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A PROSPECTIVE STUDY TO EVALUATE THE EFFICACY OF CISTIQUER IN IMPROVING LOWER URINARY TRACT SYMPTOMS IN FEMALES WITH URETHRAL SYNDROME

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A prospective study to evaluate the efficacy of Cistiquer in improving lower urinary tract symptoms in females with urethral syndrome

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Aim. **The aim of the study was to compare Cistiquer, a new phytotherapeutic product developed for chronic bladder inflammatory diseases, and intra-vesical administration of gentamicin plus betametasone, in females with urethral syndrome.**
Methods. **Between september 2013 and may 2014, 60 women with urethral syndrome and trigonitis were incuded in this study. Patients were randomly assigned to treatment with intra-vesical administration of betametasone 8 mg plus gentamicin 80 mg (group A), and oral administration of Cistiquer (group B) for 7 weeks. Before and after the therapeutic protocol, symptoms were assessed by three days voiding diary, the overactive bladder questionnaire short form and a ten points visual analogic scale adopted to assess the micturition discomfort. Histologic findings were assessed by the examination of specimens obtained by cold bladder biopsies of the bladder trigone at baseline in all the subjects.**
Results. **The two groups had significant and comparable symptoms improvement. However, the score obtained from the visual analogic scale decreased significantly only in the group submitted to oral therapy. Furthermore, in the group treated with endovesical approach, higher drop out rate and higher incidence of urinary infection were observed.**
Conclusion. **Patients with urethral syndrome and trigonitis improved symptoms either with oral therapy with Cistiquer and with intra-vesical administration of gentamicin plus betametasone. However, treatment adherence resulted higher for patients treated by oral therapy and rate of adverse events resulted higher for those submitted to endovesical treatment.**

KEY WORDS: Lower urinary tract symptoms - Urethral syndrome.

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Urethral syndrome is an ill-understood disease affecting females and responsible for lower urinary tract symptoms (LUTS), as urinary frequency, urinary urgency, burning micturition, hematuria, and pelvic pain associated with negative urine cultures.[1] Cystoscopic examination of individuals suffering from urethral syndrome reveals an inflammatory status of the bladder neck and trigone, described as trigonitis, whose histologic pattern reveals many layers of stratified squamous epithelium.[2] To cure urethral syndrome, therapies today available are symptomatic but most of them

are not effective and do not contribute to significantly improve quality of life of patients. This is also the consequence of the fact that urethral syndrome has had several sobriquets, which have led to much confusion over its existence and the useful options in the care of the afflicted patients.[3] Urethral syndrome is refractory to antibiosis and patients often do not respond to oral administration of conventional therapy, represented by steroidal and non-steroidal anti-inflammatory drugs.

However Tait J. *et al.* identified a microbiological cause in 4 patients of a cohort of 31 individuals referred to their attention with a diagnosis of recurrent urethral syndrome.[4] Cystoscopy hardly contributes to diagnosis cause it reveals hyperemia and squamous aspect of the bladder mucosa at trigone level. In his population, Tait noted trigonitis at cystoscopy in 26 of the 31 patients and bladder biopsies showed squamous metaplasia in 15 and lymphocytic infiltration of the lamina propria in 29. These findings give support to an inflammatory aetiology of this enigmatic condition and confirm the hard association between urethral syndrome and trigonitis[5]. Further evidence of this association is provided by Carreras, who reported 68% of urethritis alone or combined with trigonitis in a cohort of 350 women presenting LUTS.[6] In addition, this author specified that urine examination and cultures resulted negative in 80% of this population. Bladder histology in these patients shows pathological findings. Normal trigonal urothelium consists of 3 cell layers (basal, intermediate and superficial), whereas trigonitis constitutes many layers of stratified squamous epithelium. The basal cells contain prominent nuclei with condensed chromatin, nucleoli and nuclear bodies. The cytoplasm of these cells is rich in mitochondria. The profiles of the urothelial cells become progressively elongated, their nuclei increasingly smaller and their content of cell organelles gradually reduced as the luminal surface is approached. The squamous surface cells, linked by desmosomes, retain many longitudinally arranged fine filaments, together with an occasional degenerate nucleus.[7] Similar findings have been reported by our pathologists in patients enrolled in this protocol. These alterations are usually not found in the lateral wall of the bladder, as clearly showed by Pacchioni *et al.*, who showed also clear correspondence between the presence of steroid receptors at the squamous metaplasia of the trigonum speculating about a possible endocrine pathogenesis of trigonitis.[8] This observation is also supported by Stephenson TJ *et al.* who found the selective expression of nuclear estrogen receptor in trigonal epithelium of 10 women affected by trigonitis, in a distribution similar to that reported in vaginal epithelium by other workers. In this case the authors suggest an oestrogen mediated aetiology of trigonitis speculating that it could be consistent with an embryological derivation of the trigone, distinct from that of the rest of the bladder.[9] An association has been found among trigonitis, intestinal disorders, and inflammatory lesions of the genital tract (uterine cervix). Since 1956 J.E. Semple of the St. Paul's Hospital, London, reporting his experience in 43 females with trigonitis, has described that 11 subjects presented with lesions of the large intestine (diverticula and radiologic appearances of inflammation).[10] However, he suggested that the correlations between bowel inflammation and trigonitis was not so strong as the association that he found with alteration of the cervix and genital tract (in 66% of patients). In his experience, Semple firstly suggested the chance of treating these patients by endoscopic fulguration of the bladder or urethral calibration.[10-12] However, urethral calibration is not useful in patients with normal micturition parameters as the patients enrolled in our protocol. Endoscopic treatment is considered invasive but it is still widely used for treating this condition by monopolar or bipolar fulguration of the inflammatory area of the bladder trigone. However, no randomized prospective trials have been developed on this therapeutic option and no level of evidence is therefore available regarding its efficacy and safety. Only Costantini *et al.* reported the results of

a prospective randomized study on surgical treatment using Nd:YAG laser in 62 patients with trigonitis refractory to drugs.[1] This study concluded that side-firing laser, which produces necrotic coagulation followed by reconstitution of normal functional epithelium, was significantly more successful than end-firing and was associated with a 78% success rate. These results are encouraging in patients who are usually refractory to medical therapy. Medical therapy options are represented by oral anti-inflammatory drugs which determine short-time relief of symptoms and are very often followed by recurrence. One of the most used treatment is represented by topic administration of drugs. Shirley SW *et al*. reported favorable outcomes using Dimethyl sulfoxide. However, this study included a large population of both sexes and suffering from various disorders, as prostatitis, intractable interstitial cystitis, radiation cystitis, chronic prostatitis, and chronic female trigonitis.[13] Many physicians use topic administration of cortisone reporting satisfying results. However, for all these therapeutic options there are no large randomized trials available and some data come from old studies.[14]

Since many years various authors experienced the effects on urethral syndrome symptoms exerted by drugs capable of reducing inflammation of the bladder.[15] The high incidence of symptoms recurrence and the poor efficacy of these therapeutic choices, induce patients to receive mini-invasive treatments, consisting of intravesical instillation of drugs, or surgical approaches, such as endoscopic resection or coagulation of the pathologic bladder mucosa. Obviously, invasive treatments are not well tolerated and furthermore they have variable efficacy, thus to prompt patients to search for alternative options.

Several reports show encouraging outcomes provided by phytotherapic agents on chronic lower urinary tract inflammatory disorders. Recurrent cystitis and chronic prostatitis are the most important diseases that benefit from these therapies.

Cistiquer is a phytotherapeutic agent composed by natural elements which may contribute to reduce inflammation and pain, and to preserve the integrity of urothelium and connective tissue of the bladder. Quercitin, the principal, is a flavonoid, a plant pigment with a molecular structure like or derived from flavone. It is found in fruits, vegetables, leaves and grains. It can be used as an ingredient in supplements, beverages, or foods. Several laboratory studies show quercetin may have anti-inflammatory properties and it is being investigated for a wide range of potential health benefits.[16, 17] A study with rats showed that quercetin effectively reduced immediate-release niacin (vitamin B3) flush, in part by means of reducing prostaglandin D2 production.[18] A pilot clinical study of four humans gave preliminary data supporting this.[19] Quercetin may have properties of a calcineurin inhibitor, similar to cyclosporin A and tacrolimus, according to one laboratory study.[20] Moreover, Quercetin has been found to provide significant symptomatic improvement in most men with chronic prostatitis, a condition also known as male chronic pelvic pain syndrome.[21] Cistiquer contains also Condroitin Sulphate, a glycosaminoglycan (GAG) acting by the inibition of NO synthesis providing effective outcome on inflammatory symptoms, and glucosamine, which contributes both to restore physiological properties and anatomical integrity of urothelium, as already shown by previous studies which also demonstrated efficacy and safety of these agents on chronic bladder conditions, as trigonitis and interstitial cistytis.[22] Another agent contained in Cistiquer is bromelin, which is an extract derived from the stems of pineapples, although it exists in all parts of the fresh plant and fruit, which has many uses and also anti-inflammatory properties.[23-25] An antioxidant and anti-inflammatory activity has been also shown for another component of Cistiquer, Centella, a genus of 2 or 3 species of flowering plants in the subfamily Mackinlayaceae which has also revealed important antibacterial properties in microbiological studies.[26, 27] Other extracts included in Cistiquer are from Rhodiola, a plant of the Crassulaceae family which has shown effects on relieving mental and physical fatigue,[28]

and from Scutellaria barbata, a species of flowering plants in the mint family whose English common name is Barbed skullcap. It is used as a herbal remedy for inflammation and traumatic injury and has been tested in clinical trials for the treatment of metastatic breast cancer; moreover, its extracts induced apoptosis in prostate cancer cells in laboratory studies.[29] The properties of all these natural agents appear intriguing for treating bladder modifications observed in urethral syndrome associated with trigonitis. The action of quercetin combined with the other natural extracts and the precious contribute of condroitin sulphate and glucosamine may provide hard synergic favorable effects reducing irritative symptoms as a consequence of lower inflammation and of better bladder mucosa integrity. Considering these characteristics, the aim of this investigation was to compare the efficacy and tolerability of oral administration of Cistiquer with intravesical administration of gentamicin and betametasone in females with urethral syndrome.

Materials and methods

A total of 98 females with urgency-frequency syndrome were prospectively recruited for this study after informed consent was read by the investigator, signed and dated by the patients. All subjects were evaluated at the Urology Unit of the Department of Medico-Surgical Sciences and Biotechnologies of Sapienza University of Rome, by means of history, comorbidities assessment, physical and genital examination including stress test, microbiological tests on vaginal swab to exclude genital infections (Chlamydia, Mycoplasma, Ureaplasma, Trichomonas), urinanalysis and urine culture, renal and pelvic ultrasound, three days voiding diary, urinary cytology, pregnancy test, uroflowmetry with ultrasound evaluation of bladder residual volume, and flexible cystoscopy combined with multiple cold biopsies of bladder mucosa at trigone level (six for each patient). Symptoms were assessed by the overactive bladder questionnaire screener short form (OAB-SF, Figure 1). Furthermore, all patients were invited to indicate the grade of micturition discomfort on a ten visual analogic scale (VAS), from 0=no discomfort to 10=severe discomfort. Inclusion criteria were represented by presence of irritative symptoms as urinary urgency and urinary frequency combined with a histological diagnosis of trigonitis. Exclusion criteria were considered: urinary and/or

During the past 4 weeks, how bothered were you by...	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. An uncomfortable urge to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. A sudden urge to urinate with little or no warning	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Accidental loss of small amounts of urine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Waking up at night because you had to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Urine loss associated with a strong desire to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Figure 1.—The overactive bladder questionnaire short form (OABq SF). This questionnaire has been specifically developed to diagnose OAB, is easy to fill and is self-administered.

genital tract infection, evidence of organic disease at renal and pelvic ultrasound, genital prolapse, stress urinary incontinence at history or revealed by physical examination, neurogenic diagnosis, previous genital and/or urological surgery, previous pelvic radiotherapy, maximum flow rate <18 mL/s, bladder residual volume >50 mL, any evidence of genital dystrophy, or any anatomic alteration at genital assessment such as hypospadias, positive pregnancy test. Basing on these criteria, from the preliminary cohort, 61 patients were histologically diagnosed suffering from trigonitis and satisfied the inclusion criteria. The histological diagnosis was achieved by optical microscopy. Two different pathologists evaluated independently the specimens and provided the same diagnosis. Patients eligible for the protocol basing on inclusion and exclusion criteria were randomized 1:1 to two different treatments: 30 individuals were submitted to endo-vesical administration of gentamicin 80 mg plus betametasone 8 mg (twice/week for 7 weeks, group A) while the other 30 assumed oral therapy with Cistiquer, one tablet/day/7 weeks (group B). One patient was excluded from the protocol to obtain the same number of individuals in both groups. The outcomes provided by the reported investigational measures were assessed 7 days before and 7 days afer therapeutic protocol. Statistical analysis was performed to evaluate the outcomes: χ^2 test and odds ratios for categorical variables, and Student's *t* test to evaluate differences of continuous measurements.

Results

Clinical findings

Mean age, mean body mass index, menopausal status and comorbidities distribution did not significantly differ between the two groups compared in the study (Table I). In order of prevalence, comorbidities were represented by: type II diabetes, dyslipidemia, blood hypertension, dysthyroidism. All diabetic patients assumed only oral therapy. None of these patients presented polyuria at voiding diary examination.

Protocol development

Three patients of group A spontaneously dropped out from the protocol. One of them due to severe hematuria cured in 48 hours with bladder catheterism; 2 patients refused further catheterism after 6 and 8 procedures respectively due to pain; furthermore, these 2 patients reported no symptom improvement. One patient of the group A and 2 patients of group B needed antibiosis due to acute urinary infection during the first week of treatment and were therefore excluded from the study. Final evaluable cohort at the end of protocol resulted of 26 patients in group A and 28 patients of group B. 19/26 subjects of group A and 19/28 subjects of group B reported to be sexually active. Baseline data achieved by three days voiding diary showed severe increase of micturition episodes in the population and significant number of urinary urgency episodes. None

TABLE I.—*Demographic and clinical features two groups enroled. The results show that the two cohorts do not present significant difference about sex, age, BMI and comorbidities distribution. Diabetes, dyslipidemia and OSAS were the most represented disorders associated with obesity.*

Number of pts	Group A (26)	Group B (28)
Age: range, mean and SD	(27-57 years, 42.4±8.24)	(31-55 years, 44±6.34)
BMI: mean and SD	22±4.9	21±5.5
Diabetes	8	7
Dylsipdemia	6	7
Hypertension	11	11
Dysthyroidism	6	3
Menopausal status	12	13

Comment: clinical features of the population. The table shows that women of two groups were comparable in terms of mean age, mean BMI, comorbidities distribution, and menopausal status.

TABLE II.—*Comparison of baseline and control parameters in group A and B. Data regard patients with OAB diagnosis. P value was considered statistically significant when <0.005.*

	Before treatment	After treatment	P
Group A			
Total fluid intake per 24 h (mL	1280 ± 67.9	1309 ± 68.4	NS*
Total micturitions per 24 h	9.6 ± 1.2	6.6 ± 1.7	<0.001
Urgency episodes per 24 h	3.5 ± 1.1	0.4 ± 1.9	<0.001
UUI episodes per 24 h	1.2 ± 0.7	1	NS
Nocturnal micturitions 24 h	1.1 ± 1.2	1.1 ± 1.3	NS
Mean voided volume (mL)	189 ± 57	233 ± 26	<0.01
OAB-q score	18.69 ± 8.9	12.18 ± 3.2	<0.0001
Group B			
Total fluid intake per 24 h (mL)	1190 ± 37.4	1201 ± 33.2	NS*
Total micturitions per 24 h	9.2 ± 1.4	5.6 ± 1.1	<0.001
Urgency episodes per 24 h	3.3 ± 0.9	1.4 ± 1.0	<0.001
UUI episodes per 24 h	1.4 ± 0.8	1.4 ± 0.3	NS
Nocturnal micturitions per 24 h	1,0 ± 1.3	1.0 ± 1.1	NS
Mean voided volume (mL)	212 ± 44	232 ± 39	NS
OAB-q score	16.4 ± 1.5	12.3 ± 1.1	<0.001

N.S.: not significant; UUI: urge urinary incontinence.

patient suffered from polyuria (considered as voided urine volume > 3000 mls per 24 hours). VAS scores did not significantly differ between the two groups at baseline. Particularly, patients in group A scored at VAS a median 8, mean 6.5±2.3; patients in group B scored a median 8, mean 6.3±2.2.

Three patients of group A and 2 patients of group B presented also urinary urgency incontinence episodes. After the protocol was concluded, the examination of voiding diary data and of OAB-q SF scores showed a significant improvement of symptoms and significant reduction of urinary frequency and urgency episodes in both groups. Although the results appeared better for the group B, this outcome did not reach statistical significance (Table II). None of the patients of group B reported any adverse event secondary to drug assumption. A significant decrease of VAS score was reported by females of group B, whilst no significant modification of this parameter was observed in patients of group A. In fact, after treatment, patients in group A scored at VAS a median 5, mean 3.5±2.3, while patients in group B scored a median 0.8, mean 1.1±1.7 (P=0.001, Figure 2). In group B, 55% of

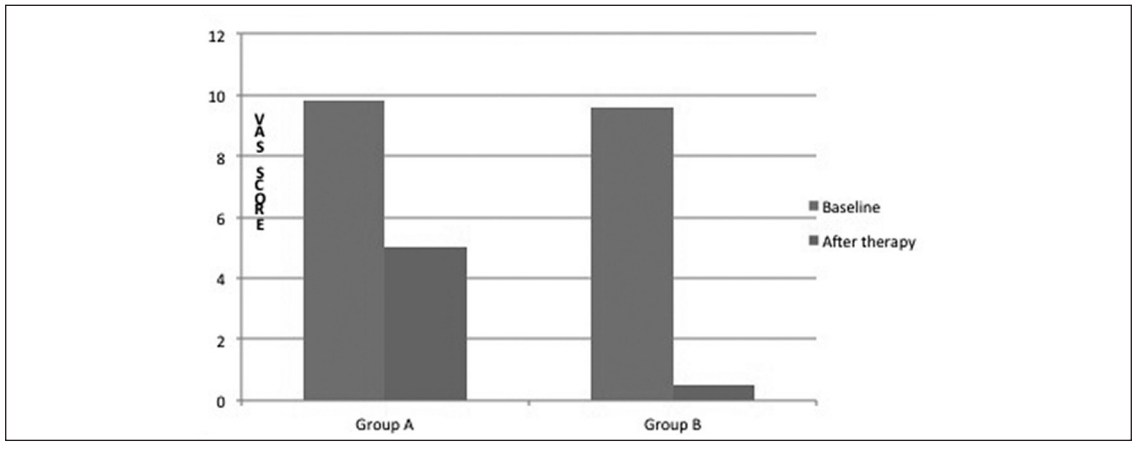

Figure 2.—Comparison of VAS before and after treatment between the two groups shows a significant higher decrease of score in group B respect to group A.

patients referred no micturition discomfort (VAS=0) while all patients in the other groups experience the persistence of some degree of discomfort. At the end of the protocol the number of individuals who reported to be sexually active increased only in group B, from 19 to 21 women. Urinary urgency incontinence episodes disappeared in 1 patient of group A and 1 of group B.

Discussion

Women with urethral syndrome present irritative symptoms which hardly lower their quality of life, limiting daily practises, social interaction and sexual activity. These patients present negative urine examinations and cultures and are consequently refractory to antibiosis. However, despite this evidence, they come to the attention of urologists and gynecologists after many attempts of treatment with different antibiotics. Of course, urinary and genital tract infections (sexually transmitted diseases) must be excluded to diagnose an inflammatory chronic abacterial condition of the bladder. In our clinical practice we use local administration of cortisone after endoscopic and histologic diagnosis of trigonitis: patients are submitted to 14 local instillations of betametasone 8 mg associated with gentamicin 80 mg to prevent acute urinary infection secondary to bladder catheterism. Patients who have no clinical improvement are then treated by bipolar electrovaporization of the inflammatory area of the trigone. In our experience, either catheterisms and endoscopic surgical treatment are not well tolerated by the patients, so much that we need to find alternative therapeutic strategies to improve symptoms. Furthermore, many patients are willing to use therapeutic strategies derived from natural/herbal extracts, capable of lowering symptoms and curing chronic conditions as alternative and/or complementary therapy to glucocorticoids, non-steroidal antirheumatics, and immunomodulators. Goals of therapy in trigonitis are: reducing the inflammation of the bladder, protecting the bladder wall from damage of deeper layers and restoring urothelium integrity. Cistiquer is a phytotherapeutic product containing various agents capable of reducing bladder inflammation and protecting urothelium. These possible advantages provided by Cistiquer seem to be supported by the outcomes of this investigation, which showed good symptoms improvement of patients with favorable effects also on sexual activity. The results confirm that oral therapy is better tolerated than catheterism, as revealed by the higher rate of adverse events and higher drop-out rate observed in group A. In fact, as shown by VAS outcomes, urinary discomfort did not significantly change in patients submitted to intravesical therapy, although urinary frequency and urinary urgency were improved. Moreover, it has to be considered that natural agents are characterized by a low rate of side effects inducing patients to well tolerate also long-term therapies, especially if associated with symptoms improvement, as shown by Cistiquer in our experience.

Limitations of the study

Limits of the study are represented by the small population included and the absence of a placebo-controlled group. It should also be noticed that some data about efficacy and therapeutical properties of some natural agents included in Cistiquer composition are lacking of rigorously-designed, well-controlled randomized control trials. However, in the Literature the use of conventional drugs to treat trigonitis is also not commonly considered. Therefore, surely this topic needs better consideration with the aim to improve our knowledge on etiopathoegeteic mechanisms and explore better therapeutic options. Basing also on this pilot experience, Cistiquer should be taken into consideration as one of the therapeutic options for treating urethral syndrome before choosing invasive procedures.

Conclusions

Both oral treatment with Cistiquer and intravesical administration of betameta-

sone plus gentamicin improved symptoms of patients with urethral syndrome. However, in the group treated with Cistiquer a lower rate of adverse events was observed and patients reported better improvement of urinary discomfort.

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Conflicts of interest.—Dr. Zanello is a scientific consultant for Deakos. The other authors do not have conflicts of interest to declare.

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