0.736 [a]
BMI, mean (SD)	26 (4)	24 (3)	27 (2)	28 (5)	0.001 [a]
Parity, mean (min-max)	1.6 (0-3)	1.5 (0-3)	1.8 (0-3)	1.9 (1-3)	0.513 [b]
MUI, # (%)	14 (24%)	5 (16%)	5 (31%)	4 (36%)	0.242 [c]
ISD, # (%)	6 (10%)	0 (0%)	1 (6%)	5 (46%)	<0.001 [c]
Postmenopausal, # (%)	25 (42%)	13 (41%)	6 (38%)	6 (55%)	0.680 [c]
Delivery mode, # (%)	_____	_____	_____	_____	0.808 [c]
No	4 (7%)	3 (9%)	1 (6%)	0 (0%)	-
Spontaneous	44 (75%)	21 (66%)	13 (82%)	10 (91%)	-
Sectio	6 (10%)	5 (16%)	1 (6%)	0 (0%)	-
Forceps/vacuum	5 (8%)	3 (9%)	1 (6%)	1 (9%)	-
Previous operations, # (%)	_____	_____	_____	_____	0.119 [c]
No	42 (71%)	25 (79%)	12 (75%)	5 (46%)	-
Abdominal hysterectomy	3 (5%)	1 (3%)	2 (13%)	0 (0)	-
Vaginal hysterectomy	6 (10%)	2 (6%)	1 (6%)	3 (27%)	-
Anterior colporrhaphy	4 (7%)	2 (6%)	0 (0%)	2 (18%)	-
Vaginal hysterectomy and anterior colporrhaphy	2 (3%)	1 (3%)	1 (6%)	0 (0)	-
Vaginal hysterectomy and posterior mesh	1 (2%)	1 (3%)	0 (0%)	0 (0)	-
Incontinence surgery	1 (2%)	0 (0%)	0 (0%)	1 (9%)	-
Assessment at baseline	_____	_____	_____	_____	
1h-pad weight, median (IQR) (min-max)	10 (7-19) (5-86)	7 (6-8) (5-14)	15 (14-18) (10-25)	35 (29-54) (22-86)	<0.001 [d]
ICIQ-UI SF, median (IQR) (min-max)	13 (10-16) (6-20)	10 (8-11) (6-19)	15 (14-16) (10-18)	18 (17-20) (14-20)	<0.001 [d]
PISQ-12, median (IQR) (min-max)	16 (13-20) (8-28)	20 (16-22) (10-28)	14 (12-15) (12-18)	12 (10-12) (8-15)	<0.001 [d]

[a] F-test for normally distributed continuous variables. [b] Poisson regression for count data. [c] Fisher-test for categorical variables. [d] Kruskal-Wallis test for continuous variables not normally distributed. SUI, stress urinary incontinence; BMI, body mass index; MUI, mixed urinary incontinence; ISD, intrinsic sphincter deficiency; SD, standard deviation; IQR, interquartile range.

Table 2. Objective outcome (1h-pad test)

Pad weight [g]	**SUI I (N=32)**	**SUI II (N=16)**	**SUI III (N=11)**
Baseline, Median (IQR)	7 (6-8)	15 (14-18)	35 (29-54)
(Min-Max)	(5-14)	(10-25)	(22-86)
1 month after 2x laser (2 M)			
Median (IQR)	3 (2-4)	9 (5-11)	24 (20-40)
(Min-Max)	(1-8)	(3-20)	(10-63)
1 month after 4x laser (4 M)			
Median (IQR)	2 (1-4)	8 (5-9)	25 (20-41)
(Min-Max)	(0-9)	(2-16)	(11-72)
6 months after 5x laser (10 M)			
Median (IQR)	2 (0-3)	7 (5-10)	30 (20-47)
(Min-Max)	(0-10)	(3-18)	(13-75)
2 years after 5x laser (28 M)			(N=7)
Median (IQR)	2 (1-3)	8 (3-12)	28 (18-33)
(Min-Max)	(0-9)	(0-21)	(16-41)

SUI, stress urinary incontinence; M, months; IQR, interquartile range

Table 3. Subjective outcome (ICIQ-UI SF questionnaire)

ICIQ-UI SF score	**SUI I (N=32)**	**SUI II (N=16)**	**SUI III (N=11)**
Baseline, Median (IQR)	10 (8-11)	15 (14-16)	18 (17-20)
(Min-Max)	(6-19)	(10-18)	(14-20)
1 month after 2x laser (2 M)			
Median (IQR)	5 (5-7)	10 (9-12)	17 (15-19)
(Min-Max)	(3-19)	(6-17)	(11-20)
1 month after 4x laser (4 M)			
Median (IQR)	5 (2-6)	10 (8-11)	17 (16-19)
(Min-Max)	(0-19)	(6-17)	(10-20)
6 months after 5x laser (10 M)			
Median (IQR)	5 (0-6)	9 (8-12)	17 (15-20)
(Min-Max)	(0-19)	(6-17)	(9-20)
2 years after 5x laser (28 M)			(N=7)
Median (IQR)	5 (4-6)	10 (8-15)	18 (16-18)
(Min-Max)	(0-16)	(4-20)	(12-18)

SUI, stress urinary incontinence; M, months; IQR, interquartile range

Table 4. Subjective outcome (PISQ-12 questionnaire)

PISQ-12 score	**SUI I (N=32)**	**SUI II (N=16)**	**SUI III (N=11)**
Baseline, Median (IQR)	20 (16-22)	14 (12-15)	12 (10-12)
(Min-Max)	(10-28)	(12-18)	(8-15)
1 month after 2x laser (2 M)			
Median (IQR)	28 (24-29)	22 (19-25)	14 (13-18)
(Min-Max)	(18-32)	(16-30)	(10-20)
1 month after 4x laser (4 M)			
Median (IQR)	30 (28-32)	23 (22-26)	14 (13-15)
(Min-Max)	(19-33)	(16-30)	(10-22)
6 months after 5x laser (10 M)			
Median (IQR)	31 (30-32)	24 (20-28)	15 (13-16)
(Min-Max)	(17-34)	(14-31)	(12-23)
2 years after 5x laser (28 M)			(N=7)
Median (IQR)	31 (29-32)	20 (18-28)	17 (14-18)
(Min-Max)	(20-33)	(14-33)	(12-20)

SUI, stress urinary incontinence; M, months; IQR, interquartile range