Efficacy of Daily Low-dose Sildenafil for Treating Interstitial Cystitis: Results of a Randomized, Double-blind, Placebo-controlled Trial—Treatment of Interstitial Cystitis/Painful Bladder Syndrome With Low-dose Sildenafil

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OBJECTIVE
To evaluate the efficacy of daily low-dose sildenafil for the treatment of nonulcer interstitial cystitis (IC) in women.

PATIENTS AND METHODS
Forty-eight women with a clinical diagnosis of IC from 3 medical centers were randomly assigned to treatment with daily low-dose sildenafil (25 mg, n = 24) or placebo (n = 24) for 3 months. The O’Leary-Sant IC symptom and problem indices, visual analog scale scores, and a micturition diary with the interval of micturition, the frequency of nocturia, and urgency episodes were recorded before treatment, every 2 weeks after the treatment until 3 months. Patient Overall Rating of Improvement in Symptoms was assessed and regarded as effective when the value was above 50%.

RESULTS
The IC symptom and problem indices scores and urodynamic index were significantly improved in sildenafil treatment group as compared with placebo group and baselines at week 4, 6, 8, 10, and 12, as well as 3 months after treatment (P < .05). Urodynamic index including first desire to void, strong desire to void, and maximum cystometric capacity was significantly improved in sildenafil treatment group at week 12 and at 3 months after treatment (P < .05). The efficiency of treatment reached 62.5%. However, no significant change of the visual analog scale values was observed between 2 groups except at week 12 in the sildenafil treatment group (P < .05). All adverse events were mild to moderate and transient.

CONCLUSION
Daily low-dose sildenafil is an easy, well-tolerated, and effective treatment for IC in women.

Interstitial cystitis (IC) is a chronic inflammatory disease associated with a number of clinical complaints such as increased frequency of urinary urgency and vesico-urethral pain, which is mostly diagnosed in females (9:1). These symptoms are commonly found in middle age and negatively impact lifestyle and careers of female patients. IC was originally described by Hanash and Pool as a condition with severe urinary symptoms, reduced bladder capacity, and typical cystoscopic findings of ulcers. Up to now, the etiology of IC/painful bladder syndrome (PBS) is unknown, resulting in controversies over the definition, pathophysiology and treatment. The diagnosis of IC is still made relying on presentation of typical syndromes and confirmed by cystoscopy with hydrodistention and generally need biopsy for exclusion of other pathologies. The diagnostic criteria of the National Institute of Diabetes and Digestive and Kidney Diseases are mainly based on exclusions, which have been found to be too rigid for clinical use. In 2008, the European Society for the Study of Interstitial Cystitis applied that the diagnosis should be changed to PBS. Approximately, 50%-90% of IC/PBS patients do not
demonstrate a classical mucosal ulcer. Epidemiological survey found 18.1 cases per 100,000 females and the prevalence in both sexes is 10.6 cases per 100,000 persons with the annual incidence of new cases being 1.2 per 100,000 persons in Finland.

At present, treatment of IC/PBS includes conservative, oral medical therapy, intravesical drug instillation, hydrodistention, neuromodulation, and surgical therapy. No general standard treatments have been recommended. Despite hydrodistention, neuromodulation and intravesical medicine are the therapy strategies recommended for refractory IC/PBS by 2010 IC guidelines; the defects of these therapies were relative invasive or complicated and might increase risk for an opportunistic infection or treatment costs due to repeated catheterization or anesthesia. For these reasons, oral medicines are easier to be accepted by patients in developing countries, especially in China. Pentosan polysulfate sodium (PPS) is the only one oral medicine approved by the Food and Drug Administration for the treatment of IC/PBS. The clinical trials showed modest improvement with PPS at a dose of 100 mg 3 times per day compared with placebo. However, subsequent clinical trials have disputed this efficacy. Therefore, oral medicines for IC/PBS still need further exploration.

Glycosaminoglycan deficiency was considered an important mechanism of IC/PBS by many researchers. The theory suggested too much cationic potassium ion penetrating into the submucosa, muscular layer, and interstitial substance via defective urothelium, which can destroy capillaries and lymphatic capillaries, inducing mast cell degranulation. By these direct or indirect ways, stimulated C-fibers and muscles lead to the presentation of a series of symptoms. The contraction of smooth muscle caused by elevating potassium or adrenergic activity can be relaxed by phosphodiesterase type 5 inhibitors (PDE5I). PDE5I are a class of drugs used to treat erectile dysfunction. Recently, PDE5I also have been used to treat various lower urinary tract symptoms (LUTS) and showed beneficial effects such as LUTS with or without erectile disfunction,

Study Design

A computer-generated block scheme for randomization was produced in the clinical research center at the First Affiliated Hospital of Wenzhou Medical College. The included patients were randomly divided into 2 groups: treatment group (daily low-dose sildenafil, 25 mg; Pitzer) and placebo groups (starch). Sildenafil or placebo was administered to these 2 groups for 12 weeks. The evaluation of symptoms and complaints were performed at 8 time points, before the treatment (baseline), every 2 weeks after the treatment, and at 3 months after treatment.

Evaluation

A micturition diary including the time of micturition interval, the frequency of nocturia, and urgency episodes were recorded. The O’Leary-Sant IC symptom indices (ICSI), IC problem indices (ICPI), and visual analog scale scores (VAS) were filled out by patients before treatment (baseline), every 2 weeks after treatment, and at 3 months after treatment. Urodynamic examinations were also conducted at baseline, at week 12 after treatment, and at 3 months after treatment. The urodynamic indices include the first desire to void (FDV), the strong desire to void (SDV), and the maximum cystometric capacity (MCC). PORIS (Patient Overall Rating of Improvement in symptoms) was assessed and divided into worse, 0%, 25%, 50%, 75%, and 100% improvement according to ICSI at the end of treatment and 3 months after treatment. A PORIS of ≥50% improvement was regarded as effective treatment.

Statistical Analysis

Data analysis was performed with statistical package for the social science (SPSS version 11.0). The data of the evaluation at 8 time points were deltas against the baselines and presented as mean ± standard deviation and the balance of randomization was assessed by appropriate exact nonparametric Mann-Whitney U test. General linear model-repeat measure test was used to compare repeated measurement data before and after treatment between the 2 groups. The Wilcoxon signed rank test was used to compare enumeration data before and after treatment intragroup. The chi square test was used for comparisons of ratio in 2 groups. P < .05 was considered statistically significant.

PATIENTS AND METHODS

Patients

From June 2009 to June 2011, 55 women (28-55 years old) had a course of 12-48 months of characteristic symptoms of IC/PBS according to the National Institute of Diabetes and Digestive and Kidney Diseases criterion. These enrolled patients are from 3 departments of Urology in the south of Zhejiang province of China, including The First Affiliated Hospital of Wenzhou Medical College, Yongjia county People’s Hospital, and Hospital of Integrative Chinese Traditional Medicine and Western Medicine in Wenzhou. All patients underwent the following diagnostic tests: positive modified potassium sensitivity test, cystoscopic findings of >10 glomerulations, and nonulcer lesion in every visual field after hydrodistention (pressure, 80-100 cm H₂O; duration, 2 minutes), under sedation or spinal anesthesia at the discretion of the clinician. Patients with diabetes mellitus, mental disorders, hypertension, hypophgetia, renal insufficiency, or receiving any treatment for IC/PBS within 3 months were excluded. Patients were observed for 1 month to eliminate interference of hydrodistention. Those still having therapeutic response to hydrodistention after 1 month were also excluded. Finally, the patients were assigned by random digits table and advised to alter their negative lifestyle choices, such as excessive drinking, smoking, staying up late and so on.
Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group (n = 24)</th>
<th>Placebo Group (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38.3 ± 5.4</td>
<td>37.8 ± 4.4</td>
<td>.548</td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>29.6 ± 8.5</td>
<td>27.5 ± 9.5</td>
<td>.297</td>
</tr>
<tr>
<td>ICSI (0-19)</td>
<td>15.3 ± 2.2</td>
<td>15.1 ± 2.0</td>
<td>.843</td>
</tr>
<tr>
<td>ICPI (0-16)</td>
<td>13.3 ± 1.8</td>
<td>13.0 ± 1.8</td>
<td>.571</td>
</tr>
<tr>
<td>Frequency (/d)</td>
<td>16.1 ± 4.7</td>
<td>15.7 ± 5.3</td>
<td>.627</td>
</tr>
<tr>
<td>Nocturia</td>
<td>4.5 ± 1.8</td>
<td>4.6 ± 2.0</td>
<td>.520</td>
</tr>
<tr>
<td>VAS (0-5)</td>
<td>3.1 ± 1.5</td>
<td>3.2 ± 1.5</td>
<td>.983</td>
</tr>
<tr>
<td>FDV (mL)</td>
<td>55.4 ± 20.7</td>
<td>59.6 ± 24.0</td>
<td>.576</td>
</tr>
<tr>
<td>SDV (mL)</td>
<td>129.2 ± 41.9</td>
<td>124.6 ± 44.3</td>
<td>.765</td>
</tr>
<tr>
<td>MCC (mL)</td>
<td>188.3 ± 41.0</td>
<td>197.5 ± 45.9</td>
<td>.421</td>
</tr>
</tbody>
</table>

FDV, first desire to void; ICPI, interstitial cystitis problem indices; ICSI, interstitial cystitis symptom indices; MCC, maximum cystometric capacity; SDV, strong desire to void; VAS, visual analog scale scores.

Values are presented as mean ± standard deviation.

RESULTS

Patients

After 1 month of cystoscopy, 7 patients were found to have a therapeutic response to hydrodistention and were excluded from the study. According to the random assignment form, each group contained 24 patients. The details of the patient’s characteristics are presented in Table 1. There was no significant difference in baselines between the 2 groups.

ICSI and ICPI Scores

In the placebo group, no significant differences were found in the ICSI and ICPI scores at each time point during the study. No significant changes of ICSI and ICPI were found among the baseline, placebo, and treatment groups at the time point of week 2 (P > .05). However, obvious decrease of the ICSI and ICPI scores were observed at the time points of weeks 4, 6, 8, 12, and 24 in the treatment group as compared with the baseline or placebo groups (P < .05; Table 2, Fig. 1). According to the ICSI scores, the number of patients with PORIS surpassing 50% improvement were 15 cases and the efficacy of the sildenaif treatment was 62.5% at the end of sildenaif treatment; 3 months after stopping administration of sildenaif, 42.7% of patients still had a PORIS above 50% improvement (Supplementary Table 1).

VAS, the Voiding Frequency and the Nocturia

Compared with baseline and placebo groups, the frequency and the nocturia significantly decreased from the time point of week 4 to week 24 in the treatment group. After the treatment, significant decreases in VAS scores in the treatment group were only achieved at week 12 between both groups, and at the other 7 time points, the VAS scores was comparable (Table 2, Fig. 2).

Urodynamic Examinations

After the study, FDV, SDV, and MCC in the treatment group were significantly higher at week 12 and at 3 months after treatment than those in the placebo group and those at baseline (P < .05; Table 2, Supplementary Fig. 1).

Adverse Effects

All 48 patients completed the study. No serious adverse reaction was observed during the period of administration of sildenaif. However, 1 patient suffered mild headache and 4 patients flushing in the beginning of taking sildenaif orally, and the symptoms remitted after 2-4 days.

COMMENT

IC/PBS is a chronic disease that causes symptoms of pain in the bladder or pelvis with or without urgency, frequency, and nocturia. IC/PBS severely impairs quality of life, leads to sleep dysfunction, depression or anxiety, and sexual and social problems. In the present study, oral low-dose sildenaif could significantly improve the symptoms of IC/PBS through the evaluation of ICSI and ICPI scores, the time of micturition interval, the frequency of nocturia, and urodynamic examinations. Urodynamic examinations also showed substantial improvement after the study according to the parameters of FDV, SDV, and MCC.

Given the lack of understanding regarding pathophysiological causal factors in IC/PBS and the consequence that treatment goals are to control symptoms to optimize quality of life, the 2011 American Urological Association guideline judged that the most appropriate course was to preserve treatments as clinical choices as long as some efficacy for some patients was demonstrated and the risk of serious harms was low. Oral drug therapy was recommended as a second-line treatment for IC/PBS by the guideline including amitriptyline, cimetidine, hydroxyzine, or PPS. Trials reported efficacy of oral amitriptyline (25 mg daily titrated over several weeks to 100 mg daily if tolerated), 50%-64% of treatment groups significantly improved after 1-19 months. But adverse events such as sedation, drowsiness, and nausea were extremely common (up to 79% of patients), although not life-threatening, and had substantial potential to compromise quality of life. Medication side effects were the major reason for withdrawal from the studies; 44%-57% of patients reporting clinically significant improvement at follow-up intervals of 1 and >2 years by oral cimetidine and no adverse events were also reported; 92% of patients experienced clinically significant improvement by oral hydroxyzine (25 mg daily titrated up to 75 mg daily over several weeks), but like amitriptyline, adverse events such as systemic allergies were extremely common. The clinical trials showed modest improvement with PPS at a dose of 100 mg 3 times per day compared with placebo. However, subsequent clinical trials have disputed this efficacy. Similar to the aforementioned research, in the present study, the results demonstrated clinically significant improvement in the
symptom scores of subjective experience was first observed at week 4 after sildenafil treatment. FDV, SDV and MCC, which substantially reflect function recovery of bladder, were markedly higher at the end of treatment and 3 months after treatment. All these parameters supported daily low-dose sildenafil could effectively improve the symptoms of IC/PBS and recovery of function. The efficiency of sildenafil reached 62.5% at the end of treatment, and 42.7% patients can maintain an improvement state for 3 months after treatment. However, in treatment group, the main improvement of symptoms was voiding symptoms; no favorable outcomes on bladder pain were found during 8 weeks. Bladder pain was relieved at week 12 transiently, but it regained at 3 months after treatment. The short length of treatment duration and lower therapy effect on bladder pain might be the potential explanation. No serious adverse reaction was observed after the treatment. Hence, similar to other oral treatments, oral low-dose sildenafil might benefit only a subset of patients not readily identifiable a priori; the fact that no single treatment has been found to be effective for a majority of patients, and that adequate

### Table 2. Urodynamic examinations of 2 groups

<table>
<thead>
<tr>
<th>Parameter (Delta)</th>
<th>Treatment Group (n = 24)</th>
<th>Placebo Group (n = 24)</th>
<th>Difference (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDV (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 12</td>
<td>49.8 ± 19.2</td>
<td>5.8 ± 13.4</td>
<td>44.0 (34.3, 53.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>39.6 ± 20.9</td>
<td>-0.8 ± 7.0</td>
<td>40.4 (31.2, 49.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SDV (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 12</td>
<td>173.1 ± 17.2</td>
<td>18.1 ± 39.9</td>
<td>155.0 (137.0, 173.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>132.0 ± 18.0</td>
<td>8.3 ± 33.1</td>
<td>123.8 (108.3, 139.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MCC (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 12</td>
<td>186.6 ± 25.6</td>
<td>20.4 ± 35.8</td>
<td>166.3 (148.1, 184.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>129.5 ± 35.8</td>
<td>9.6 ± 54.0</td>
<td>120.0 (93.3, 146.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Values are presented as mean ± standard deviation.

### Figure 1. Scores of ICSI and ICPI. Compared with placebo group, P <.01 using general linear model-repeat measure test. ICSI, interstitial cystitis symptom indices; ICPI, interstitial cystitis problem indices.

### Figure 2. The scores of IC/PBS symptoms. Compared with placebo group, *P = .477, ΔP <.05 using general linear model-repeat measure test. IC, interstitial cystitis; PBS, painful bladder syndrome; VAS, visual analog scale scores.
symptom control is achievable but may require trials of multiple therapeutic options to identify the regimen that is effective for patients with IC/PBS. Hence, combining pain management tools including urinary analgesics, nonsteroidal anti-inflammatory drugs, narcotics, and a wide variety of nonnarcotic medications in the early treatment stages may be a preferable option.

Although the mechanism of sildenafil therapy on IC/PBS was unknown, Truss et al. reported a high PDE5 expression in human bladder detrusor muscle in 1996. Potassium stimulation of the bladder detrusor muscle was an important factor in the pathogenesis of IC/PBS. Sildenafil (PDE5I) could relax the smooth muscle in the vesical neck, which was precontracted in vitro by potassium or adrenergic activity. The daily low-dose sildenafil improved the vascular endothelial function, whereas excessive potassium could damage the microcirculation in the bladder of patients with IC. Our previous research also found that sildenafil was effective in treating an overactive bladder by the cyclic guanosine monophosphate (cGMP)-dependent protein kinase G-RhoA/Rho kinase signaling pathway. Thus, we inferred that the potential treatment mechanisms of sildenafil therapy on IC/PBS were related to the reduction in the contraction sensitivity of the detrusor muscle, which related to the relaxation of the bladder detrusor muscle, improvement of microcirculation, and reabsorption of excessive potassium in the bladder through the cGMP-dependent protein kinase G-RhoA/Rho kinase signaling pathway and cGMP-dependent nitric oxide or carbonic oxide signaling pathway. However, these mechanisms need further confirmation.

In conclusion, daily low-dose sildenafil is an effective, simple well-tolerated therapy for IC. Our study was the first trial using daily low-dose sildenafil therapy for IC/PBS; however, some limitations including small sample sizes, race, and the lack of objective parameters are present. Due to lack of previous studies, the optimum dose and duration for sildenafil treatment need further study. Moreover, further randomized, controlled multicenter trials with a larger population and a longer follow-up period will be required to confirm these primary encouraging results.

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References


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Many new ideas for the treatment of bladder pain syndrome are proposed every year and few ultimately pan out. The vast majority is accepted for publication prematurely and highlight case reports, anecdotal results, and nonrandomized, small, uncontrolled trials. I think this article should be a model for publication of new treatments. It reveals the results of a small, randomized, double-blind, placebo-controlled trial using low-dose sildenafil for the treatment of non–Hunner lesion bladder pain syndrome in women meeting National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria. Although the numbers are small, the end point parameters are multiple and all but the visual analog pain scale shows a signal that further studies are worthwhile and should be pursued using phosphodiesterase type 5 (PDE5) inhibitors for bladder pain syndrome (BPS). I suspect that the reason that the visual analogue scale scores (VAS) does not suggest efficacy is that the benefits of pain reduction are reflected in the global response, improvements in nocturia and frequency, and urodynamic parameters. Patients modulate their pain by emptying their bladder, and as their pain improves, their voiding intervals would tend to increase, with the pain recurring at similar intensity at a longer interval, which drives micturition. This would not necessarily be judged by the patient as having less pain intensity.

The authors’ rationale for use of the drug is obvious in retrospect and one wonders why it took so long for this idea to surface. Phosphodiesterase type 5 inhibitors are generally safe, well tolerated, and easily available. Future studies may determine if a specific phosphodiesterase inhibitor is most effective for BPS. Trials with larger numbers of patients of various phenotypes are needed. Would the drug work best in BPS patients with Hunner lesions, without Hunner lesions, with non–bladder pain syndromes, or in bladder centric disease? This small, well-designed study points the way for further testing to determine whether the findings are a fluke or open new avenues for treatment. With the results evident in 4 weeks, it would not seem unreasonable for the clinician to give it a try in patients with significant symptomatology that has not responded to conservative management, be they male or female, at least until more definitive data on which to make a treatment judgment becomes available.

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We appreciate Dr. Hanno’s insightful comments on our paper. They were objective and accurate. The treatment of interstitial cystitis/bladder pain syndrome with daily low-dose sildenafil was based on our clinical investigation and basic science research. Since the first introduction of sildenafil in China, we have continuously observed that it could improve sexual function and simultaneously relieve dyspareunia and pelvic area pain in patients with these combined symptoms. However, the evidence of the sildenafil’s efficacy on treating interstitial cystitis was limited. After the accumulation of documents suggested that phosphodiesterase type 5 inhibitors can improve lower urinary tract symptoms, as well as considering the positive results of our basic study, the clinical trial was designed.

The study used the enrollment criteria outlined by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), resulted in a relatively small number of patients. However, as earlier interstitial cystitis diagnostic criteria, NIDDK is strict and accounts for the homogeneity of enrolled patients in this clinical research. Because of a lack of similar reports and existed potential uncertainties, it seemed unreasonable to conduct a large sample research. On the other hand, the evaluation of pain, which affects the quality of life, was important for assessing the treatment effects. In our study, pain score measured by visual analog scale was regularly reduced in sildenafil treatment group, and it was improved significantly at time point of 12 weeks. But this effect diminished gradually with drug dose withdrawal and suggested that the long-term administration of the phosphodiesterase type 5 inhibitor was beneficial and necessary.

To obtain sufficient evidence, according to Doctor Hanno’s comments, further study should use comprehensive design. The development of international multicenter and the replacement of NIDDK by the criterion introduced by the “2011 American Urological Association guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome” will significantly enlarge the number of enrolled patients with various phenotypes. A longer half-life phosphodiesterase type 5 inhibitor, such as Cialis, would be even more effective for daily low-dose usage. Which phosphodiesterase inhibitor is the most effective for interstitial cystitis/bladder pain syndrome still needs to be studied before conducting a clinical trial. Long-term administration of the phosphodiesterase type 5 inhibitor may also be considered. Future studies should improve these mentioned factors to provide the data that would allow us to make a more definitive treatment judgment.

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