

# Fractional CO<sub>2</sub> Laser Versus Urogynecological Physiotherapy in Women With Stress Urinary Incontinence: Study Protocol for a Randomized Clinical Trial

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## Abstract

**Background:** Stress urinary incontinence (SUI) is recognized as an involuntary loss of urine during physical exertion or a sudden increase in intra-abdominal pressure, such as sneezing and coughing. It is a condition that affects 15% to 30% of women and can negatively impact quality of life, including professional, social, psychological and sexual aspects. Although surgical treatment is considered the gold standard for SUI, it is necessary to offer non-invasive treatments for women with this condition. Pelvic floor muscle training (PFMT) is a physiotherapy modality with proven effectiveness for SUI. The carbon dioxide (CO<sub>2</sub>) laser is a new tool that has been offered to women with urogenital atrophy, but its effectiveness for SUI is not yet known. We present a study protocol for a prospective non-inferiority randomized clinical trial, comparing the efficacy and safety of CO<sub>2</sub> laser versus physiotherapy for treatment in women with SUI.

**Methods:** Participants recruited for this study (n = 94) will be randomly assigned to two groups. The laser group will receive three vaginal CO<sub>2</sub> laser applications at monthly intervals. The physiotherapy group will undergo 12 weeks of PFMT, twice a week. The impact on SUI, colorectal-anal, pelvic organ prolapse and sexual function will be assessed using validated questionnaires. The response rate to interventions will also be measured. Patients will be assessed at baseline, 3 and 6 months after the intervention. As this is a study protocol, the study is ongoing with an expected end of recruitment and analysis date of 2022.

**Discussion:** The results of this trial will make it possible to evaluate the efficacy and safety of a non-invasive method for the treatment of women with SUI, and offer it as a conservative alternative and a potential option for doctors before making the surgical decision. To date, such evaluation has not been performed, and this intervention we will evaluate is the impact of laser therapy on SUI, quality of life, and sexual dysfunction.

**Keywords:** Fractional CO<sub>2</sub> laser; Vaginal laser; Pelvic floor muscle training; Stress urinary incontinence; Physiotherapy; Randomized controlled trial

## Introduction

Urinary incontinence is defined by the International Continence Society (ICS) and International Urogynecological Association (IUGA) as any involuntary loss of urine with impaired quality of life, and is subdivided into three types: stress urinary incontinence (SUI), urge urinary incontinence (UII) and mixed urinary incontinence (MUI). SUI is recognized as an involuntary loss of urine during physical exertion or a sudden increase in intra-abdominal pressure, such as sneezing and coughing [1]. It is a condition that affects 15% to 30% of women and can negatively impact quality of life, including professional, social, psychological and sexual aspects [2]. It is estimated that 16% of women under 30 and 29% between 30 and 60 years of age suffer from SUI, which is the predominant type of urinary incontinence in young women [3].

Physiotherapy, a safe and non-invasive form of treatment is recommended as the initial management of SUI, including supervised pelvic floor muscle training (PFMT) [4]. Approximately 65% of women report improvement with physical therapy and 15-25% will be completely cured in the short term; however, adherence to treatment is problematic in the long term (> 5 years) of follow-up with approximately 30-50% of patients undergoing surgical treatment [5].

There are approximately more than 150 surgical procedures for the treatment of SUI; however, there have been changes in terms of techniques, access routes and minimally invasive options such as slings in recent years [6]. For situations in which the patient cannot progress to surgery, more conservative options are needed to treat this patient. The application of devices with energy in the vaginal canal is an innovative concept in urogynecology that aims to provide the emission of electrical oscillations and electromagnetic radiation together with photothermal heating [7]. In the transvaginal laser, it is estimated that 37% of the energy is absorbed in the endopelvic fascia [8], reaching structures such as the bladder and urethra; a possible positive effect, therefore, on the symp-

Manuscript submitted December 25, 2020, accepted February 13, 2021  
Published online March 17, 2021

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doi: <https://doi.org/10.14740/jcgo713>

toms of SUI. However, in addition to the systematic reviews considering the methodology of some low-quality studies, there is no consensus on the effectiveness and type of laser applied in the treatment of SUI [9].

As far as we know, no clinical trial has demonstrated the efficiency and safety of fractional carbon dioxide (CO<sub>2</sub>) laser compared to physiotherapy in the treatment of SUI. Thus, this study will compare the safety and efficacy of treatment with fractional CO<sub>2</sub> laser (SmartXide2 V2 LR, Monalisa Touch; DEKA) versus physiotherapy in women with SUI not indicated for surgical treatment.

## Materials and Methods

This study is a randomized, prospective, non-inferiority, two-arms, clinical trial, and will investigate the efficacy and safety of fractional CO<sub>2</sub> (SmartXide2 V2 LR, Monalisa Touch; DEKA) laser versus physiotherapy in women with SUI.

### Sample size and setting

There are no randomized studies, to our knowledge, comparing fractional CO<sub>2</sub> laser versus PFMT. We have considered an alpha risk of 0.05 and a beta risk of 0.20 with an estimated loss of follow-up of 10%, and using the final mean scores of the frequency of urinary loss of the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) questionnaire from a previous study (1.36: laser; 1.95: promestriene) and a standard deviation of 1, the present study was developed to address the main objective by enrolling 94 randomized women into two groups, with 47 participants with symptoms and clinical signs of SUI [10]. This study follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the results will be reported according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) [11]. The research will be carried out at the State University of Campinas, UNICAMP, Brazil, and is approved by Ethics Committees and registered with The Brazilian Registry of Clinical Trials (ReBEC) (<http://www.ensaiosclinicos.gov.br/>) U1111-1229-4652 and ClinicalTrials.gov CN02071218. This study is in line with the Helsinki Declaration. Written informed consent will be provided and signed by enrolled patients prior to randomization.

Two groups of women with symptoms and clinical signs of SUI will be enrolled. The efficacy and safety of the intravaginal CO<sub>2</sub> laser (SmartXide2 V2LR, Monalisa Touch; DEKA) will be compared to the physiotherapy group (Table 1).

### Eligibility criteria and recruitment

Women  $\geq$  18 years old with symptoms of SUI, with positive stress test or Valsalva maneuver and/or urodynamic findings of SUI and residual volume less than 100 mL or 20% of urinary volume greater than 300 mL will be included in this study. In cases in which the stress test is negative, women will be

included if there is a complaint in the anamnesis that suggests SUI. The recruited participants will meet the following criteria at the time of randomization.

Women will be excluded in the following circumstances: symptoms of overactive bladder or urodynamic finding of detrusor overactivity; repetitive urinary tract infection; previous urogynecological surgeries; previous radiotherapy treatment; pelvic organ prolapse (POP) > stage 2 for more than 2 years; previous and recent history of bladder stones; and urinary fistula or diverticulum.

The patients will be recruited in a women's health clinic with specialized urogynecology care, in the city of Rio de Janeiro, Brazil. Patients will be invited through advertisements on pamphlets and on social media to attend the clinic where they will receive clarification on SUI. Patients will be evaluated by an experienced urogynecologist who will evaluate whether they meet the inclusion criteria. Patients diagnosed with SUI will be invited to participate in the study and to read and sign the consent form.

### Randomization

Randomization in a 1:1 ratio will be performed by an independent statistician using the free webpage in a sealed envelope (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>). To ensure balance in each group, the block randomization kit will be used. Allocation concealment will be performed by sealed, opaque envelopes. Each number in each group will be placed in opaque envelopes and will be opened by an independent nurse and by each participant after signing the consent form.

### Primary outcome

The impact on SUI will be assessed by the Urinary Impact Questionnaire from Pelvic Floor Impact Questionnaire (PFIQ-7) [12], and by the ICIQ-SF [13].

### Secondary outcomes

The impact on colorectal-anal conditions will be assessed by PFIQ-7 and POP will be also assessed by PFIQ-7 [12] and Pelvic Organ Prolapse Quantification system (POP-Q) [14]. The Female Sexual Function Index (FSFI) [15] will evaluate the patients' sexual function. The intensity of vulvovaginal symptoms will be measured using a 0 - 10 Visual Analogue Scale (VAS) and the patients' impression of improvement after intervention will be recorded using the Patient Global Impression of Improvement (PGI-I) [16].

### Description of the intervention

#### Baseline assessment

Ninety-four women will be submitted to an urogynecology

**Table 1.** Study Schedule of Enrollment, Interventions and Assessment

Time point	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	3 and 6 months follow-up
Enrollment														
Eligibility screen	X													
Informed consent	X													
Allocation														
	X													
Interventions														
Laser group					X				X				X	
Physiotherapy group		X	X	X	X	X	X	X	X	X	X	X	X	
Assessment														
Vaginal examination	X													X
POP-Q	X													X
Valsalva maneuver for SUI	X													X
PFIQ-7	X													X
ICIQ-SF	X													X
FSFI	X													X
PGI-I														X
VAS														X
Adverse events monitoring					X				X				X	X

POP-Q: Pelvic Organ Prolapse Quantification System; SUI: stress urinary incontinence; PFIQ-7: Pelvic Floor Impact Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form; FSFI: Female Sexual Function Index; PGI-I: Patient Global Impression of Improvement; VAS: Visual Analogue Scale.

physical exam in a lithotomy position. The women will undergo vaginal examination, POP-Q staging, and Valsalva maneuver or stress test for SUI. Questionnaires will be applied before the intervention and after 3- and 6-month follow-up, as following: SUI assessment using PFIQ-7 and ICIQ-SF; sexual function assessment using FSFI.

The PFIQ-7 [12] is a questionnaire with seven questions and three subscales: Urinary Impact Questionnaire, Colorectal-Anal Impact Questionnaire, and Pelvic Organ Prolapse Impact Questionnaire. The final score is calculated by multiplying the subscale scores by 33.3 and the total value ranges from 0 to 300.

The ICIQ-SF [13] is a subjective six-item instrument for measuring the severity and impact of urinary incontinence on women's quality of life. The scores for items 1 and 2 are demographic, and 3, 4 and 5 are taken for the final ICIQ-SF score.

The FSFI [15] is a 19-item questionnaire that assesses sexual function in the past 4 weeks. It consists of six domains and a total score is presented at the end of the application. The result of the sum of the scores for each of the six domains is multiplied by a specific factor for each domain and the total score is obtained.

#### *Laser group*

Three CO<sub>2</sub> laser therapies will be applied at monthly intervals. The laser parameters will be as follows: power of 40 W, dwell time of 1,000 ms, dot spacing of 1,000 mm, and a smart stack of 2.0 [17] on the vaginal mucosa, and participants will be advised to avoid sexual activity for at least 5 days after each laser application. Women should return with 3 and 6 months for evaluation.

#### *Physiotherapy group*

A physiotherapist will assess pelvic floor muscles (PFM) function by digital palpation and evaluate if the patient has voluntary control over and awareness of her pelvic floor. The modified Oxford Grading System [18] measurement scale will be used by a physiotherapist and will be incorporated with vaginal palpation in the clinical assessment. Patients will receive an intravaginal electrical stimulation (IES) for four sessions if the Oxford scale is rated 0 point or no contraction is determined. High-frequency stimulation (around 50 Hz) and pulse width greater than 500  $\mu$ s, respecting the patient's sensitivity will be used; ideal intravaginal intensity should be in accordance with the patient's maximum tolerance; rise and fall time = 2/2. On/Off cycle must be calculated according to the initial assessment. The On time must be longer than the support achieved by the patient in the patient's functional examination and the Off time must be three times longer (in cases of weakness) or equal to On (in cases of strengthened muscles). The application of the IES chain in the PFM will be performed with patients in lithotomy. The intravaginal electrode will be introduced into the vaginal cavity with the use of a neutral conductive gel, and the metal rings of the electrode should be positioned at the height of the levator ani muscles (middle third of the vagina). Thus,

the parameters will be selected, and the patient will be stimulated. When the current is passed, the patient must perform voluntary contraction in order to optimize muscle contraction [19]. Patients classified with 1 point according to the Oxford scale, will be introduced in sessions of exercises to strengthen the pelvic floor. The PFMT sessions include a series of contractions sustained for 8 s. Patients will be asked to perform eight times. Between each series, there must be a moment of rest for 6 s; at the end of the sustained contraction repetitions, a series of four rapid contractions should be performed. At the end of these contractions, the patient must change posture and repeat the same sequence. Regarding the postures adopted during the exercises, the patient should adopt variations in the supine position (lying with the knees flexed; lying with the knees extended; with hip elevation), lateral decubitus (with the hip and knees flexed), prone position (with one knee bent); sitting position and four supports, sitting and standing [19, 20]. Patients will undergo 12 weeks of PFMT, twice a week, and will be reassessed at 3 and 6 months after the intervention [19].

#### **Follow-up**

Participants will be assessed at 3 and 6 months follow-up visits and will fill in the previously described questionnaires. Participants will report the pain intensity and will be asked about adverse events after each session of fractional CO<sub>2</sub> laser with 4 weeks intervals between three sessions, which will allow us to monitor immediately and observe for 3 and 6 months findings throughout the trial. The VAS will be used in the laser group for the measurements of pain intensity after laser intervention. Patients will be asked to rate pain symptoms from 0 (no symptom) to 10 (very severe symptom).

The response of the interventions, PGI-I, will be evaluated after the interventions. The PGI-I [16] is a 7-point scale instrument of patient-reported outcome measures following treatment of SUI.

#### **Statistical analysis**

Continuous variables are described as mean/standard deviation or median/percentile and compared by Student's *t*-test. Categorical variables will be displayed by percentages and compared using the Chi-square test or Fisher's test. The subjective and objective cure rates at 3 and 6 months will be compared, respectively, by the Cochran's Q test and by the analysis of variance (ANOVA) test for repeated measures. The analysis of the results will be carried out both by intention to treat and by protocol analysis. A significance level of 5% will be calculated. The data will be stored in a Microsoft Excel tool and analyzed in a statistical package (Intercooled Stata 13.0).

#### **Discussion**

The present randomized clinical trial will evaluate two types of nonsurgical treatments on SUI and other pelvic floor dysfunc-



tions.

PFMT has been recommended as an initial treatment for women with urinary symptoms with level A of evidence [21]. On the other hand, there are fewer studies assessing the safety and efficacy of vaginal laser in treating SUI alone and more studies have evaluated the Erbium YAG therapy for the treatment of SUI compared with CO<sub>2</sub> laser therapy [22].

Regarding laser therapy, the duration of follow-ups varies among studies. In a review of laser therapy for SUI, Conte et al [23] reported a large follow-up interval of 3 - 36 months. Dabaja et al [24] used CO<sub>2</sub> laser therapy in a prospective cohort of women with SUI and showed a significant decrease of symptoms, but without a comparison group of treatment and in a shorter follow-up of 1 - 3 months. The present study will have 6 months of follow-up.

Most trials [7-9, 11, 25-34] evaluated the effects of laser therapy for women with SUI with functional questionnaires but one trial used pad test as the primary outcome measure [35].

The efficacy of vaginal laser therapy for SUI has not been assessed in comparative trials with adequate powered; and to our knowledge, the present study will be the first to evaluate the effects of fractional CO<sub>2</sub> laser compared to physiotherapy for SUI, considered the gold standard for this type of disorder. Besides, our study will also assess the impact of both treatments on symptoms quality of life, bowel control, and the sexuality of women with SUI. Following the release of a US Food and Drug Administration warning in July 2018 regarding the use of vaginal lasers, more robust data will be required to report fractional CO<sub>2</sub> laser indications and adverse events to make an informed decision about vaginal symptoms and SUI.

Thus, this randomized trial will provide data to assist in the management of this prevalent condition and the strong impact on psychological, social, and urogynecological aspects on health and quality of life of women. In addition, the CO<sub>2</sub> laser can become a potentially safe and effective alternative procedure.

## Acknowledgments

None to declare.

## Financial Declaration

Grant 2019/26723-5, Sao Paulo Research Foundation (FAPESP) attributed to Glauca Miranda Varella Pereira as a PhD scholarship.

## Conflict of Interest

The authors declare that they have no competing interests.

## Informed Consent

Written informed consent will be provided and signed by all

enrolled patients.

## Author Contributions

SCRR, LGOB and CRTJ: study protocol development, data collection, methodology, writing of original draft and writing of review and editing. GMVP: writing of review and editing.

## Data Availability

Not applicable.

## Abbreviations

SUI: stress urinary incontinence; PFMT: pelvic floor muscle training; CO<sub>2</sub>: carbon dioxide; ICS: International Continence Society; IUGA: International Urogynecological Association; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; SPIRIT: Standard Protocol Items, Recommendations for Interventional Trials; CONSORT: Consolidated Standards of Reporting Trials; POP: pelvic organ prolapse; POP-Q: pelvic organ prolapse quantification system; PFIQ-7: Pelvic Floor Impact Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form; FSFI: Female Sexual Function Index; PGI-I: Patient Global Impression of Improvement; VAS: Visual Analogue Scale; PFM: pelvic floor muscles; IES: intravaginal electrical stimulation

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