

Vaginal CO2 Laser for Stress Incontinence: A randomized controlled trial (1)

Trial registration: [to come at clinical trialgs.gov](#)

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Written by: Benny Kirschner, Josephine Obel and Jeppe Bennekou Schroll

This protocol has been developed in accordance with the SPIRIT guidelines. Numbers referring to requirements from Danish Ethics Committee has been written in parenthesis.

Introduction (2)

Urinary incontinence (UI) is a common condition affecting nearly 50% of women at some point in their life (MinassianVA, *Obstet Gynecol.* 2008). The prevalence is increasing with age and is often a great burden for the patient with serious implications on the quality of life (Schreiber, ACTA 2017). Studies report that only 25% of affected women seek help for their incontinence symptoms and of those, less than half receive treatment (MinassianVA, *Int Urogynecol J.* 2012). UI is typically divided into 3 main types, namely (i.) stress urinary incontinence (SUI), which affects up to 30% of women (Ogah, Neurol. and uro., 2011) and is characterized by involuntary loss of urine with increases in intra-abdominal pressure such as exercise and coughing, (ii.) urgency incontinence, which is characterized by a sudden compelling desire to pass urine that is difficult to defer (Abrams, Neurolourol. Urodyn, 2010) and (iii.) mixed urinary incontinence, where symptoms of both stress and urgency incontinence are found. SUI is caused by poorly functioning urethral closure and is characterised by loss of anatomic support in the pelvic area. This anatomic defect can be caused by multiple pregnancies, vaginal childbirth, obesity and repetitive increase in intra-abdominal pressure, such as seen in chronic obstipation or coughing, heavy lifting and high-impact exercise (HandaVL, *Obstet Gynecol.* 2011// HandaVL, *Am J Obstet Gynecol.* 2004 //LawrenceJM, *Diabetes Care.* 2007// Nygaard IE, *Am J Obstet Gynecol.* 2016). Urgency incontinence is typically idiopathic although it is also seen in women with general neurologic disorders, such as Parkinson disease, multiple sclerosis and pelvic or spinal nerve injury.

Initial treatment of urinary incontinence typically starts with non-invasive measures, due to the fact that related benefits are associated with low risks and limited expenses. These measures include lifestyle modifications, such as weight loss, smoking cessation, treatment of obstipation, alcohol- and caffeine-restriction, avoidance of excess fluid intake and fluid- and voiding-management. Systematic reviews report that pelvic floor exercises in women with IU are beneficial (Hay-Smith EJ *Cochrane Database Syst Rev.* 2011). A systematic review found that 59% of women with stress urinary incontinence were cured after 12 months of supervised pelvic floor muscle training. (RiemsmaR,HagenS, *BMC Med.* 2017).

Treatment of SUI aims at strengthening the pelvic floor and stabilize urethral mobility. Non-invasive treatment of SUI includes pelvic floor muscle training and use of vaginal devices. There are studies that indicate that bladder control pessaries are effective and may be preferable for women, who have SUI during specific situations as for example, during exercise (Lipp A, *Cochrane Database Syst Rev* 2014.) Furthermore, there are over-the-counter vaginal devices, such as Contrelle® or Impressa® that are SUI specific, and may be better tolerated as they are easier to self- administer. Women with symptoms of SUI in spite of conservative non-invasive treatment may be candidates for surgery. Currently, the most commonly performed surgery for SUI is the midurethral sling, a 30-minute outpatient procedure in which a synthetic mesh sling is placed through either a retropubic or transobturator approach. (Nager CW. *Am J Obstet Gynecol.* 2016). The midurethral sling is the most extensively studied procedure for SUI, with documented short-term efficacy (>5 yrs.) between 43- 92% (Ford AA, *RCochrane Database Syst Rev.* 2015// Schimpf MO, *Am J Obstet Gynecol.* 2014). Complication rates of this procedure is low, but includes risk of bladder- or

urethral lesion, urinary retention, haematoma, pain, worsening of urgency, dyspareunia and sling erosion (Ford AA, *R Cochrane Database Syst Rev*. 2015// Morling JR, *Lancet*. 2017// Anger JT, *Urology*. 2014)

A novel minimal-invasive method of treating UI, has been introduced in the recent years, namely vaginal laser treatment. The use of laser has now been described in pelvic organ prolapse, UI and genito-urinary symptoms of menopause. Bhide et al have recently published a review article, where they describe 5 prospective cohort studies of laser-treatment of SUI (Table 1) (Bhide AA, *Int. Urogyn. Journ.*, 2018). Gambacciani et al. published a study of 45 women with IU, of whom 19 had SUI (Gambacciani M, *Ital J Gynaecol Obstet*. 2015). Vaginal treatment included application of YAG laser 3 times with 1 month apart and symptoms were evaluated at baseline and at a 3- and 6-month follow-up with ICIQ-U1 SF questionnaire. The treatment induced a significant decrease in ICIQ-U1 at 3 months with decrease of ICIQ scores from 12.0+/- 1.8 to 5.6+/-2.6 and this was still significant at 6 months. Ogrinc et al published a study on the use of YAG laser on women with IU, of whom 115 had SUI. Symptoms were evaluated at baseline and at 12-months follow-up with Incontinence Severity Index (ISI) and all women showed significantly decreased ISI scores (Ogrinc UB, *Lasers Surg Med*. 2015). Fistonic et al published two studies of the use of a single application of YAG laser in the treatment of SUI and evaluated with ICIQ-U1 SF. The first study evaluated 31 women with SUI and follow-up at 1- 2- and 6- months showed significantly reduced ICIQ-IU SF scores albeit many of women were lost to follow-up (Fistonić N., *YAG. Lasers Med. Sci.* 2016). The next study of 73 women with SUI showed 72.3% experiencing improvement of symptoms, 23.4% experiencing no change and 4.3% experiencing worsening (Fistonić N, *Climacteric*. 2015). Pardo et al. evaluated the vaginal erbium:YAG laser in a longitudinal prospective study in 42 patients with SUI (Pardo JI, *Eur J Obstet Gynecol Reprod Biol*. 2016). Treatment was applied twice with 21- 28 days apart and median ICIQ-IU SF scores, which was reported at 3- and 6- months follow-up, was significantly reduced; 78.6% reported improvement of SUI and 38.1% reported a complete remission of SUI. Gambacciani et al. studied 205 post-menopausal women of which 114 were diagnosed with SUI. In this study, three vaginal erbium:YAG laser applications were administered at 30-day intervals, and ICIQ-SF was used to evaluate before and after treatment with follow-up up to 24 months post treatment (Gambacciani M, *Climacteric*. 2018). The results demonstrated a significant decrease in ICIQ-SF scores from baseline to 12 months post treatment. However, at 18 and 24 months, ICIQ-SF scores were not significantly different from baseline. All 5 studies used a non-randomised selection of patients and treatment effect was estimated by using pre-treatment incontinence scores for comparison . Only the YAG laser has been evaluated in a randomized trial with 114 women which found significant improvement in the ICIQ-SF scores in the treatment arm compared with placebo (Bleganje 2018). None of the mentioned studies showed any serious complications or side effects of the laser treatment.

The FDA has recently pointed out that there is a lack of evidence of efficacy and safety of vaginal laser in the treatment of urogenital symptoms in women

(<https://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm615013.htm>). Of this reason, it is important to investigate this type of treatment in controlled, protocol-based studies, before general use is disseminated. Vaginal laser is a relatively new approach in the treatment of women with SUI. The treatment has shown promising results, and only the YAG laser has been evaluated in a randomized trial (Blaganje 2018).

Furthermore, many of the earlier studies have been supported by the private sector and so sceptics will claim that there is a potential of biased results (Conte C, Journal de l'Association française d'urologie et de la Societe française d'urologie. 2017). It is important that all new treatment-regimes in the public health care are tested and compared to existing regimes and placebo, not only medical drugs.

Transvaginal treatment with the MonaLisa Touch laser system has been shown to be safe and without major complications or side effects, when used in women with vaginal atrophy. The system is thought to work by stimulating growth and remodelling of collagens in the vaginal support tissue. Furthermore, it is assumed, that intravaginal laser treatment can stimulate the growth of urethral collagen, thereby reducing urethral mobility and increasing intraurethral pressure, and so should potentially reduce symptoms of SUI.

Our aim with this study is to determine if transvaginal CO₂ laser- treatment (DEKA SmartXide² Laser System, MonaLisa Touch), renders significant effect in women with SUI. To best test this hypothesis, the study will be performed in a prospective, randomised controlled fashion in our institution. We will measure the effect as patient reported improvement using a validated scale as well as an objective measurement.

Methods (3)

Study setting

Patient will be included from our hospital (a Danish academic hospital) among women referred with incontinence. Eligible patients will be randomized to either laser treatment or "sham" laser treatment.

Eligibility criteria (5)

The study will take place in the department of Gynecology and Obstetrics of Hvidovre University Hospital, Copenhagen Denmark in the period of May 2019 to May 2020. Inclusion criteria for the study cohort and controls will be patients i. referred from specialist gynecologists or GPs with SUI; ii. speak and understand Danish; iii. has a voiding diary that indicates stress incontinence; iv. older than 18 years of age; vii. with BMI under 35; viii. and present with mild to severe SUI evaluated after ICIQ-SF (slight (1-5), moderate (6-12), severe (13-18) and very severe (19-21), Kloving 2009). Exclusion criteria presence of pelvic organ prolapse greater than stage II by the POP-Q system, previous pelvic surgery, current infections, keloid formation, vaginal pain, dyspareunia and ongoing pregnancy.

Interventions

In this study, women will receive a series of three treatments using a fractional (pulsed) CO₂ laser system (SmartXide² MonaLisa Touch, DEKA M.E.L.A Srl, Florence, Italy), each performed in an outpatient setting without analgesia. A tubular laser-probe is inserted in the vaginal canal until reaching the vaginal vault. A burst of laser pulses is transmitted through the probe and deflected at 90° in four directions towards the vaginal wall, then rotated 45° for a second burst of pulses. Guided by markings on the probe, it is withdrawn

4mm and the procedure is repeated until reaching the introitus. Treatment parameters include power 30W, dwell time 1000 μ s, 1000 μ m spacing, using normal scan mode, with Smartstack setting for 1 at first application and 3 for the next two applications.

Both study- and placebo- treatments will be performed by specialist gynecologists employed in the department. Patients, who meet inclusion criteria and consent to study participation, will be randomized by computer service [REF] to conservative treatment, which encompass local estrogens (Vagifem 10 μ g twice weekly) if relevant (postmenopausal women) and pelvic floor training supervised by specialised physiotherapists in our own institution, whilst the study cohort will receive the same treatment with the addition of transvaginal laser applied thrice with 25- 45 days apart (CO₂ laser- treatment (DEKA SmartXide² Laser System, MonaLisa Touch). The controls will receive placebo treatment, with the use of the inactive laser, but relevant sound effects.

Outcomes

Primary outcome of the study is patient experienced improvement of SUI evaluated by standardized ICIQ-SF questionnaire.

Our secondary outcome is objective improvement as measured by standardized stress test performed by specialist nurse before treatment and 1-2 month after last laser or placebo treatment. The bladder is emptied with a catheter and 300ml of saline is inserted. The patient is then stood up wearing a pad with legs slightly apart and asked to forcefully cough 3 timers. The examiner registers whether there is incontinence as either yes or no as well as grams of urine leakage in the pad. Furthermore, side- effects both positive and negative as well as patient satisfaction will be registered by the use of patient questionnaires at 1-2 months post treatment.

Participant timeline

Timeline after inclusion

- 1st visit in outpatient clinic: evaluation by nurse or physician; instruction in minimal care treatment, pelvic examination, evaluation of bladder diary, evaluation of study eligibility and randomization. Baseline information registered in case report form and referral to physiotherapy.
- 2nd visit. 1st Laser/placebo treatment
- 3rd visit 2nd Laser/placebo treatment (between 20 and 40 days after previous treatment)
- 4th visit 3rd Laser/placebo treatment (between 20 and 40 days after previous treatment)
- 5th visit. Follow up 1-2 months after last treatment. ICIQ-SF questionnaires, clinical examination and standardized stress test. Information registered in case report form.

Both study-cohort and controls will receive pelvic floor training supervised by specialised physiotherapists. If the treatment is evaluated as unsuccessful, next treatment option will be considered.

4. Sample size

Based on variation and observed effect of more than 2 points from other studies (Blagajna 2018) on the ICIQ-UI SF scale we have calculated that 20 patients in each group would be sufficient even with 20% dropout to show a difference. The assumptions are significance level of 0,05 and a risk of type 2 error set to 20%.

Recruitment

All urogynecologist and specialised urogynecological nurses at the department will be actively involved in the study and will be actively including patients.

Methods: Assignment of interventions (for controlled trials)

Sequence generation

A computer will generate the numbers using blocks of 6.

Allocation concealment mechanism

Allocation will be hidden in a computer program.

Implementation

The data manager will do the sequence generation. Doctors at the urogynecological clinical will enroll patients and assignment will occur when patient data is submitted in the electronical case report form.

Blinding (masking)

The patient and the outcome assessor (nurse) will be blinded. However, the doctor performing the laser treatment cannot be blinded.

Unblinding will occur if a patient suffers adverse events that requires treatment or exclusion of the trial.

Methods: Data collection, management, and analysis

Data collection methods

Baseline data will be recorded: age, BMI, parity, ICIQ-UI SF, standardized stress test, degree of pelvic prolapse. All data will be saved in RedCAP, which will provide facilities for randomization as well as ensure that data are being stored according to Danish legislation.

ICIQ-UI SF is a validated scale for measuring degree of stress incontinence and has been used in many studies.

Data collection forms will be constructed in RedCap.

Both the study cohort and controls will be contacted by telephone, if they do not come for follow-up treatment or data-collection.

Nurses will be instructed in the standardized stress test.

Statistical methods

The post treatment scores will be compared using Students t-test for the primary outcome and chi square test for dichotomous outcomes. Our strategy is an intention to treat analysis when possible. Clinically significant differences of our primary outcome is probably at least 2 points.

Methods: Monitoring (6)

Data monitoring

All investigators will be part of the monitoring board and will decide whether the trial should be terminated. No interim analysis are planned due to the few patients involved.

Harms

All harms will be reported verbatim. Serious adverse events will be discussed by the monitoring board within two work days.

Auditing

No auditing is planned as the procedures and measurements will be carried out by very few health workers.

Ethics and dissemination

Research ethics approval

Relevant approvals from ethics committee and data protection agency will be obtained.

Protocol amendments

Protocol amendments will be reported to ethics committees and trial registries.

Consent or assent (12)

Written and oral consent will be obtained and documented recruiting gynaecologist or specialized nurse in the outpatient clinic. At the clinic patients are attended individually in a separate room. If they are interested they will be scheduled for treatment. In the mean time they can consult with their doctor or family.

Confidentiality

Data will be collected, stored and reported in accordance with Danish legislation and approval from the data protection agency will be obtained.

Declaration of interests

All investigators will have to provide a declaration of interest before the study begins. Investigators with conflicts to the manufacturer of the Laser device will not be able to participate in this study.

Access to data

Only investigators will have access to data. Data will either be anonymized or destroyed a few years after the study finishes.

Ancillary and post-trial care (11, 15)

As this treatment is already being used in Denmark, patients that suffer damage will be eligible to compensation through the 'Patienterstatningen'.

No participation fee for participant will be given.

Dissemination policy (13)

Results will be reported in peer reviews journals and the study results will be registered at clinicaltrials.gov.

Professional writes will not be used. We will share our data to the extent it does not interfere with privacy and Danish legislation.

Economy (10)

Hvidovre hospital has so far funded the project with 60.000. The project has been initiated by the authors of the protocol. Additional funding will be sought to employ a PhD student for managing data, doing analyses and writing the paper. The department will pay for salary of the nurses and treating physicians and the Laser is already at our institution.

Additional information to Danish ethics committee

7. Biological material

No biological material will be collected

8. Information from patient charts

We will ask patients permission to look up weight, height, medicine and prior illnesses from their chart. We will also ask permission to look up admission 12 months following last treatment. This is required to monitor adverse events.

9. Handling of patient information

All patient data will be safely stored in accordance with Danish legislation. Approval from the data protection agency will be obtained.

14. Research ethics

The treatment has already been introduced at several hospitals and private clinics and the risk is considered acceptable. Future patients could potentially avoid a surgical procedure that is associated with complications.

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Table 1.

Gambacciani et al., 2015 [6]	19	60.9 ± 8.1	Prospective cohort	Vaginal erbium:YAG	SUI	Follow-up at 3 months post-treatment	ICIQ-UI SF
Ogrinc et al., 2015 [7]	175	49.7 ± 10	Prospective cohort	Vaginal erbium:YAG	MUI	Follow-up at 12 months	ICIQ-SF, ISI
Fistonic et al., 2016 [8]	31	46.6	Prospective cohort	Vaginal erbium:YAG	SUI	Follow-up at 1, 2 and 6 months	ICIQ-SF UI
Fistonic et al., 2016 [9]	73	47 (41–54)*	Prospective cohort	Vaginal erbium:YAG	SUI	Follow-up at 1, 2–6 months	ICIQ-SF UI
Pardo et al., 2016 [10]	42	46.5 (30–70)*	Prospective cohort	Vaginal erbium:YAG	SUI	Follow-up at 3–6 months	ICIQ-SF
Pitsoumi et al., 2016 [11]	53	57.2 ± 5.4	Prospective cohort	CO ₂ laser	LUTS	Follow-up 3 months	ICIQ-FLUTS, ICIQ-UI SF, UDI, KHQ
Gaspar et al., 2017 [12]	22	57.9	Prospective cohort	Intra-urethral erbium:YAG	Type III stress incontinence	Follow-up at 3 and 6 months	ICIQ-UI SF
Gambacciani et al., 2018 [13]	114	64.6 ± 4.4	Prospective cohort	Vaginal erbium:YAG	SUI	Follow-up at 12, 18 and 24 months	ICIQ-SF

