Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Feb 09; 11(B):239-245.
https://doi.org/10.3889/oamjms.2023.10756
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Nephrology*

Urethral Pain Syndrome: Treatment with Oxygen and Hyaluronic Acid

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Edited by: Mirko Spiroski
Citation: Vadalà M, Veronesi E, Garoia F. Urethral Pain Syndrome: Treatment with Oxygen and Hyaluronic Acid. Open Access Maced J Med Sci. 2023 Feb 09; 11(B):239-245. https://doi.org/10.3889/oamjms.2023.10756
Keywords: Urethral; Pain; Syndrome; Treatment; Oxygen therapy; Hyaluronic acid
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Received: 29-Jul-2022
Revised: 11-Jan-2023
Accepted: 06-Feb-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The aim of our clinical study has been to evaluate the efficacy of the association between high concentration oxygen and hyaluronic acid (HA) for the treatment of urethral pain syndrome (UPS).

MATERIALS AND METHODS: Twenty women (45–65 years old) with suspected UPS diagnosis appealing to our Second Opinion Medical Consultation Network signed an informed consent form and were treated with oxygen/HA therapy treatment, 7 times a week, for a total of 5 weeks at the outpatient clinic (Clinic Ester Veronesi, Modena, Italy). The physicians of the Second Opinion Network followed up weekly from remote (WhatsApp, Skype) each treated patient as to state the effectiveness, tolerability, and side effects of the treatment.

RESULTS: We observed significant reductions in 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), and micturitions per 24 h (−44.01 vs. −20.12 mean value). Analyses of the pre- and post-treatment scores showed a statistically significant improvement in Vaginal assessment scale, pain urgency frequency, and patient perception of bladder condition scale scores ($p < 0.0305$, $p < 0.0001$, and $p < 0.0001$, respectively). No side effects associated with the treatment were reported by the patients.

CONCLUSIONS: We can highlight that Caressflow® is effective and very well tolerated in UPS syndrome: The oxygen flow mixed with HA gives immediately a sense of freshness and urethro-bladder relaxation that lasts several hours. 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.

Introduction

The female urethral pain syndrome (UPS), also formerly defined urethral syndrome, is identified by recurrent urethral daily pain, emptying the bladder and nocturia, without infectious agents such as the urinalysis or any inflammatory background [1], [2], [3]. 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 proven infection or other obvious local pathology [4], [5]. Thus, it cannot be identified with the classic urethritis, rather is enclosed into the "genitourinary pain syndromes" with complaints of lower urinary tract, sexual, intestinal, or gynecological disorders [1], [5].

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 [6]. Different clinical trials confirmed that 15–30% of women with lower urinary tract symptoms were diagnosed with UPS [7], [8]. The syndrome is most frequent in women (typically 13–70 years of age), in white women in westernized societies than in women of other races but is also seen in men and children [6], [9]. This syndrome has also a high rate of spontaneous remission [10].

According to the classification of the International Association for the Study of Pain, 2019, several concurrent causes of UPS have been identified such as vascular lesions, inflammation of 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.*), food that can irritate the urethra (caffeine, alcohol, and spicy food), and psychological distress involving reactions of anxiety, depression, dysphoria, and even hostility, with cognitive, behavioral, sexual, or emotional consequences [4], [6], [11], [12], [13], [14], [15]. Parson [16] supposed, as UPS main cause, a dysfunction of the mucosal barrier layer, that allows to solutes/metabolites (e.g., potassium which is normally present in urine at levels that are toxic to the bladder interstitium) in the urine to seep through the urothelial barrier leading to inflammatory changes, spasm, and fibrosis. Stamm

et al., and coworkers asserted that the syndrome could be caused by a long standing low-grade bacterial infection (bacterial counts $<10^2$/mL) in the urine [17].

Symptoms: Dysuria is the commonest symptom in 40% of the UPS cases [18] but very often no real physiopathological 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 anesthetics, steroids and estrogens, antibiotics, alpha-blockers, topical urethral dilation, epitheliotropic compounds, acupuncture, antidepressants, bladder training, dietary and lifestyle changes, and rehabilitation therapy [6], [19], [20], [21]. The antibiotic treatment empirically administered in the out-patient clinics, in the absence of a true bacterial infection, should be avoided, because of the risk of resistance and toxicity [22]. In the absence of approved guidelines of UPS syndrome therapy, each specialist gives a proper prescription tailored on the psycho-physical complaints of the patient, and often a multimodal therapy gives some temporary positive results [21].

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

Recently, a new cosmetic and hygienic gynecological protocol gained our attention because of the synergic action of a pure oxygen flow (intended as drug delivery system) and low molecular weight hyaluronic acid (HA), a natural mucopolysaccharide sprayed over the mucosa: It penetrates into the submucosal spaces to modulate the connective tissue matrix elasticity, hydrating, and wandering cells chemotaxis.

The oxygen has a powerful regenerative, antibacterial, and anti-inflammatory effect [23]; increases the availability of oxygen to the tissues, promoting the increase in tissue repair processes and the disposal of pain and inflammation mediators (histamine, serotonin, and prostaglandins) [24]. HA has remarkable adhesive, moisturizing, and repairing properties of the mucosa [25].

The rational of UPS treatment hypothesis with Caressflow® (Caress Flow Srl, Bologna, Italy) is substantiated by the clinical study of Streltsova *et al*. [26]: Accordingly with her observation, the urethra and the bladder are embryologically and physiologically joined in “the painful bladder syndrome” [27] and the common connective tissue matrix of both the structures with its protective and trophic functions, displays a mechanosensitive signalling system [28], [29] and might be responsible of the disease. The authors in their utmost interesting paper describe also the routinary diagnostic methods, such as ultrasound (US) and uroflowmetry, but also US elastography and cross-polarization optical tomography (CP OCT); the last one seems be the most appealing method to detect UPS, on an investigational basis, being able to explain the fine neurovascular disorder of urethra [30], [31], [32], [33], [34]. Streltsova *et al*. compared transvaginal US (TVUS) with compression elastography and CP OCT in 55 patients with UPS against 14 control healthy patients [26]. TVUS showed enlargement of the internal lumen of the upper third of the urethra. Compression elastography detected fibrotic stiffness (in urethral and periurethral tissues). The CP OCT in UPS confirmed some hypertrophy or atrophy of epithelial mucosa and increased connective tissue density [35]. The proximal urethra of UPS and the bladder neck above showed overlapping pathological changes. Oxygen together with HA is supposed to relieve the UPS symptoms acting specifically on the soft-tissue matrix, and carefully also stimulating the urethra channel with the gas flow, to help it to increase the tone and reduce its enlarged diameter [26].

The UPS clinical stages are usually defined by the classification (Urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness of skeletal muscles) [30] and the bladder voiding diary, reaching only the diagnosis of exclusion after cystoscopy, urethroscopy, cytologic, and bacteriologic all negative findings.

As to our study, an open spontaneous trial, it has mainly been focused on the life quality score before and after Caressflow® treatment, being this original cosmetic approach never previously attempted in the UPS therapy.

Materials and Methods

The 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 enrollment of 20 women (45–65 years old) 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 [36], [37], [38], [39]. The UPS diagnosis was made

Table 1: Characteristics and baseline values of study population

No patients	20
Age (years)	37.2 ± 8.2
Symptoms history (months)	18
Number of micturition per 24 h (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

accordingly with the presence of clinical symptoms, including frequency, urgency and suprapubic discomfort, no abnormal findings at gynecological examination with negative neurologic and pelvic findings, and no inflammation at all at the urinalysis and no infections at the urine culture. The examination and enclosed bimanual pelvic examination, to evaluate the cervical motion adnexal masses and/or uterine enlargement with tenderness in each explored district; echography, cystoscopy, and urodynamic test were required to each patient by the same gynecologist, before the treatment, to exclude bacterial infections or interstitial cystitis with micturition problems.

After signed the informed consent form, all the participants answered a life quality questionnaire describing the personal history.

Inclusion and exclusion criteria

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

Criteria of exclusion

We excluded patients with interstitial cystitis, tuberculosis, and 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 past 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/HA therapy treatment, 7 times a week, for a total of 5 weeks at the outpatient clinic (Clinic Ester Veronesi, through Giardini 470, Modena, Italy).

Detailed instructions about healthy hygienic, good, and healthy nutrition, and sexual behavior were given before and then the treatment: The patient should avoid intravaginal medications, vaginal douching, and sexual intercourse within 24 h of her clinical procedure and also then it.

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

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

Treatment protocol

It included seven/weekly sessions (total 5 weeks) with a specific device for gynecological practice (Caressflow®, Caress Flow Srl, Bologna, Italy): An airbrush connected to the machine body, capable to carry and to spray an oxygen-HA combined solution (Figure 1). The instrument transforms the outside air into 93 ± 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 [40], [41].

Figure 1: Description of the airbrush connected to the machine body

Each patient is treated, inserting the vaginal cannula equipped with outlet holes, and releasing molecular oxygen alone at a flow of 1–6 l/min (for the first 5 min) and subsequently combined with sprayed 10 mL of low molecular weight HA- (for the next 15 min). This HA 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 superficial cells metabolism. After the oxygen session, HA 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 HA 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 and (2)

scores of three self-reported questionnaires: Vaginal assessment scale (VAS), patient perception of bladder condition scale (PPBC), and pain urgency frequency (PUF) scale. The micturition diary included 3-day S recordings of urine output per 24 h, number of urgencies, incontinence, and nocturia episodes per 24 h, intensity of urgency using the five-point URS (1 = no urgency, 2 = mild urgency, 3 = moderate urg, 4 = severe urg, and 5 = UUI), and additionally the volume voided during each micturition at timeline and after the five session's treatment. The VAS questionnaire identifies the vulvar symptoms (dryness, itching, burning, and pain) and consists in 4-item questionnaires that determine the severity scale (range 0–3 points: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) of dryness, soreness, irritation, and pain (dyspareunia or painfulness to touch with external stimulation) for both the vaginal and vulvar areas. In the validated PPBC scale, each participant filled in his perceived bladder condition on a 6-point scale (1 point = no problems and 6 points = many severe problems) [42]. Finally, the valid and reliable PUF scale measures urinary symptoms, for example, 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 ≥5 = urinary symptoms) [43].

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. $p < 0.05$ was considered significant.

Results

All patients successfully completed this study. We observed significant reductions in 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), and micturitions per 24 h (−44.01 vs. −20.12 mean value). There was statistically significant difference ($p < 0.0001$) between the baseline and post-treatment values in any parameter (Figure 2).

There was a decrease in all the scores evaluated 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 ($p < 0.0305$, $p < 0.0001$, and $p < 0.0001$, respectively). The VAS value scale showed that pain was reduced after the treatment.

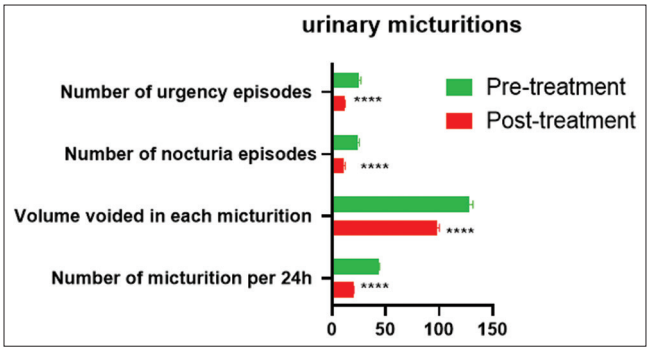

*Figure 2: Urinary micturition's parameters values pre- and post-treatment. There were significant differences. ****p < 0.0001 pre- versus post-treatment*

In fact, the mean value of VAS = 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-score <10 with significant reduction of 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 at 5 weeks after the last treatment PUF symptom scores 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 HA has proven to be a valid method for treating symptoms associated with urethral syndrome. It is a totally painless therapy, with excellent compliance by patients. It is a fast, non-invasive, and repeatable treatment.

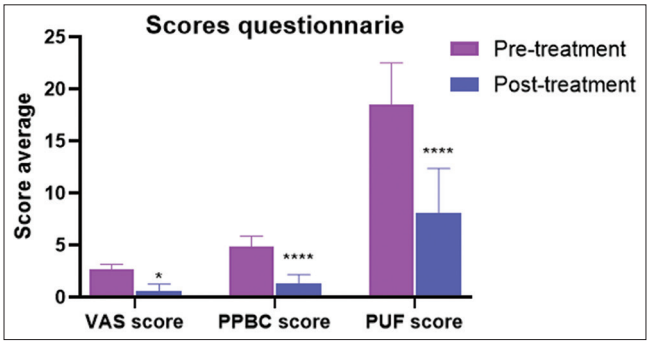

*Figure 3: VAS, PPBC, and PUF values questionnaires pre- and post-treatment. There were significant differences. ****p < 0.0001 pre- versus post-treatment*

Discussion

UPS is an hard challenge for the practicing physician due to some gaps of evidence-based treatments, and of standardized diagnostic guidelines ("diagnosis of exclusion" is mandatory). Petros *et al*. (Petros, 2010) showed that the urothelium

controls the activity of the afferent nerves, acting as a mechanoreceptor and contributing to chronic pelvic pain, typical symptom of urethral syndrome. Findings confirmed by Strelrsova and coworkers that reported in UPS women thinning of urothelium and an enhance in the thickness of the connective tissue matrix of the bladder neck (Streltsova, *et al*. 2020). Furthermore, Kiseleva *et al*. confirmed that urethral tissues in UPS can be linked to chronic bacterial inflammatory processes (Kiseleva *et al*. 2020). In addition, Gittes and Nakamura affirmed that a local infection within the short urethra 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 prostate specific antigen (Gittes and Nakamura 1996); a paraurethral gland inflammation promoting tenderness in the urethra through the anterior vaginal wall might be responsible of UPS.

Different types of antibiotic therapy have been proposed for the treatment of female urethral syndrome; however, the results of these treatment methods are disappointing, as they might be not necessary or might cause side effects or induce resistance (Llor and Bjerrum 2014). Ivarsson *et al*. (Ivarsson *et al*. 2019) analyzed the UPS treatment schedules of 137 Swedish hospital clinics and showed that this syndrome is treated at all medical specialty departments (urology, gynaecology, gynecologic oncology, venereology, and primary care), with different methods: For example urologists and gynecologists primarily use local corticosteroids, alone or in combination with urethral dilation; general practitioners, oncologists, and venereologists use instead estrogens and oral/local antibiotics. In our study, the efficacy of Caressflow® was associated with a statistically significant decrease in VAS, PPBC, and PUF questionnaires at the end of treatment. These effects are due to the oxygen-HA combination: The oxygen enhances the reparative processes of the inflamed mucosa and the collagen synthesis by the hydroxylation pathway and induces a neoangiogenetic stimulation through the release of the vascular endothelial growth factor [44], [45], [46], [47]. On the other side, HA binds large amount of water molecules rehydrating and restructuring the inflammation-injured skin and mucous surfaces [48]. We recorded a high patient satisfaction grade (97%) among patients after the five sessions' therapy that declared improvement in life quality, in particular in social daily life relationships, partner relationships, and sexual intercourse.

The limitation of this study is the lack of a control arm and 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 the future research with larger sample size. However, this preliminary observation and the positive outcomes are very promising and recommend a further major evidence-based clinical trial.

Conclusions

In this study, we highlight that Caressflow® 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 HA, gives immediately a sense of freshness and urethro-bladder relaxation that lasts several hours; the reasonable hypothesis explaining the action mechanism of HA 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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