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ORIGINAL PAPER

Effectiveness of CO_2 micro-ablative vaginal laser therapy in the treatment of recurrent cystitis

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Summary *Background: Cystitis is the most common clinical manifestation of urinary tract infection (UTI) in women. Aim: the current study intends to assess the effectiveness of CO_2 micro-ablative vaginal laser therapy in the treatment of recurrent cystitis RC.*

Methods: A total of 75 women were divided in 2 Groups: the Group 1 included 34 women (22 were menopausal women and 12 were non-menopausal women) with bacterial cystitis who were positive to urine culture analysis. The Group 2 included 41 women (34 were menopausal women and 7 were non-menopausal women) with interstitial cystitis who were negative to urine culture analysis. Patients received three treatment sessions with a dual-wavelength (10600 nm/1540 nm) laser system. A visual analog scale (VAS) evaluation, ranging from 0 to 10, was administered to assess baseline and post laser treatment urinary symptoms associated with cystitis. Concerning IUS (stress urinary incontinence) and Urgency score measurements a VAS ranging from 0 to 5 was used. The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) was used as treatment outcome measures.

Results: in both groups, a significant reduction in the average number of cystitis episodes after treatment was observed and the VAS scale showed a significant reduction in pre and post-treatment symptoms. VAS results for patient's satisfaction and expectations showed positive outcomes revealing that more than 90% of patients were satisfied following the treatment.

Conclusions: CO_2 vaginal laser may represent an advantageous therapeutic approach to treating recurrent cystitis.

KEY WORDS: *Recurrent cystitis; CO_2 micro-ablative vaginal laser; Urine culture.*

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INTRODUCTION

One of the most prevalent bacterial infection in the world is *urinary tract infection* (UTI) (1). Recurrent UTIs are defined by symptoms that persist after a previous UTI has resolved; usually in 25% of patients with a previous episode of cystitis, at least 2 other episodes are recorded in 6 months, or 3 in 12 months (2). They have a detrimental effect on patients' quality of life, which lowers their ability to work, their self-esteem, and the quality of their social and sexual connections (3). Patients with UTIs account for 20% of all antibiotic prescriptions written by general practitioners. The GP's selection of antibiotics usually relies on national treatment guidelines and customs, and patients with UTIs are frequently treated empirically without first undergoing culture or susceptibility testing recommendations (4).

Our ability to diagnose, treat, and long-term manage rUTI has evolved due to additional insights into the pathophysiology of rUTI, a new appreciation for the adverse effects of repetitive antimicrobial therapy, rising rates of bacterial *antimicrobial resistance* (AMR), and better reporting of the natural history and clinical outcomes of acute cystitis and rUTI (5).

Cystitis is the most common clinical manifestation of UTIs in women: after puberty, 50-60% of women complain of at least one bout of cystitis (6). Cystitis is defined as bladder inflammation often caused by a bacterial infection. Burning during urination, frequent impulses to urinate, haematuria and suprapubic pain unrelated to urination are all possible symptoms.

In contrast, *interstitial cystitis* (IC), also known as *painful bladder syndrome* (PBS), both non-ulcerative and ulcerative, remains a poorly understood entity that lacks effective, evidence-based treatments. Approximately 5-10% of patients presenting with this symptom complex will have ulcerations in the bladder known as *Hunner lesions* (HL) (7).

Because the term "*interstitial cystitis*" (IC) has different meanings in different centers and different parts of the world, the *European Society for the Study of Interstitial Cystitis* (ESSIC) has worked to create a consensus on definitions, diagnosis, and classification in an attempt to overcome the lack of international agreement on various aspects of IC.

It was agreed to name the disease *Bladder Pain Syndrome* (BPS). BPS would be diagnosed on the basis of chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency.

To facilitate the change of the name, ESSIC agreed to include IC in the overall term (BPS/IC) during this transition period (8).

Today, interstitial cystitis (often referred to as bladder pain syndrome – BPS/IC) is a chronic condition characterized by pain, pressure, or discomfort perceived as referred to the bladder, associated with at least one urinary symptom (e.g., frequency or urgency), in the absence of urinary infection or other identifiable pathology that explains the symptoms. The diagnosis is clinical, with the exclusion of alternative causes.

IC involves immunological inflammation likely resulting from autoimmunity and is associated with severe inflammation of the entire bladder accompanied by plasma cell infiltration and urothelial denudation. Current guidelines therefore recommend a stepwise approach: starting first with conservative measures and self-care (education, behavioural modification, pelvic floor physiotherapy), then progressing to pharmacological, intravesical, and urological procedures based on severity and phenotype. The approach must therefore be multimodal and personalized (9).

Particularly in postmenopausal women, where oestrogen deficiency affects the vaginal microbiota and frequently lowers the amount of lactobacilli, *recurrent cystitis* (RC) can be troublesome (10). Initially, it was hypothesized that germs that colonize the vagina enter the urinary tract because of their close proximity (11). In the case of RC, the vagina may act as a reservoir for enteric bacteria, and RC may result from vaginal dysbiosis, which is characterized by a reduction in Lactobacilli and an increase in *Escherichia coli* (E. coli) in the vaginal microbiota (12-14). A recent study examined the connection between vaginal microbiota and RC development, revealing that vaginal microbiota plays a role in RC pathogenesis, elucidating the aetiology of RC from vaginal microbiota, and highlighting the significance of vaginal Lactobacillus. The authors discovered that the vaginal microbiome of postmenopausal women with RC differs from that of healthy controls and uncomplicated cystitis for the absence of Lactobacilli (15). The way RC is managed varies greatly between and within nations (4). Because clinical, biochemical, and/or general risk variables are not considered, the case definition and diagnosis are not definitive. Antimicrobial-resistant microorganisms and serious side effects arise from this monolithic method, which uses recurrent antibiotic treatment rounds (16). Pathological processes, antimicrobial treatment and its substitutes, antibacterial resistance, and inappropriate antibiotic usage have been the main subjects of scientific research on RC. In consideration of these aspects, the current study intends to assess the effectiveness of CO_2 micro-ablative vaginal laser therapy in the treatment of RC.

Material and methods

This retrospective study was carried out at *Ospedale di Stato of St. Marino Republic* between September 2013 and July 2024. where pre- and post-menopausal women diagnosed with recurrent cystitis were recruited.

All enrolled patients signed an informed consent to be enrolled in the study.

The inclusion criteria were the following: patients with recurrent cystitis diagnosed like *interstitial/bladder pain syndrome* (BPS/IC) or bacterial cystitis via urine culture analysis; patients who have filled out the O'Leary-Sant questionnaire; patients who underwent 3 laser treatment sessions.

The exclusion criteria were the following: previous urological or gynecological surgery, prolapse of the lower genital tract, presence of suburethral mesh or sling in place, previous or ongoing urinary tract neoplasms, previous pelvic radiation, ongoing genital infections, urinary tract abnormalities, poorly controlled diabetes mellitus, hypertension and psychiatric disorders, pregnancy, alcohol or drug addiction, ongoing therapy with diuretics, β3-adrenergic and anticholinergic drugs.

A total of 75 women with recurrent cystitis/bladder pain syndrome (BPS/IC) were recruited in this study. The patients were divided in two groups: the Group 1 included 34 women (22 were menopausal women and 12 were non-menopausal women) with bacterial cystitis who were positive to urine culture analysis (UR 1). The Group 2 included 41 women (34 were menopausal women and 7 were non-menopausal women) with *interstitial cystitis/bladder pain syndrome* (BPS/IC) who were negative to urine culture analysis (UR 0). Patient's demographic characteristics are reported in detail in Table 1.

All women enrolled in this study received three treatment sessions with a dual-wavelength system (*DuoGlide, Deka m.e.l.a, Calenzano, Italy*) that includes a 10600 nm CO_2 laser device and a 1540 nm. Each treatment lasting 5 to 10 min, with a period of 75 days between sessions.

A complete course of treatment included at least 3 laser sessions, after that patients were invited to perform a single annual maintenance treatment or a new treatment cycle if several years have passed since the last laser session. The following laser setting parameters were applied: power of 40 W, scan time of 2000 ms, spacing of 1000 µm, and Smart stack 4. The patients received the 1540 nm treatment with an energy of 200 mJ (power of 5 W, dwell time of 10 ms), using the same handpiece.

Scan time is the time interval required for the light beam to perform a predetermined movement across a surface or within a treatment area, following a precise, well-defined pattern (linear, circular, matrix). In practice, it influences the uniformity of energy distribution, thermal depth, and consequently the safety of the treatment.

Dot spacing (DOT) is the distance between two consecutive emission points in a fractional treatment. In other words, it indicates how far apart the micro-thermal columns created by the laser are on the skin or mucosa.

SmartStack (typically in fractional CO_2 lasers) indicates the number of consecutive pulses delivered to the same micro-

Table 1.
Population sociodemographic characteristics.

Patient's sociodemographic characteristics		Group 1 (UR 1)	Group 2 (UR 0)
Number of patients		**34**	**41**
Age (mean ± sd)		**53 ± 9.3 years**	**56.4 ± 7.4 years**
Menopause	Yes	22	34
	No	12	7
Cause of the alteration	Recurrent cystitis	34	41
	Estrogen deprivation	25	38
	Urethral hypermobility	7	5
	Lichen	2	4
	Perineal injuries from childbirth	2	
	Hormone suppressive therapy		2
	Chemotherapy		1

UR1: Positive Urine culture; UR0: Negative Urine culture.

spot before the laser moves on to the next point. In practice, the higher the SmartStack, the greater the thermal/ablation depth achieved at that point, while the lower the SmartStack, the more superficial and gentle the treatment. It is therefore a parameter that controls the vertical intensity of the laser action on each dot.
The pulses are delivered by a specialized handpiece emitting energy at 90° pattern.
Before starting the sessions, all women underwent a complete gynecological examination and urinalysis.
Medical history demonstrated that all the patients had experienced recurrent episodes of cystitis (at least three in 12 months), taking various antibiotics (fosfomycin trometamol, nitrofurantoin, trimethoprim/sulfamethoxazole, and amoxicillin/clavulanate), often with poor results. A *visual analog scale* (VAS) evaluation, ranging from 0 to 10, was administered to assess baseline and post laser treatment urinary symptoms associated with cystitis (dyspareunia, introitus, dryness, itching, burning, heat, dysuria and cystitis).
Furthermore, the enrolled patients were asked to indicate their satisfaction and expectations after the last laser treatment with a VAS evaluation ranging from 0 to 10.
Stress urinary incontinence (SUI) and urgency were measured by a VAS ranging from 0 to 5.
In addition, the O'Leary-Sant *Interstitial Cystitis Symptom Index* (ICSI) was used as treatment outcome measure. The O'Leary-Sant ICSI is a widely used scale that assesses the 4 cardinal symptoms of IC/BPS (17). It consists of the ICSI (a questionnaire on symptoms related to IC) and the *IC Problem Index* (ICPI) (a questionnaire on problems related to IC); each includes three questions related to urgency/frequency and one question on bladder pain.
Urine culture analysis was repeated at the end of treatment cycle.

Statistics

All statistical tests were valuated at a significance level $p \leq 0.05$ with Student-t-test. The O'Leary-Sant questionnaire scores were presented as median values along with the *interquartile range* (IQR).

Results

Both groups of patients showed positive outcomes after treatment sessions.
The results of VAS mean scores for Group 1 measured at baseline and after the first, second and third laser session for PH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria and cystitis are reported in Figure 1 and Table 2.

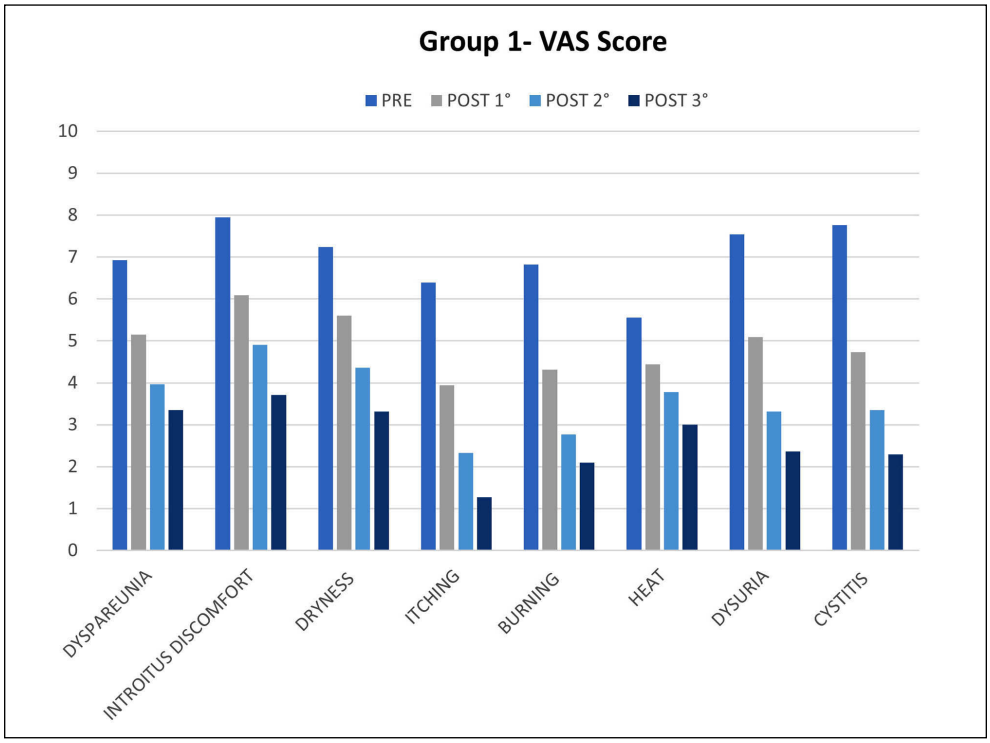

Figure 1.
Graphical representation of means values of all VAS items scores for Group 1 measured at baseline, after the first laser session, after the second laser session and after the third laser session.

Table 2.
The results of VAS mean scores for Group 1 measured at baseline and after the first, second and third laser session for PH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria and cystitis.

VAS score		pH	Dyspareunia	Introitus	Dryness	Itching	Burning	Heat	Dysuria	Cystitis
Group 1	pre	6.1/10	6.9/10	8.0/10	7.2/10	6.4/10	6.8/10	5.6/10	7.5/10	7.8/10
	post 1st laser	5.9/10	5.2/10	6.1/10	5.6/10	3.9/10	4.3/10	4.4/10	5.1/10	4.7/10
	post 2nd laser	5.8/10	4.0/10	4.9/10	4.4/10	2.3/10	2.8/10	3.8/10	3.3/10	3.4/10
	post 3rd laser	5.8/10	3.3/10	3.7/10	3.3/10	1.3/10	2.1/10	3.0/10	2.4/10	2.3/10

According to O'Leary-Sant Questionnaire the ICSI Symptom Index was 7.8 before treatment and 4.9 post treatment, while the ICPI Problem Index was 7.4 before treatment and 4.7 post treatment (Figure 2).
The results of VAS mean scores for Group 2 measured at baseline and after the first, second and third laser session for PH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria and cystitis are reported in Figure 3 and Table 3.
According to O'Leary-Sant Questionnaire the ICSI Symptom Index was 9.3 before treatment and 3.3 post treatment, while the ICPI Problem Index was 8.2 before treatment and 2.5 post treatment (Figure 4).

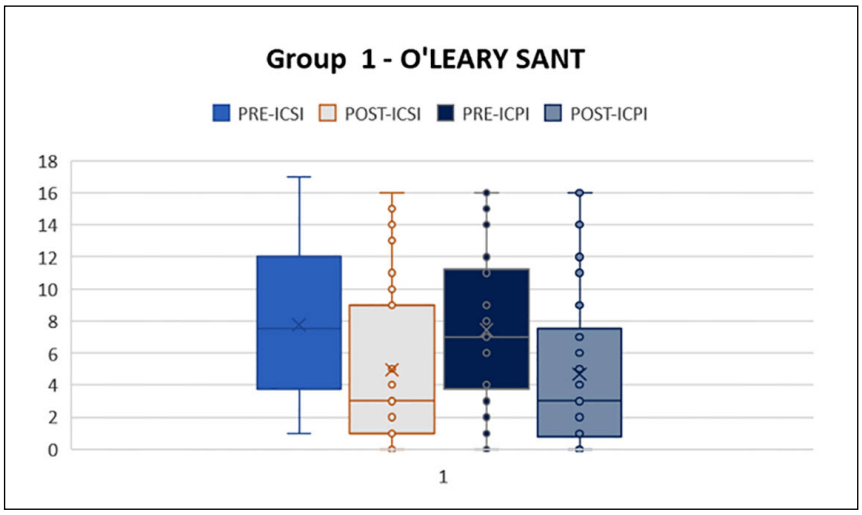

Figure 2.
The O'Leary-Sant Questionnaire results for Group 1.
The ICSI Symptom Index and ICPI Problem Index measured before and post laser treatment are graphically represented as interquartile.

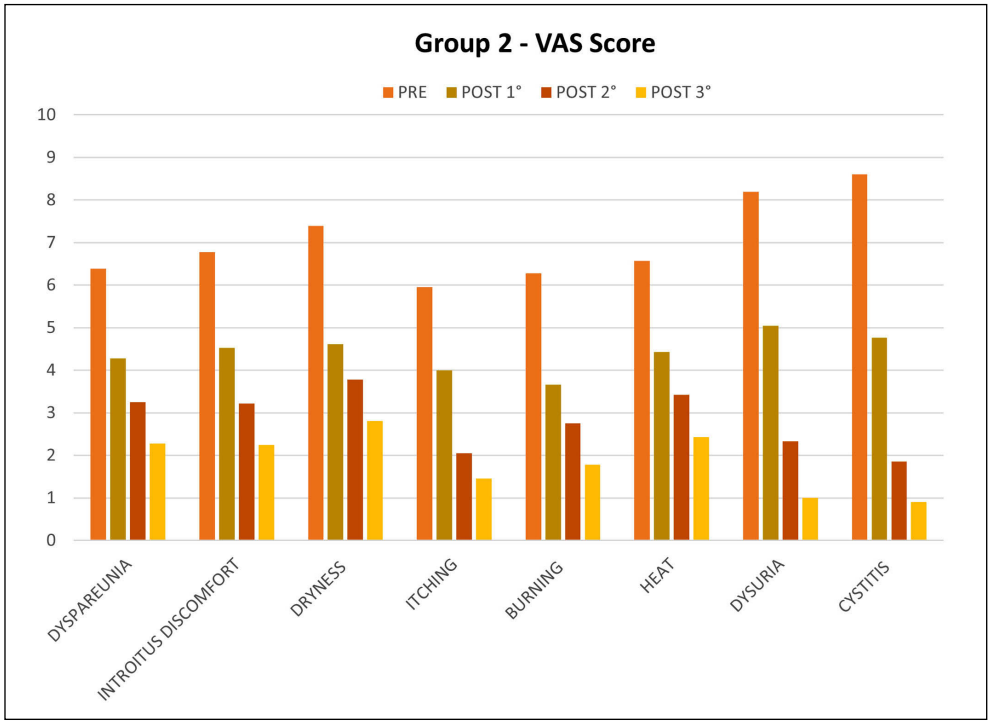

Figure 3.
Graphical representation of means values of all VAS items scores for Group 2 measured at baseline, after the first laser session, after the second laser session and after the third laser session.

Table 3.
The results of VAS mean scores for Group 2 measured at baseline and after the first, second and third laser session for PH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria and cystitis.

VAS score		pH	Dyspareunia	Introitus	Dryness	Itching	Burning	Heat	Dysuria	Cystitis
Group 2	pre	6.4/10	6.3/10	6.7/10	7.4/10	5.9/10	6.3/10	6.9/10	7.7/10	8.6/10
	post 1st laser	6.1/10	4.2/10	4.4/10	4.6/10	3.9/10	3.6/10	4.7/10	5.0/10	4.7/10
	post 2nd laser	6.0/10	3.1/10	3.0/10	3.8/10	1.8/10	2.6/10	3.6/10	2.3/10	1.5/10
	post 3rd laser	5.8/10	2.1/10	2.1/10	2.8/10	1.2/10	1.6/10	2.5/10	1.0/10	0.9/10

The VAS scale administered for the assessment of patient's satisfaction and expectations for Groups 1 and 2 revealed good outcomes for both groups examined as shown in Figures 5, and 6 and Table 4.

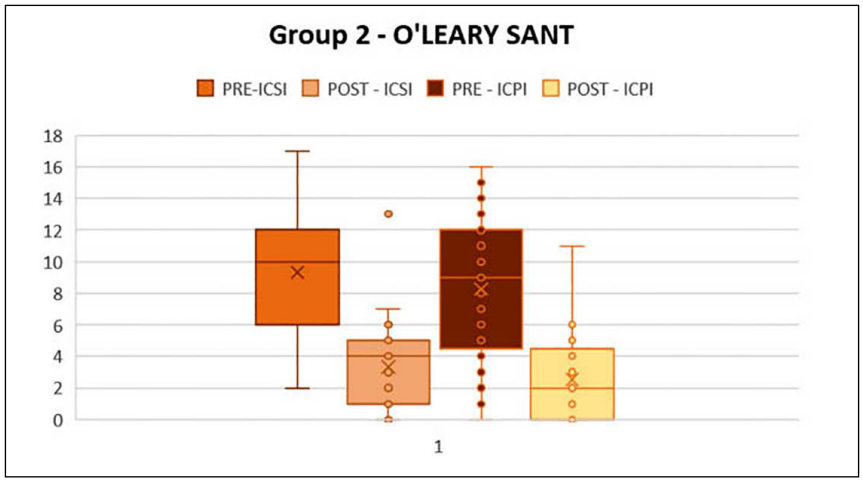

Figure 4.
The O'Leary-Sant Questionnaire results for Group 2.
The ICSI Symptom Index and ICPI Problem Index measured before and post laser treatment are graphically represented as interquartile.

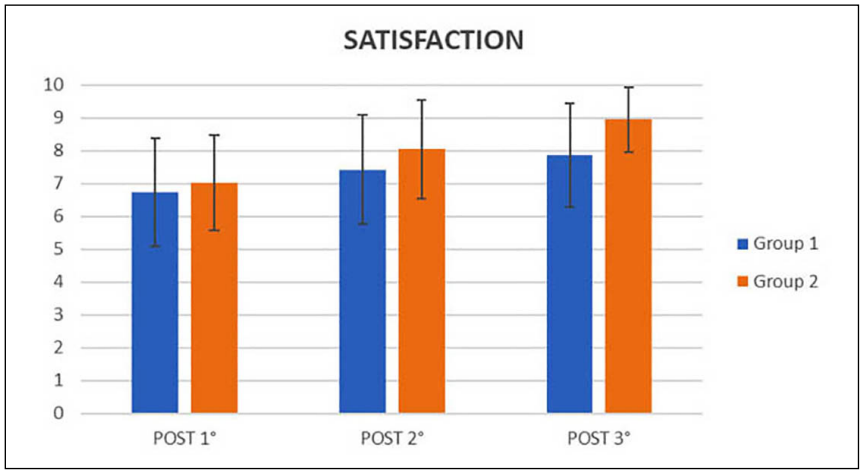

Figure 5.
Histogram representation of means values of patient's satisfaction VAS scores for Group 1 and 2 measured after the first laser session, after the second laser session and after the third laser session.

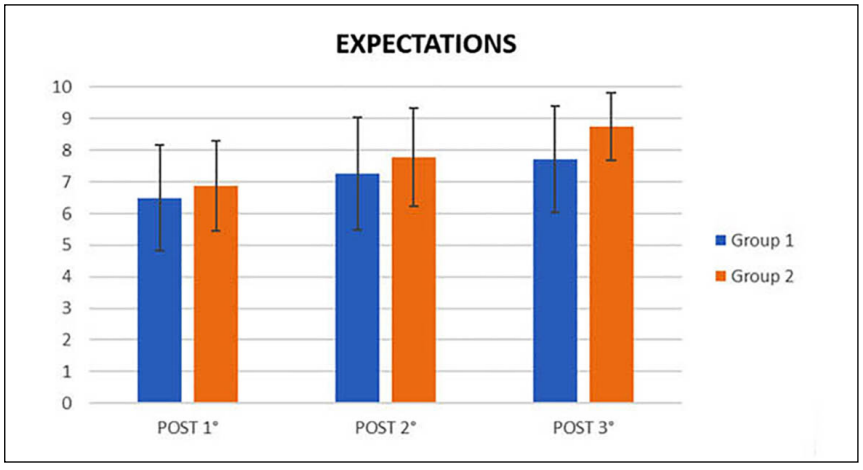

Figure 6.
Histogram representation of means values of patient's expectations VAS scores for Group 1 and 2 measured after the first laser session, after the second laser session and after the third laser session.

VAS Score		Group 1	Group 2
Satisfaction	post 1st laser	6.7/10	7.0/10
	post 2nd laser	7.4/10	8.0/10
	post 3rd laser	7.9/10	9.0/10
Expectations	post 1st laser	6.5/10	6.9/10
	post 2nd laser	7.3/10	7.8/10
	post 3rd laser	7.7/10	8.8/10

Table 4.
The results of VAS mean scores for Groups 1 and 2 measured after the first, second and third laser session for patient's satisfaction and expectations.

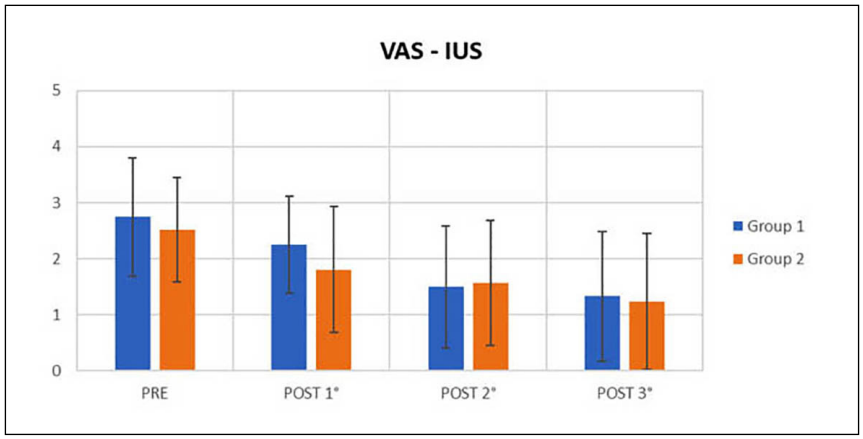

Figure 7.
Histogram representation of means values of VAS scores of SUI (IUS) for Group 1 and 2 measured before, after the first laser session, after the second laser session and after the third laser session.

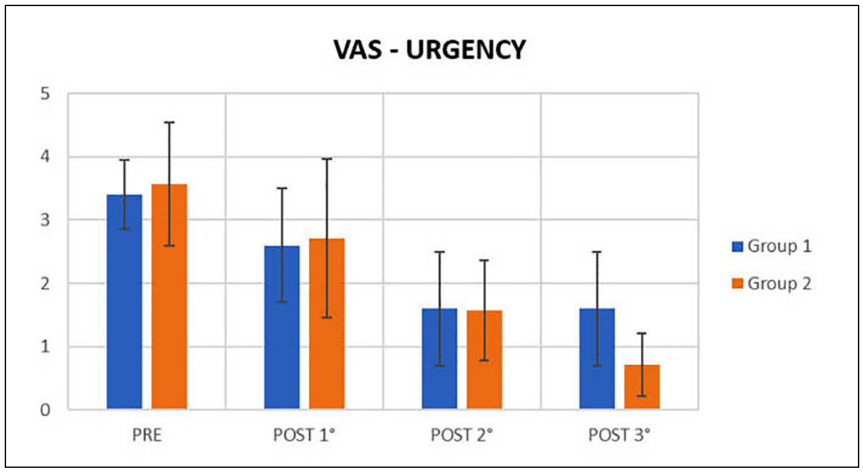

Figure 8.
Histogram representation of means values of VAS scores of Urgency for Group 1 and 2 measured before, after the first laser session, after the second laser session and after the third laser session.

For Group 1 the mean VAS for IUS was 2.8/5 at baseline, 2.3/5 after the first laser session, 1.5/5 after the second laser session, 1.3/5 after the third laser session, while for Group 2 the mean VAS for IUS was 2.5/5 at baseline, 1.8/5 after the first laser session, 1.6/5 after the second laser session, 1.2/5 after the third laser session (Figure 7, Table 5).
For Group 2 the mean VAS for Urgency was 3.4/5 at baseline, 2.6/5 after the first laser session, 1.6/5 after the second laser session, 1.6/5 after the third laser session, while for Group 2 the mean VAS for Urgency was 3.6/5 at baseline, 2.7/5 after the first laser session, 1.6/5 after the second laser session, 0.7/5 after the third laser session (Figure 8, Table 5).
Urine culture analysis performed before treatment showed a negative culture in 41 patients (55% - Group 2 - UR 0), while in the remaining 34 patients (45% - Group 1 - UR 1) a positive culture was found (59% *E.Coli*, 13% *Klebsiella Pneumoniae*, 10% mixed type, 10% *Staphylococcus*, 4% *Enterococcus Faecalis*, 2% *Citrobacter* and 2% *Freundi*).
According to the urine culture analysis performed at the end of laser treatment cycle, we observed that about 73,5% of patients of Group 1 (25 out of 34 patients) obtained negative urine culture while the patients of Group 2 (41 patients) preserved their negative urine culture, as shown in Table 6.
After the treatment, patients no longer need to take antibiotics and 2 days after the treatment, the burning and irritation disappear completely. No major side effects were observed.

Table 5.
The results of VAS mean scores for Groups 1 and 2 measured at baseline and after the first, second and third laser session for IUS and urgency.

VAS Score		Group 1	Group 2
IUS	pre	2.8/5	2.5/5
	post 1st laser	2.3/5	1.8/5
	post 2nd laser	1.5/5	1.6/5
	post 3rd laser	1.3/5	1.2/5
URGENCY	pre	3.4/5	3.6/5
	post 1st laser	2.6/5	2.7/5
	post 2nd laser	1.6/5	1.6/5
	post 3rd laser	1.6/5	0.7/5

Table 6.
Results of urine culture analysis at the end of the three treatments.

	Positive	Negative
UR 1	9	25
UR 0	0	41

Discussion

The CO_2-based lasers take advantage of a technology that is frequently used to treat micro-lesions in superficial tissues and is appropriate for structural regeneration. Notably, the formation of collagen and extracellular matrix is triggered by the fractional CO_2 laser's penetration of deeper layers, which aids in tissue trophism restoration (17181819). Water is an excellent medium for absorbing laser light with a wavelength of 10,600 nm. Given the substantial amount of water present in mucosal tissues, these tissues are essentially vaporized to promote collagen formation (20). The rationale of this technology is to specifically stimulate neocollagenase, which will help new collagen migrate to the mucosal surface resulting in a rise of fibroblast activity and the fibrillar component of the extracellular matrix.

These effects translate into a marked increase in the thickness and glycogenic load of the vaginal epithelium in order to reduce symptoms such vaginal dryness, vaginal tightness, vaginal dyspareunia and prolapse signs as well as to improve bladder function, urgency, and stress incontinence (21-24).

According to a 2024 retrospective study by *Yingying et al.* that examined the effects of CO_2 laser therapy in altering vaginal bacterial flora in women with *genitourinary syndrome of menopause* (GSM) (25), both CO_2 micro-ablative vaginal laser and estrogen therapies can regulate the vaginal microbiota imbalance of GSM and improve the associated symptoms.

Several researchs have examined how laser treatment works to manage urogenital complaints. In fact, this therapy has been extensively used and studied by experts of the subspecialties of functional urology and uro-gynecology, Interstitial cystitis, trigonitis, mesh problems, stress/urge incontinence, and pelvic organ prolapse are just a few of the functional illnesses that can be effectively treated with lasers. The effectiveness and adaptability of this treatment approach have been significantly increased by the availability of a wide variety of laser types and administration procedures (26, 27).

In this retrospective study the authors analyze the efficacy and effectiveness of the micro-ablative vaginal CO_2 laser on recurrent cystitis (interstitial and bacterial cystitis) in pre- and post-menopausal women for the management of pH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria, cystitis, urgency and SUI. In particular, the interest of the present study is mainly focused on urinary symptoms, which are most frequently associated with disorders such as SUI.

The study results suggest that both groups benefitted similarly from the treatment. In fact, the VAS scale showed a significant reduction of symptoms after treatment in both groups. Furthermore, in both groups, a significant reduction in the average number of cystitis episodes after treatment was observed. According to urine culture analysis at the end of laser treatment cycle 73% of patients of Group 1 obtained negative urine culture and the patients of Group 2 preserved their negative urine culture.

Finally, VAS results for patient's satisfaction and expectations showed positive outcomes revealing that more than 90% of patients were satisfied following the treatment.

The study results are in line with the study of *Luvero et al.* (28) who proposed fractional CO_2 laser therapy as a safe, effective, non-hormonal treatment for pre- and post-menopausal women with recurring, post-coital, and interstitial cystitis. The current study revealed that the micro-ablative CO_2 vaginal laser was effective in treating symptoms such as dysuria, daytime pollakiuria, and urgency in individuals with interstitial, post-coital, and recurrent infective and non-infective cystitis.

Additionally, the treatment reduced the number of acute episodes on a yearly basis.

Three hypotheses were formulated by the authors in order to explain the laser action on the improvement of cystitis symptoms. The first is the thermal heat hypothesis: according to this hypothesis, the heat create by laser system action leads to an improvement in the blood flow at the level of the bladder tissue reduced by the vascular alteration. In fact, as previously demonstrated in literature (29) the CO_2 vaginal laser action, by stimulating and supporting the activity of fibroblasts and capillaries, promotes neovascularization (development of new blood vessels) resulting in a rich content of blood vessels within the connective tissue that penetrate the newly formed papillae into the underside of the extremely thick epithelium that improve local metabolism. Many studies suggested the hypothesis of blood flow impairment in the bladder as a cause of IC/BPS. Indeed, when ischemia induces hypoxia and damages the bladder tissues the improvement of the compromised blood flow is essential to increase the supply of oxygen and nutrients (see Figure 9).

The second is the neurological mechanism hypothesis (viscero-somatic reflex): according to this hypothesis the

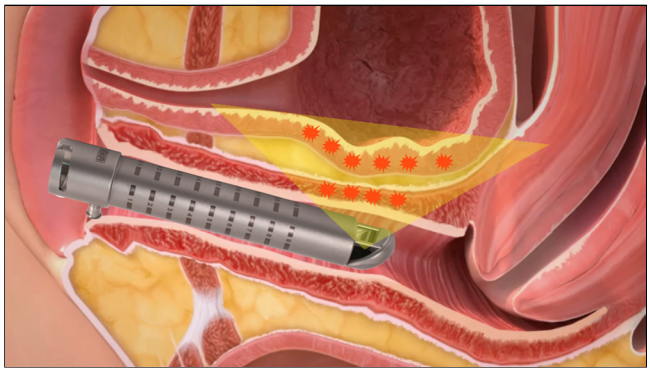

Figure 9.
Graphical representation of the tissue improvement generated at the level of the vaginal epithelium following the emission of laser thermal energy.
Laser emission also reverberates at the level of the urinary epithelium, since during development both the genital and urological organs derive from a common embryological origin (primitive urogenital sinus).
The improvement of vascular blood flow induced by the laser improves both hypoxia and ischemia, which are the basis of many epithelial alterations in these districts.
Courtesy of DEKA M.E.L.A (modified by Dr M. Filippini).

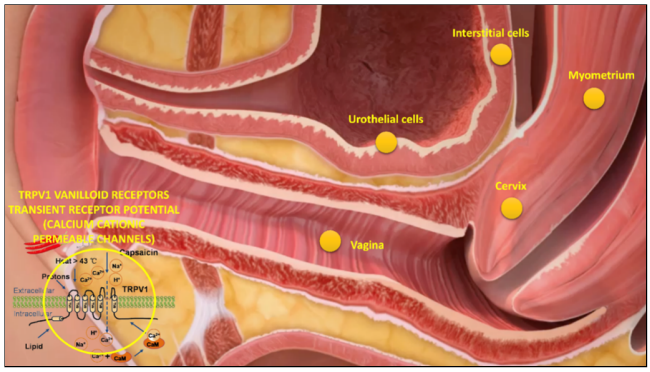

Figure 10.
Graphical representation of the nociception modulation due to the presence of TRPV1 at the level of female urogenital tract. The heat generated by the laser would probably lead to the desensitization of these receptors, with inhibition of the afferent neuron, and consequent reduction of inflammation, edema and even analgesia.
Courtesy of DEKA M.E.L.A (modified by Dr M. Filippini).

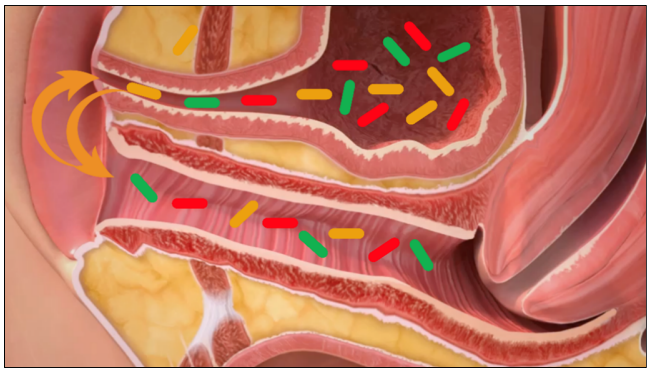

Figure 11.
Graphic representation of the hypothetic gene communication channel between the bacteria of the bladder and vaginal districts.
Courtesy of DEKA M.E.L.A (modified by Dr M. Filippini).

treatment would have an analgesic effect by acting on the heat sensitivity vanilloid receptor 1 or transient receptor potential cation channel subfamily V (TRPV). Specifically, the subtype TRPV1 is involved in the transmission and modulation of pain (nociception), as well as the integration of diverse painful stimuli (30). These receptors can be considered sensors of chemical substances (capsaicin), thermal (heat) and/or noxious stimuli, and they have the ability to transduce inflammatory signals into electrical signals with the activation of sodium and calcium channels, both voltage-gated, located at the level of nociceptors. In the female urogenital tract, TRPV1 are expressed at the level of the vagina, the myometer, the subepithelium of the cervix, but also at the level of the urothelium cells and the interstitial cells of the human bladder. Probably the heat generated by the laser would lead to the desensitization of this receptor, and to a neuronal inhibition, reducing the afferent nervous activity and the contractility of the detrusor muscle (see Figure 10).
The third is the microbiome modulation hypothesis: according to this hypothesis the action of the treatment can interfere with the vaginal microbiome reducing the infection risk associate with some bacterial species maintaining optimal vaginal wellness. Indeed, a trend in reduction of species associated with vaginal infections, such as Gardnerella vaginalis and Atopobium vaginae, due to a microbiome rebalancing can reduce infection risk and support overall vaginal health (31, 32).
This hypothesis is supported by the patient's urine culture analysis which revealed that more than 60 percent of patients had negative urine cultures.
Furthermore, the study laser system could modulate some species such as Lactobacillus crispatus and Lactobacillus gasseri and jensenii, which are known for their protective roles in the vaginal environment, as they produce lactic acid, which maintains an acidic vaginal pH unfavorable to pathogenic bacteria.
Furthermore, lactobacilli increased the production of type I *interferon* (IFN), which in turn increased the expression of cathepsin D in lysosomes *harboring pathogenic endothelial cells* (UPEC) (33, 34). Comparative genomic analysis has revealed that the taxonomies and functions of the bladder microbiota share more similarities with the vaginal microbiota than with the intestinal one. For many decades, the urinary tract of healthy individuals has been considered sterile. Sequencing of the 16S rRNA gene has instead demonstrated the existence of a microbial community in the bladder of healthy women that is rather dynamic, with intermittent changes and potential influence of sexual activity and menstruation, similar for 40% with that of the vagina. Therefore, due to the anatomical proximity, the changes that occur in the vaginal district are reproduced in the bladder district. Consequently, the improvement of the vaginal microbiota induced by the thermal energy of the laser is inevitably reflected also at the level of the bladder microbiota, probably through a gene communication channel between the bacteria of the two districts (35). The vaginal microbiota appears to be a key factor influencing susceptibility to urinary tract infections and other urological conditions, with some microorganisms from the vaginal microbiome often being detected in urine. Since the urinary tract can be temporarily exposed to vaginal bacteria, causing injury to the bladder epithelium, it is well understandable that improving the vaginal microbiota has a major impact on that of the urinary tract (see Figure 11). Gardnerella vaginalis can move from the vagina to the

bladder causing the exfoliation of the bladder epithelium (urothelium) by apoptosis induced by Gardnerella and releasing the latent intracellular reservoirs of E. Coli in the urine in the bladder (36).
Summarizing and correlating the three hypotheses of the investigation with the results obtained, it was shown that significant improvements were identified on all genitourinary examined symptoms (pH, dyspareunia, introitus, dryness, itching, burning, heat, dysuria, cystitis and urgency) among both pre- and post-menopausal women.
The CO_2 micro-ablative vaginal laser has outstanding outpatient applicability, with simple administration, a good cost-effective ratio, remarkable patient compliance and tolerance, and no short- or long-term adverse effects. The treatment is quick, easy, and not painful, and the monthly application ensures good patient adherence to the therapeutic regimen.
The strength of our study is represented by the number of measurements connected to the various aspects of cystitis.
The main limitation of the study is represented by the fact that the three hypotheses formulated are not supported by any histological analysis but represent only the personal interpretation of the authors extrapolated through the numerous scientific data present in the literature and, in largee part, deriving from personal experience in the treatment of this pathology.
Further research, presumably with a larger sample size, conducted over a longer period of time, and supported by histological analysis, will be required to effectively demonstrate efficacy and symptom management benefits in the introduction of CO_2 vaginal lasers as an advantageous therapeutic approach to treating recurrent cystitis.

Declarations

Ethical approval and consent for participate: *No activity was carried out outside the scope of the device intended purpose or that no additional invasive or burdensome procedures were carried out compared to procedure performed under the normal condition of use of the device.*

Consent for publication: *Informed consent was obtained from all subjects involved in the study.*

Availability of data and material: *The data that support the findings of this study are available from the corresponding author upon reasonable request.*

Competing interests: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

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