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Urethral instillations of clobetasol propionate and lidocaine: a promising treatment of urethral pain syndrome

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Summary

Purpose: To evaluate topical treatment with clobetasol propionate and lidocaine in women with urethral pain syndrome (UPS) in a retrospective pilot study. *Materials and Methods:* Urethral instillations of two ml clobetasol propionate cream and two ml lidocaine gel in 30 Caucasian women age 15-74 years with UPS between 1999 and 2006 were evaluated retrospectively. Instillations were given approximately once a week until the patient improved. Between one and 15 (median three) instillations were given. In substudy I a review was undertaken of the medical records to register the treatment effect at the end of the treatment (the last instillation) and any relapses six months thereafter. Substudy II was a follow-up at least five years after last instillation based on medical records and a written questionnaire. *Results:* Substudy I (n=30): By the end of the treatment 18 women had no symptoms and 12 were improved. Five patients had relapsed within six months. Substudy II (n=28): Twenty-eight women responded to the questionnaire. Four women remained with no symptoms, 18 remained improved, and six had the same symptoms as before treatment. Twenty women thought the treatment was very effective, five rather effective, and three women reported poor effect. Twenty-six women would ask for retreatment if a relapse occurred, two patients would not. No side effects, except transient pain, were reported. *Conclusions:* This retrospective study and long-term follow-up suggests that urethral instillation of clobetasol propionate and lidocaine is effective in treating women with UPS. Randomized control studies are warranted.

Key words: Clobetasol; Lidocaine; Urethral pain syndrome; Urethral syndrome; Urethritis.

Introduction

Gallagher *et al.* coined "urethral syndrome" in 1965, defined as recurrent urinary irritation without urinary tract infection [1]. In 2002 the International Continence Society changed the terminology to "urethral pain syndrome" (UPS) as a part of the "genito-urinary pain syndromes". UPS is defined as the occurrence of recurrent episodic urethral pain, usually on voiding, with daytime frequency and nocturia, in the absence of proven infection or other obvious pathology [2]. In this article the authors will consider the urethral syndrome and the UPS as the same condition and they generally use the term UPS for both. UPS is a diagnosis of exclusion and the etiology is unknown. Theories of etiology to UPS include infection of low activity, urethral stenosis, early manifestation of interstitial cystitis (i.e. painful bladder syndrome), stress, trauma, allergy, mechanical obstruction, neuropathic hypersensitivity as a result of urinary infection, traumatic intercourse, an incomplete relaxation or spasm of the external striated sphincter, periurethral fibrosis, estrogen deficiency in the urethral mucosa, dysfunctional epithelium, and inflammation of the paraurethral glands [3, 4].

UPS is a common condition but the true incidence is unknown due to lack of consensus in diagnosis and overlap with other conditions. In a study from England, about half the patients visiting their general practitioner with frequency and/or dysuria did not have significant bacteriuria [5]. UPS is often a recurrent chronic disease. It is not a life-threatening condition but it can have a significant impact on the quality of life. In the most severe cases of UPS the condition can lead to long periods of sick-leave, affect sexual functions, and social relations [4, 6]. A study in 1989 showed higher levels of hostility, irritability, anxiety, dysphoria, and depression in the group of patients with urethral syndrome than in the control group [6].

There is no golden standard in the treatment of UPS. Kaur and Arunkalaivanan stated in 2007 that "treatment at its best is by trial and error" [3]. In 2006 the present authors sent a questionnaire to 21 gynecology clinics and nine urology clinics in Sweden with questions about how they treated UPS in women. Sixteen different modalities of treatment were given singly or in combination. None of the clinics gave treatment with strong or extra strong corticosteroids (Europe class III-IV, US class I-II) to patients with UPS. The response rate from the clinics was 90% (unpublished data).

The present authors' hypothesis is that an important cause of symptoms of UPS is urethral inflammation. The aim of this study was to retrospectively evaluate treatment with urethral instillations of the more potent corticosteroid clobetasol-propionate (CP) cream (US class I, Europe class IV) with lidocaine (L) gel.

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Materials and Methods

This study is a retrospective evaluation of urethral instillations of CP cream 0.05% in 30 women with UPS during the period of September 1999 to November 2006. During this period 40 Caucasian women were diagnosed with UPS at the outpatient gynecology clinic in Bjursås, Sweden. UPS was diagnosed with symptoms urethral pain and or dysuria, with or without urgency, and palpation tenderness of the anterior vaginal wall without signs of infection or other pathology. To exclude other pathology, all patients had, apart from the taking of medical history, dipstick urinalysis, clinical gynecological examination with vaginal ultrasound of the uterus and adnexa to exclude common lower urinary tract infection, gynecological tumors, and atrophic colpitis. If any clinical suspicion of other conditions existed, laboratory tests for sexual transmitted disease, common urine culture or cystoscopy was carried out. Patients without estrogen therapy that were diagnosed with UPS were first offered treatment with local estrogen therapy. If the estrogen therapy did not relieve the patient from the symptoms, she was offered treatment with CP and L. Inclusion criterion was diagnosis of UPS as described above. Exclusion criteria were the finding of any other possible cause of the UPS symptoms as described above, or that the patient achieved any other treatment method for UPS during the study period. Out of the 40 women diagnosed with UPS, ten women were excluded from the study; two patients were lost to follow-up, one patient received one instillation of betamethasone valerate (strong steroid, Europe class III) instead of CP and became free of symptoms, three patients were excluded because UPS occurred only after coitus and were treated effectively with a short course of antibiotics post coitus, one postmenopausal patient received local estrogen, and did not get further relapse of UPS. The remaining 33 patients were offered CP and L instillations; three patients with mild symptoms were satisfied with the diagnosis and explanation and refrained from treatment.

The study included the remaining 30 women. Age at inclusion was 15-74 years (mean 56, median 62). Six women were pre- and 24 were postmenopausal. Two women (7 %) were smokers and 20 (67 %) were sexually active. Altogether 26 (87%) had estrogen treatment. Thirteen (43%) had local estrogens, eight (27%) had local estrogens and hormone replacement therapy (HRT), four (13%) had HRT, and one (3%) combined oral contraceptives. Four patients (13%) did not accept estrogen treatment (two premenopausal and two postmenopausal). All the patients were treated with CP and L the same way and all completed treatment as recommended by the doctor (AKL). At each treatment session, the patient first emptied her bladder to be able to refrain from urination for at least two hours after the urethral instillations. The urine was also checked with dipstick urinalysis to exclude signs of current urinary infection or hematuria. Thereafter two ml CP cream was instilled into the urethra, immediately followed by instillation of two ml of L gel. L was instilled to alleviate the transient burning urethral pain typically caused by the CP cream in the UPS patient. Instillations were given approximately once a week. The patient decided when to stop treatment by stating she was either free from symptoms, improved, unchanged or worsened. Between one and 15 (median three) instillations were given. All treatments were given the same way each time by one of the authors (AKL).

In substudy I, a protocol for retrospective evaluation was constructed by a person not involved in the treatment (DH). A review of the medical records was carried out, to register the treatment effect at the end of the treatment and to document any relapses within six months. A relapse was defined as recurrence of the UPS symptoms, exclusion of other cause of the symptoms was then carried out as described above. Evaluation of the medical records was conducted by a person not involved in the treatment and blinded for patient identification (BEL). Substudy II was a long-term follow-up through a written questionnaire distributed in 2012 to the patients of substudy I at least five years after the end of treatment. Substudy II included 29 women as one women was deceased. Twenty-eight women responded to the questionnaire (response rate 97%). The patients who stated that they were still free from symptoms had their medical records rechecked and if any of those had attended for UPS in the follow-up time they were not recorded as asymptomatic but improved. The study was approved by the research ethical committee in Uppsala. Written informed consent was obtained.

Table 1. — *Substudy I (n=30). Effect of treatment at completion of treatment and six month follow-up.*

	No. of patients	No effect	Improved	Free from symptoms	Relapse within 6 months
1 instillation	12	0	6	6	2
2-7 instillations	9	0	4	5	1
8-15 instillations	9	0	2	7	2
Sum	30	0	12	18	5

Results

Effects

In substudy I (n=30), 18 (60.0%) of the patients were totally relieved of their UPS symptoms by the end of the treatment and 12 (40.0%) were improved. By the six-month follow-up, 17 (56.7%) were free from symptoms, eight (26.7%) remained improved, and five (16.7%) patients had relapsed. The number of instillations until the treatment was considered finished were one to 15 (mean 4.9, median three). To 12 (40.0%) patients, one instillation was sufficient, nine (30.0%) patients had two to seven, and nine (30%) patients had eight to 15 instillations (Table 1). All five patients that relapsed within six months in substudy I were further treated with CP and L instillations. In substudy II (n=28) the > five years follow-up showed that four (14.3%) patients were still free from symptoms, 18 (64.3%) patients had symptoms but milder than before treatment, and six (21.4%) had relapsed to the previous degree of symptoms. None had more severe symptoms compared to before treatment.

Side effects

In substudy II two (7.1%) patients reported transient urethral pain in connection with the instillation of CP cream and four (14.3%) patients could not recall whether they had any side effects. Other side effects were not observed in substudy I or reported in substudy II.

The patients' judgment of the treatment

In substudy II (n=28), the patients' reported effectivity was high (Figure 1) and the large majority would undergo re-treatment in case of relapse (Figure 2). For one of the

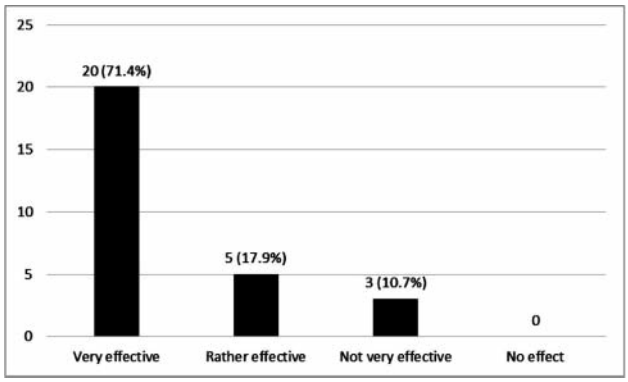

Figure 1. — Answers to the question: How effective do you consider that the treatment of UPS with clobetasol/lidocaine is? Substudy II (n =28).

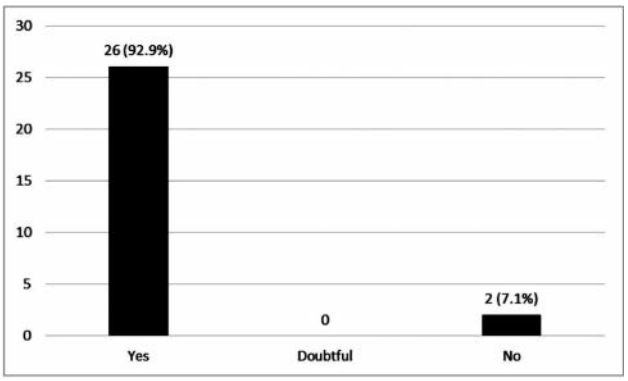

Figure 2. — Answers to the question: Would you take clobetasol/lidocaine treatment again if you got a relapse of the UPS? Substudy II (n =28).

two patients who would not undergo the treatment again, the reason was because of the transient urethral pain at the moment of the instillation and the other woman was convinced that in her case the causal factor was estrogen deficiency.

Discussion

The search for an answer to the etiology of UPS and related conditions such as trigonitis, interstitial cystitis, and other pelvic pain syndromes is intriguing. Within UPS there might be different conditions, with different etiologies, and therefore different appropriate treatments. The present authors believe that the favorable effects of CP treatment in this study are due to the anti-inflammatory properties of CP. Histopathological examination of biopsies from women with UPS has shown inflammatory changes in trigonum, the urethral mucosa, and the paraurethral glands [7-9]. The search for an infectious cause has so far been unsuccessful [4, 10, 11].

There are studies showing varying effect with antibiotic treatment in treating UPS or trigonitis [12, 13]. In these studies, tetracyklines or macrolides have mainly been used and it is important to remember in this discussion that they also have anti-inflammatory properties [14-16]. There is a theory that UPS is due to dysfunctional urethral epithelia leading to entry of urine and bacteria causing inflammation [4]. One could speculate an analogy to eczema where a dysfunctional epithelial barrier plays a crucial part of the inflammatory process and were microbiological colonization is seen. In dermatological guidelines for treatment of atopic eczema, skin care, emollient treatment, and anti-inflammatory topical corticosteroids without any antibiotics, is the first line of treatment, although it is known that microbial colonization most probably is present [17]. There are strong indications that the paraurethral glands are homologous to the male prostate and that they are not only silent embryological remnants but active glands [18-20]. It has been hypothesized that UPS could be a female equivalent to non-bacterial "prostatitis" [8, 18, 20]. There has been histological findings of inflamed paraurethral ducts in patients with UPS [8, 21]. In case of a female "prostatitis" the present authors believe that the urethral instillation of CP could reach and quench such an inflammation. In male prostatitis, acute bacterial infection of the prostate exists, but in the chronic form of male prostatitis, studies have not been able to prove convincing evidence of an infectious cause but signs of inflammatory activity have been seen [22, 23]. Given the rising global problem of antibiotic resistance, it is desirable to minimize any unnecessary use of antibiotics.

The present findings suggest that the strong anti-inflammatory properties of CP [24] could alleviate or remove the symptoms of UPS, although an effect of L could not be ruled out. Perhaps CP cream or the L gel could also anoint and provide protection to a possible dysfunctional urethral epithelia and in this way relieve symptoms. The only observed side effect in this study was transient urethral burning pain in association with the instillation. The local anesthetic L was added to the treatment to remove this side effect. Instead of CP 0.05% cream with the addition of L, the authors now use CP 0.05% ointment without addition of L as the clinical experience is that the ointment more seldom gives this side effect. The present authors have not found any studies on the pharmacokinetics of CP on the urethral or bladder epithelia and its possible local or systemic side effects. Topical treatment with CP is used on other types of mucosa such in treating oral lichen planus (OLP), mucous membrane pemphigoid (MMP), lichen sclerosus (LS) in vulva, as well as children with severe phimosis. In treating OLP, MMP, phimosis, vulvar LS the frequency of topical application of CP (ranging from three times per day to twice weekly) is higher and the length of treatment (from four up to 48 weeks) is often longer than

the treatment with CP and L given in this study, suggesting that this treatment of UPS is not aggressive [25-27]. The present authors have not found any studies of urethral administration of CP, though a few studies can be found in treating interstitial cystitis with triamcinolone or hydrocortisone as ingredients in bladder instillations. To their knowledge, two earlier studies have reported corticosteroid treatment of UPS, but these were on weaker corticosteroids. In a Swedish randomized study from 1972, urethral dilatation combined with instillation of chloromycetin-hydrocortisone (very low potency corticosteroid US class VII, Europe class I) was shown to relieve or remove symptoms in 44 % of women with symptoms of cysto-urethritis without concurrent findings of urinary tract infection [28]. In 1976 an American study presented a very good response in 54 women treated with sub-mucosal injections of the corticosteroid triamcinolone acetonide (moderate potency corticosteroid US class III, Europe class II) around the paraurethral glands [29]. In these studies no side effects were observed or mentioned.

Although not noticed in this study, there could theoretically be a risk of local side effects such as infection, atrophy, eczematic reactions or systemic such as adrenal suppression, hirsutism or moon face from urethral instillations of CP. Systemic side effects due to installation of CP in this dosage seem unlikely.

Local deficiency of estrogens is a differential diagnosis to UPS, or an aggravating factor. Postmenopausal women presenting with UPS should initially be given local estrogen therapy [30], even premenopausal women may sometimes benefit. The present authors believe that local (vaginal) estrogen therapy in doses that give effect on the urethral epithelium is important, at least in postmenopausal patients, in order to exclude it as a sole cause or for general improvement of the UPS. In this study 86% of the studied women had some kind of estrogen therapy which could be a confounding factor. Nevertheless in all cases the estrogen therapy was started in a sufficient amount of time before the CP and L treatment so that any estrogen effect on the UPS already ought to have been shown. Most of the patients had their estrogen therapies since years before starting CP and L treatment. As mentioned earlier patients whose UPS were efficiently treated by estrogens were excluded from the study.

When evaluating treatments to UPS, one has to keep in mind the common intermittent course of the UPS [4], spontaneous remission independent of the treatment is also a risk of bias. This intermittent course also gives a risk for recall bias in the follow-up questionnaire. Other risk of bias is the risk of placebo. Also, in this study the physician treating the patients had set the model of treatment and had a positive attitude to the effect of the treatment. There is a risk that the patients declared better results so as to not affect their doctor-patient relation negatively. The high number of satisfied patients and their positive responses to the treatment could also be because they, in the present authors' experience, often describe what they experience as lack of interest or knowledge by other medical practitioners, while they in this study are met with interest.

In conclusion, this study indicates a good effect in treating the UPS with CL and L instillations. No significant side effects have been noticed. Some previous findings support the rationale for local treatment with potent corticosteroids. It will always be important to rule out infection or other pathological conditions before the treatment is administered and to be vigilant for possible side effects. All UPS patients may not benefit from this treatment since there could be different and so far unknown causes to the UPS. Multicenter double blinded randomized placebo controlled clinical trials with urethro-cystoscopy and preferably urethral histology prior to and after treatment are warranted.

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References

[1] Gallagher D.J., Montgomerie J.Z., North J.D.: "Acute Infections of the Urinary Tract and the Urethral Syndrome in General Practice". *Br. Med. J.*, 1965, *1*, 622.

[2] Abrams P., Cardozo L., Fall M., Griffiths D., Rosier P., Ulmsten U., *et al.*: "The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society". *Am. J. Obstet. Gynecol.*, 2002, *187*, 116.

[3] Kaur H., Arunkalaivanan A.S.: "Urethral pain syndrome and its management". *Obstet. Gynecol. Surv.*, 2007, *62*, 348.

[4] Phillip H., Okewole I., Chilaka V.: "Enigma of urethral pain syndrome: why are there so many ascribed etiologies and therapeutic approaches?" *Int. J. Urol.*, 2014, *21*, 544.

[5] Hamilton-Miller J.M.: "The urethral syndrome and its management". *J. Antimicrob. Chemother.*, 1994, *33*, 63.

[6] Baldoni F., Baldaro B., Ercolani M., Emili E., Trombini G.: "Urethral syndrome: a study in psychosomatic urology". *Psychother Psychosom.*, 1989, *52*, 114.

[7] Morita Y., Ohashi H., Mino-Oka M.: "Histological investigation on the so-called urethral syndrome". *Int. Urol. Nephrol.*, 1979, *11*, 95.

[8] Rieser C.: "A new method of treatment of inflammatory lesions of the female urethra". *JAMA*, 1968, *204*, 378.

[9] Tait J., Peddie B.A., Bailey R.R., Arnold E.P., Russell G.L., Bishop V.A., et al.: "Urethral syndrome (abacterial cystitis)--search for a pathogen". *Br. J. Urol.*, 1985, *57*, 552.

[10] Gillespie W.A., Henderson E.P., Linton K.B., Smith P.J.: "Microbiology of the urethral (frequency and dysuria) syndrome. A controlled study with 5-year review". *Br. J. Urol.*, 1989, *64*, 270.

[11] Cooper J., Raeburn A., Brumfitt W., Hamilton-Miller J.M.: "Single dose and conventional treatment for acute bacterial and non-bacterial dysuria and frequency in general practice". *Infection*, 1990, *18*, 65.

[12] Burkhard F.C., Blick N., Hochreiter W.W., Studer U.E.: "Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help?" *J. Urol.*, 2004, *172*, 232.

[13] Potts J.M., Ward A.M., Rackley R.R.: "Association of chronic urinary symptoms in women and Ureaplasma urealyticum". *Urology*, 2000, *55*, 486.

[14] Schultz M.J.: "Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis". *J.*

Antimicrob. Chemother., 2004, *54*, 21.
[15] Bosnar M., Dominis-Kramaric M., Nujic K., Stupin Polancec D., Marjanovic N., Glojnaric I., *et al.*: "Immunomodulatory effects of azithromycin on the establishment of lipopolysaccharide tolerance in mice". *Int. Immunopharmacol.*, 2013, *15*, 498.
[16] Leite L.M., Carvalho A.G., Ferreira P.L., Pessoa I.X., Goncalves D.O., Lopes Ade A., *et al.*: "Anti-inflammatory properties of doxycycline and minocycline in experimental models: an in vivo and in vitro comparative study". *Inflammopharmacology*, 2011, *19*, 99.
[17] Ring J., Alomar A., Bieber T., Deleuran M., Fink-Wagner A., Gelmetti C., *et al.*: "Guidelines for treatment of atopic eczema (atopic dermatitis) part I". *J. Eur. Acad. Dermatol. Venereol.*, 2012, *26*, 1045.
[18] Gittes R.F., Nakamura R.M.: "Female urethral syndrome. A female prostatitis?" *West J. Med.*, 1996, *164*, 435.
[19] Wimpissinger F., Stifter K., Grin W., Stackl W.: "The female prostate revisited: perineal ultrasound and biochemical studies of female ejaculate". *J. Sex Med.*, 2007, *4*, 1388.
[20] Heller D.S.: "Lesions of skene glands and periurethral region: a review". *J. Low. Genit. Tract. Dis.*, 2015, *19*, 170.
[21] Huffman J.W.: "The detailed anatomy of the para-urethral ducts in the adult human female". *Am. J Obstet. Gynecol.*, 1948, *55*, 86.
[22] Lee J.C., Muller C.H., Rothman I., Agnew K.J., Eschenbach D., Ciol M.A., *et al.*: "Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls". *J. Urol.*, 2003, *169*, 584.
[23] Alexander R.B., Ponniah S., Hasday J., Hebel J.R.: "Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome". *Urology*, 1998, *52*, 744.
[24] Jacob S.E., Steele T.: "Corticosteroid classes: a quick reference guide including patch test substances and cross-reactivity". *J. Am. Acad. Dermatol.*, 2006, *54*, 723.
[25] Lee C.H., Lee S.D.: "Effect of topical steroid (0.05% clobetasol propionate) treatment in children with severe phimosis". *Korean J. Urol*., 2013, *54*, 624.
[26] Neill S.M., Lewis F.M., Tatnall F.M., Cox N.H., British Association of D.: "British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010". *Brit. J. Dermatol.*, 2010, *163*, 672.
[27] Gonzalez-Moles M.A., Ruiz-Avila I., Rodriguez-Archilla A., Morales-Garcia P., Mesa-Aguado F., Bascones-Martinez A., et al.: "Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays". *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.*, 2003, *95*, 688.
[28] Nilsson S.: "Local treatment of female urethritis". *Lakartidningen.*, 1971, *68*, 581. (Article in Swedish)
[29] Altman B.L.: "Treatment of urethral syndrome with triamcinolone acetonide". *J. Urol.*, 1976, *116*, 583.
[30] Youngblood V.H., Tomlin E.M., Davis J.B.: "Senile urethritis in women". *J. Urol.*, 1957, *78*, 150.

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