

# The efficacy of high concentration oxygen and hyaluronic acid for the treatment of urethral pain syndrome

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## ABSTRACT

**Objective:** To evaluate the efficacy of the association between high concentration oxygen and hyaluronic acid for treatment of urethral pain syndrome (UPS) identified by persistent or recurrent urethral daily pain usually on emptying the bladder and nocturia, in the absence of proven infectious agents such as the urinalysis or any inflammatory background.

**Methods:** Twenty women (45-65 years) with suspected UPS diagnosis appealing to our Second Opinion Medical Consultation Network, signed an informed consent form and were treated with oxygen +hyaluronic acid therapy, once a week, for a total of five weeks at the outpatient clinic (Clinic Ester Veronesi, Modena, Italy). The physicians of the Second Opinion Network followed up remotely once a week (WhatsApp, Skype) assessing effectiveness, tolerability, and side effects of the treatment.

**Results:** There was a reduction in the number of urgency urinary incontinence (-25.37 vs. -12.01 mean value), nocturia episodes (-24.01 vs. -11.23 mean value), volume voided in each micturition (-127.79 vs. -98.20 mean value), micturition per 24 hours (-44.01 vs. -20.12 mean value). Analyses of the pre- and post-treatment scores showed a statistically significant improvement in Vaginal Assessment Scale (VAS), the Pain Urgency frequency (PUF) and Patient Perception of Bladder Condition scale (PPBC) scores ( $p < 0.0305$ ,  $p < 0.0001$ ,  $p < 0.0001$ , respectively). No side effects associated with the treatment were reported by the patients.

**Conclusions:** We can highlight that the combination of oxygen + hyaluronic acid was effective and well tolerated for the management of the UPS syndrome. Oxygen flow mixed with hyaluronic acid, provides an immediate sense of freshness and urethro-bladder relaxation that lasts several hours. Further studies are recommended that include larger sample sizes, comparison with placebo and/or challenge with other local and systemic treatments and different administration schedules versus longer follow up.

## KEYWORDS

Urethra, pain, syndrome, treatment, oxygen therapy, hyaluronic acid.

## Introduction

The female Urethral Pain Syndrome (UPS), also formerly defined as urethral syndrome, is identified by persistent or recurrent urethral daily pain usually on emptying the bladder and nocturia, in the absence of proven infectious agents such as the urinalysis or any inflammatory background<sup>[1-3]</sup>. Accordingly, with the European Urology Association, UPS is defined by chronic or recurrent episodic pain fixed in the urethra, lasting for more than 6 months, in the absence of a proven infection or other obvious local pathology<sup>[4,5]</sup>. Thus, it cannot be identified with the classic urethritis, rather it is enclosed into the “genito-urinary pain syndromes” with complaints of the lower urinary tract, sexual, intestinal, or gynaecological disorders<sup>[1,5]</sup>.

The exact UPS incidence and prevalence is unknown because of a lack of consensus in the method of diagnosis and overlap with other clinical conditions, including early interstitial cystitis or urethral spasm<sup>[6]</sup>. Different clinical trials have confirmed that 15-30% of women with lower urinary tract symptoms (LUTS) were diagnosed with UPS<sup>[7,8]</sup>. The syn-

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drome is most frequent in white women (typically 13-70 years of age) of westernized societies than in women of other races but has also been seen in men and children<sup>[6,9]</sup>. This syndrome also has a high rate of spontaneous remission<sup>[10]</sup>.

According to the classification of the International Association for the Study of Pain (IASP, 2019), several concurrent causes of UPS have been identified such as vascular lesions, inflammation of the skene gland or paraurethral glands (female prostatitis), urethral spasm and/or stenosis, subclinical early cystitis, oestrogen impairment, dysfunction of the pelvic floor musculature, environmental chemicals (bubble bath, soaps, contraceptive gels, condoms et al), certain foods and beverages

that can irritate the urethra (caffeine, alcohol, spicy food) and psychological distress involving reactions of anxiety, depression, dysphoria and even hostility, with cognitive, behavioural, sexual or emotional consequences [4,6,11-15]. Parson *et al.* [16] have proposed as the main cause of the UPS a dysfunction of the mucosal barrier layer, that allows solutes/metabolites (e.g., potassium which is normally present in the urine at levels that are toxic to the bladder interstitium) pass into the urine and seep through the urothelial barrier leading to inflammatory changes, spasm and fibrosis. Stamm *et al.* asserted that the syndrome could be caused by a long standing urinary low-grade bacterial infection (bacterial counts  $<10^2/\text{mL}$ ) [17].

Dysuria is the commonest symptom observed in 40% of the UPS cases [18], but very often no real physio-pathological cause can be identified, and the drug therapy is based on different approaches: anti-inflammatory painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, steroids and oestrogens, antibiotics, alpha-blockers, topical urethral dilation, epitheliotropic compounds, acupuncture, antidepressants, bladder training, dietary and lifestyle changes, and rehabilitation therapy [6,11,19,20]. Empirically administered antibiotics in out-patient clinics, in the absence of a true bacterial infection should be avoided, due to the risk of resistance and toxicity [21]. In the absence of approved guidelines for the treatment of the UPS syndrome, each specialist should provide a proper tailored prescription focused on patients' psycho-physical complaint, and often a multimodal therapy provides some temporary positive results [20].

The difficulty in identifying the pathophysiology of the syndrome, makes it difficult to plan an effective therapeutical strategy.

Recently, a new cosmetic & hygienic gynaecological protocol has gained our attention owing to the synergic action of a pure oxygen flow (intended as a drug delivery system) and low molecular weight hyaluronic acid, a natural mucopolysaccharide sprayed over the mucosa. This combination penetrates the submucosal spaces to modulate the elasticity of the connective tissue matrix, hydrating and wandering cell chemotaxis.

Oxygen has a powerful regenerative, antibacterial and anti-inflammatory effect [22]; it increases the availability of oxygen in the tissues, promoting tissue repair processes and the disposal of pain and inflammation mediators (e.g. histamine, serotonin, prostaglandins) [23]. Hyaluronic acid has remarkable adhesive, moisturizing and repairing properties of the mucosa [24].

The rationale of the hypothesis to treat UPS with the combination of oxygen + hyaluronic acid is substantiated by the clinical study of Streltsova *et al.* [25]. In accordance with their observation, the urethra and the bladder are embryologically and physiologically joined in "the painful bladder syndrome" [26] and the common connective tissue matrix of both the structures with its protective and trophic functions, displays a mechanosensitive signalling system [27,28], which might be responsible of the disease. The authors in their utmost interesting paper describe also the routine diagnostic methods, such as ultrasound (US) and uroflowmetry, but also ultrasound elastography (USE) and cross-polarization optical tomography (CP OCT). On an investigational basis, the latter seems to be the most appealing method to detect UPS, being able to explain the fine neurovas-

cular disorder of the urethra [29-33]. Streltsova *et al.* compared transvaginal ultrasound (TVUS) with compression elastography and CPOCT in 55 patients with UPS against 14 healthy control [25,34]. TVUS showed enlargement of the internal lumen of the upper third of the urethra. Compression elastography detected fibrotic stiffness (in urethral and periurethral tissues). CPOCT confirmed some hypertrophy or atrophy of epithelial mucosa and increased connective tissue density in UPS patients [29]. In UPS patients, the proximal urethra and the bladder neck above showed overlapping pathological changes. Oxygen together with hyaluronic acid are supposed to relieve UPS symptoms acting specifically on the soft tissue matrix, and also carefully stimulating the urethra channel with the gas flow, in order to help it increase tone and reduce its enlarged diameter [25].

Clinical stages of the UPS are usually defined by the UP-OINT classification (Urinary, Psychosocial, Organ Specific, Infection, Neurologic/Systemic, Tenderness of Skeletal Muscles) [30,34] and the bladder voiding diary, reaching exclusion diagnosis only after cystoscopy, urethroscopy, cytologic and bacteriologic all demonstrate negative findings. Regarding our study, an open spontaneous trial, it has mainly been focused on the quality of life score before and after oxygen + hyaluronic acid treatment, with this original cosmetic approach never been previously attempted for the treatment of the UPS.

## Materials and methods

This clinical study was approved by the local institutional review board and conducted in accordance with the ethical standards of the Declaration of Helsinki.

### Patients

The protocol provided for the enrollment of 20 women, aged 45-65, with suspected UPS diagnosis appealed to our Second Opinion Medical Consulting, from March 2019 to March 2020 (Table 1). The Second Opinion Medical Network is a consultation referral web and medical office system enclosing a wide panel of specialists, to whom any patient with any illness or syndrome not adequately satisfied with diagnosis or therapy can ask for an individual clinical audit [31-33,35].

**Table 1** Patient's demographic characteristics and baseline values of study population.

No. patients	n=20
Age (years)	37.2 ± 8.2
Symptoms history (months)	18
Number of micturition per 24h (Mean ± SD)	14.01 ± 0.29
Volume voided in each micturition during 3-day micturition diary (mL) (Mean ± SD)	127.79 ± 3.78
Number of nocturia episodes during a 3-day micturition diary (Mean ± SD)	4.01 ± 1.45
Number of urgency episodes during 3-day micturition diary (Mean ± SD)	5.37 ± 1.28

UPS diagnosis was made accordingly with the presence of clinical symptoms, including frequency, urgency and suprapubic discomfort, no abnormal findings at gynaecological examination with negative neurologic and pelvic findings and no inflammation at all found at the urinalysis and no infection determined by urine culture. The examination enclosed bimanual pelvic examination, to evaluate cervical motion, adnexal masses and/or uterine enlargement with tenderness in each explored section. An echography, cystoscopy and a urodynamic test were required to be performed for each patient by the same gynaecologist, before the treatment, to exclude bacterial infections or interstitial cystitis with micturition problems.

After signing the informed consent form, all the participants answered a quality-of-life questionnaire describing their personal history.

### Inclusion criteria

We enrolled women, aged 18 or above, with self-reported UPS syndrome that had failed at least 6 months of conventional treatments, including NSAIDs. In addition, patients complaining of pollakiuria (bladder voiding 6-8 times daily and 2-4 times nightly), painful intercourse and/or painful pollakiuria soon after were also included, as well as those with common unpleasant symptoms (pain, pressure, discomfort) of the urinary bladder lasting more than 6 months, in the absence of infections, bladder lesions, coagulopathy or positive cystoscopy findings.

### Exclusion criteria

We excluded patients with interstitial cystitis, tuberculosis, active sexually transmitted diseases (e.g., chlamydia, genital herpes, or human papilloma virus), or with positive findings of glomerulation or Hunner's ulcer, or with previous vaginal surgery or toning therapy, or with conservative pelvic floor treatment (e.g., pelvic floor exercises and estrogenic cream) in the last 6 months. We also ruled out women with urethral anatomical pathology or with neurological disorder, or psychopathology, as well as pregnant or lactating volunteers and women with diabetes, history of cancer, in chemo- or radiotherapy or with obesity.

The patients accepted to undergo oxygen + hyaluronic acid treatment (Caressflow® (Caress Flow Srl, Bologna, Italy), once a week, for a total of five weeks at the outpatient clinic (Clinic Ester Veronesi, via Giardini 470, Modena, Italy).

Detailed instructions about healthy hygienic, good, and healthy nutrition, and sexual behavior were given before and after the treatment. Patients were instructed to avoid intravaginal medications, vaginal douching, and sexual intercourse within 24 hours of her clinical procedure and also after it.

The physicians of the Second Opinion Medical Consulting Network remotely followed up (telemedicine) each week each treated patient as to state the effectiveness, tolerability, and side effects of the treatment, through WhatsApp and Skype or physical visit when required.

This study did not utilize a separate control group, but it compared the patient's outcomes with their baseline clinical conditions through the previous attempts to be cured.

### Treatment protocol

It included one session per week (total 5 weeks) with a specific device for gynecological practice (Caressflow®, Caress Flow Srl, Bologna, Italy) consisting of an airbrush connected to the machine body, capable to carry and to spray an oxygen-hyaluronic acid combined solution (Figure 1). The instrument transforms ambient air into  $93\pm 3\%$  pure oxygen, by the action of zeolite molecular sieves with non-uniform electrostatic fields and absorb molecules with higher polarizability or higher quadrupole moments, such as nitrogen, argon, helium and hydrogen [36,37].

Each patient is treated by inserting the vaginal cannula equipped with outlet holes and releasing molecular oxygen alone at a flow of 1-6 l/minute (for the first 5 minutes) and subsequently combined with sprayed 10 ml of low molecular weight hyaluronic acid (for the next 15 minutes). This hyaluronic acid has been previously dissolved in distilled water, to form a 0.2% (w/v) solution. Highly concentrated oxygen spreads easily through the vaginal mucosa, counteracting the critical hypoxia of microcirculation impairment and recovering the metabolism of the superficial cells. After the oxygen session, the hyaluronic acid solution is sprayed through a special injection hole located in the upper part of the cannula (Figure 1). Due to its low molecular weight, it is easily absorbed by the mucosa preconditioned with the pure oxygen flow. The low molecular weight hyaluronic acid penetrates easily in the mucosa prepared by the action of oxygen.

The efficacy of the treatment was evaluated, before and after, by 1) micturition diaries, 2) scores of three self-reported questionnaires: Vaginal Assessment Scale (VAS), Patient Perception of Bladder Condition scale (PPBC) and the Pain Urgency frequency (PUF) scale. The micturition diary included 3-days of recordings of urine output per 24 hours, number of urgencies, incontinence and nocturia episodes per 24 hours. The intensity of urgency was assessed using the five-point urgency rating scale URS [1=no urgency, 2=mild urgency, 3= moderate urgency, 4=severe urgency, 5=urgency urinary incontinence

**Figure 1** Description of the airbrush connected to the machine body.



(UII)]. In addition, the volume voided during each micturition was recorded at baseline and after the five session's treatment. The VAS questionnaire identifies vulvar symptoms (dryness, itching, burning, pain) and consists of 4-items that determine the severity (range 0-3 points: 0=none, 1=mild, 2=moderate, and 3=severe) of dryness, soreness, irritation, and pain (dyspareunia or painfulness upon external stimulation) for both the vaginal and vulvar areas. Regarding the validated PPBC scale, each participant filled in his perceived bladder condition on a 6-point scale (1 point= no problems, 6 points=many severe problems) [38]. Finally, the valid and reliable PUF scale measures urinary symptoms, e.g., pain and urgency, and symptoms related to sexual intercourse, consisting of eight items related to urinary frequency (daily and nightly), symptoms associated with sexual intercourse or with the bladder, and discomfort caused by these symptoms (range score=0-35 points, a score  $\geq 5$ = urinary symptoms) [39].

### Statistical analysis

Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The data were analyzed using an unpaired t-test with Welch's correction. A p value of  $< 0.05$  was considered significant.

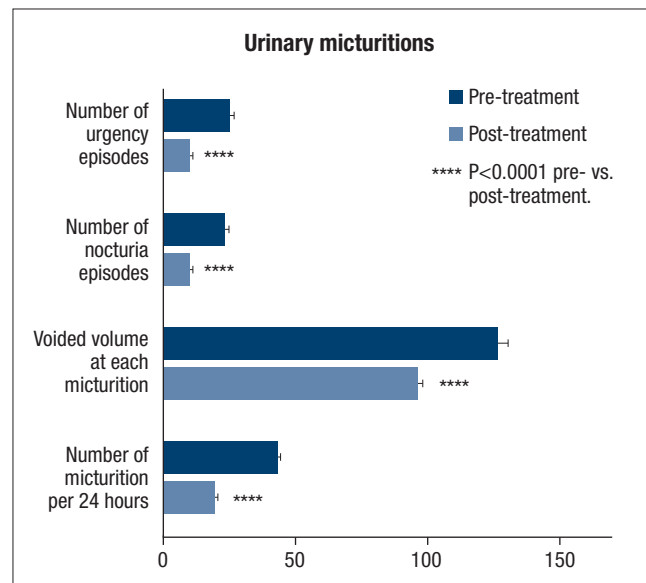
## Results

All patients successfully completed the study. We observed significant reductions in the number of urgency urinary incontinence ( $-25.37$  vs  $-12.01$  mean value), nocturia episodes ( $-24.01$  vs  $-11.23$  mean value), voided volume in each micturition ( $-127.79$  vs  $-98.20$  mean value), micturition per 24 hours ( $-44.01$  vs  $-20.12$  mean value). There was a statistically significant difference ( $p < 0.0001$ ) between the baseline and post-treatment values for all parameters (Figure 2).

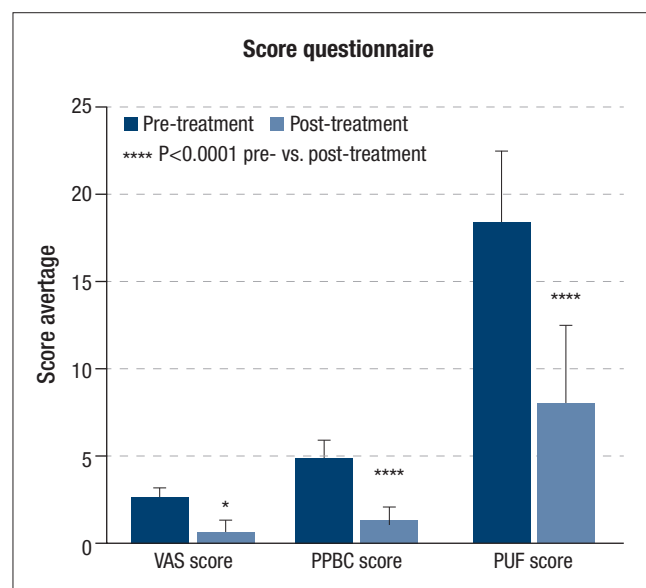
There was a decrease in all the evaluated scores at the end of the treatment compared with the pre-treatment. In fact, analyses of the pre- and post-treatment scores showed a statistically significant improvement in VAS, PUF and PPBC scores ( $p < 0.0305$ ,  $p < 0.0001$ ,  $p < 0.0001$ , respectively). The VAS score showed that pain was reduced after the treatment. In fact, the mean VAS score of 0.6 after treatment (mean value VAS, before treatment=2.65) confirmed an improvement of symptomatology.

The PPBC scores were linearly correlated before ( $p < 0.0001$ ) and after treatment ( $p < 0.0001$ ). At the end of therapy, 13/20 participants (65%) had PPBC-scores  $< 10$  with a significant reduction of the urinary urgency rate and of nocturnal micturition episodes and resolution of burning sensation. Statistical analysis showed, from baseline to 150 days of treatment, significant improvements ( $p < 0.0001$ ) in all PPBC parameters. PUF mean value, after 5 weeks of treatment from baseline, decreased by 10.45 points ( $p < 0.0001$ ) (Figure 3). No side effects associated with the treatment were reported by the patients. Combined oxygen therapy with hyaluronic acid proved to be a valid method for treating symptoms associated with the UPS. It is a fast, non-invasive and repeatable treatment, totally painless, with excellent compliance by patients.

**Figure 2** Urinary micturition parameters values pre- and post-treatment. There were significant differences.



**Figure 3** Values for the VAS, PPBC, PUF questionnaires pre- and post-treatment. There were significant differences.



## Discussion

The UPS is a hard challenge for the practicing physician due to some gaps of evidence-based treatments, and of standardized diagnostic guidelines ("exclusion diagnosis" is mandatory). Petros *et al.* [40] (showed that the urothelium controls the activity of the afferent nerves, acting as a mechanoreceptor and contributing to chronic pelvic pain, typical symptom of the UPS. Findings confirmed by Streltsova *et al.* indicate that women with UPS present thinning of the urothelium and an enhance in the thickness of the connective tissue matrix of the bladder neck [25]. Also, Kiseleva *et al.* confirmed that urethral tissues in patients with the UPS can be linked to chronic bacterial inflammatory processes [41].



In addition, Gittes and Nakamura affirmed that a local infection within the short urethral segment can be the cause of the syndrome, since the paraurethral gland, within the prevaginal zone, is located at 1/3 of the distance from the urethra (an identical prostatic homologue tissue in the men, stained similarly with the prostate specific antigen (PSA) <sup>[12]</sup>). The inflammation of this paraurethral gland promotes tenderness in the urethra through the anterior vaginal wall which might be responsible of the UPS.

Different types of antibiotic therapy have been proposed for the treatment of the female UPS; however, results have been disappointing, as they might in fact not necessary or might cause side effects or induce bacterial resistance <sup>[42]</sup>. Ivarsson *et al.* <sup>[43]</sup> analysed UPS treatment schedules of 137 Swedish hospital clinics and showed that this syndrome was treated at all medical specialty departments (urology, gynaecology, gynecologic oncology, venereology, and primary care), with different methods: for example urologists and gynaecologists primarily used local corticosteroids, alone or in combination with urethral dilation; general practitioners, oncologists, and venereologists instead used oestrogens and oral/local antibiotics. In our study, the efficacy of Caressflow<sup>®</sup> was associated with a statistically significant decrease in scores of the VAS, PPBC, PUF questionnaires at the end of treatment. These effects are due to the oxygen-hyaluronic acid combination: oxygen enhances the reparative processes of the inflamed mucosa and the collagen synthesis by the hydroxylation pathway and induces a neo-angiogenetic stimulation through the release of the Vascular Endothelial Growth Factor (VEGF) <sup>[44-47]</sup>. On the other hand, hyaluronic acid binds large amount of water molecules rehydrating and re-structuring the inflammation-injured skin and mucous surfaces <sup>[48]</sup>. We recorded a high patient satisfaction rate (97%) after the five sessions. Women declared improvement in their quality of life, in particular social daily life relationships, partner relationships and sexual intercourse.

The limitation of this study was the lack of a control group and the small sample size. Consequently, we cannot exclude error rates (Type 1 and Type 2 errors) and cannot ensure that our results may be replicated in future research with a larger sample size. But this preliminary observation and the positive outcomes are very promising and recommend a further major evidence based clinical trial.

## Conclusion

In this study, we highlight that the combination of oxygen + hyaluronic acid is effective and very well tolerated in UPS: the symptomatic benefit is perceived by the treated patients since the first session; the oxygen flow mixed with hyaluronic acid, gives immediately a sense of freshness and urethro-bladder relaxation that lasts several hours; the reasonable hypothesis explaining the action mechanism of hyaluronic acid across the periurethral soft tissue is that this highly hydrophilic molecule mobilizes CD44 cells into the lymphoreticular network that crosstalk with local inflammatory cells to modulate the lymphokine cascade; in the following sessions increased softness and elasticity of the urethral segment

is steadily achieved, accordingly with the persisting benefit several weeks after the conclusion of the treatment schedule. In order to provide more clear-cut evidence-based data, further studies including larger sample sizes, placebo and or challenge with other local and systemic treatments and different administration schedules versus longer follow up are recommended.

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