

Phase II clinical study of an association for the treatment of interstitial cystitis (Cystex®)

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Abstract

Painful bladder syndrome associated with interstitial cystitis (PBS/IC) is a clinical condition characterized pelvic pain, urinary urgency, and urinary frequency. In this study, 22 patients were assigned to make two visits over a three weeks period. The patients were randomly, double-blinded assigned in two groups. The first group received Cystex® capsules. The second group received placebo capsules. Two capsules were taken three times a day away from meals. The change from baseline in the O'Leary-Sant IC symptom and problem index was the primary outcome parameter. Changes in functional bladder capacity and intensity of pain and urgency have been chosen as secondary outcome parameters. Mood as well as physical and sexual activity were rated by 10 questions on a scale 0 to 6. The ratings were analyzed and the average for each patient in both groups Cystex® and placebo was determined as the quality of life index. For the primary outcome there was a statistically significant difference between the groups. Mean symptom score-sum decreased from 28.4 to 20.5 in the Cystex® group compared with 29.5 to 26.8 in the placebo group ($p < 0.05$). For the secondary end points, pain and urgency intensity improved statistically significantly in the Cystex® group compared with the placebo group ($p < 0.05$). The frequency and functional bladder capacity improved to greater degree in the Cystex® group. The differences were statistically significant for comparison of frequency ($p < 0.05$) and not for functional bladder capacity ($p > 0.05$). In our study,

Cystex® enhanced quality of life over the placebo showing a statistically significant. This trial have shown that the efficacy and safety of therapy with Cystex® in the treatment of interstitial cystitis and is an alternative for patients suffering from this pathology. Therefore, it can be concluded that the composition of Cystex®, increased the quality of life in treated patients.

Key words: Interstitial cystitis, clinical trial, painful bladder, quality of life.

Introduction

Painful bladder syndrome/ interstitial cystitis (PBS/IC) is a clinical condition characterized by 3 symptoms: pelvic pain, urinary urgency, and urinary frequency (1).

Interstitial cystitis (IC) is a chronic and debilitating bladder syndrome, affecting primarily women, characterized by pelvic/ bladder pain associated with urinary urgency, frequency and sterile, cytologically normal urine (2).

In individuals with a normal bladder, the epithelial layer is relatively impermeable and does not allow potassium ions to be absorbed. The glycosaminoglycans (GAG) layer lining the bladder urothelium has been implicated in the pathogenesis of IC/PBS (3). Relevant components of the GAG layer include hyaluronic acid, sulfated forms of heparin, dermatan, keratin and chondroitin. A deficiency in the GAG layer changes the permeability of the urothelium to urinary components, principally to potassium ions. In this sense, an excess

of potassium ions in the urothelial layer may be responsible for the intense urgency and/or pain of painful bladder syndrome (4). It has been diagnostic that this layer may be impaired, abnormal, or disrupted in patients with IC/PBS (5). This compromised epithelium becomes permeable to urinary solutes, resulting in local inflammation and neural upregulation and subsequent pain, frequency, and urgency. In the event the epithelium has a lesion, potassium ions will be absorbed, generating symptoms of pain and urgency through the stimulation of the chemical sensitive component of type C nerve fibres (6,7). GAGs are an important structural part of bladder mucosal integrity and therapeutic GAG or GAG-like agents, such as sodium hyaluronate (8), heparin (9) and pentosan-polysulfate (10) have been previously examined with some variable results.

Systemic treatment options for patients with painful bladder syndrome associated with interstitial cystitis are limited. The first report Hanno and Wein (1987) on the use of the tricyclic antidepressant amitriptyline was in 1987 (11) and, although amitriptyline has subsequently become the most frequently prescribed oral drug for IC (2).

Many treatments are available for IC, but it is generally accepted that the results are disappointing, and few have been subjected to rigorous clinical evaluation (2).

The aim is to verify the safety and effectiveness of treatment with Cystex[®] in patients with painful bladder syndrome.

Pacients and Methods

Females and males with the clinical diagnosis of IC/PBS and no medical condition or therapy that would exclude safe concomitant use of Cystex[®] were evaluated in this clinical trial. The diagnosis of IC/PBS used clinical definitions, including the diagnostic criteria described in the IC Data Base Study (12). IC/PBS was diagnosed on the basis of pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one urinary symptom, such as urgency or frequency. Urine must have been sterile at time of diagnosis and assessment and urinary cytology negative. All other diseases that could cause pelvic symptoms were excluded.

The following inclusion criteria for this study were: female or male; negative bacterial urine culture; a patient-reported average urinary frequency of at least 11 times per 24-hour period during the screening period.

In this study, 22 patients, aging between 50 to 60 years, were assigned to make two visits over a three week period. The patients were randomly, double-blinded assigned in two groups to complete the assessment of the questionnaire (13, 14, 15).

The patients enrolled were both male and female and known to be subjected to physical and mental stress and/or to present fatigue symptoms not related to any exclusion criteria. An informed written consent was obtained from each patient after a lecture about the study to make it clear to them. Prior to conducting this study, we trained four medical doctors (MDs) to establish consistency in research methods. All MDs attended initial training and orientation in Alfenas, MG at the beginning of the study. In addition, each of them coded sample cases and received feedback from the project senior researcher prior to their first case. The research was conducted at Alzira Velano Hospital. Data collection began on March 6, 2000 and ended on March 27, 2000. The patients were randomly divided in two groups. Randomization is being performed by computer-generated random allocation sequence. The first group (group A) had received Cystex[®] capsule containing Acriflavin hydrochloride 15.00 mg; Methenamine 250.00 mg; Methylene blue 20.00 mg; Beladona extract 15.00 mg. The second group (group B) had received placebo capsules, identical in form, color and taste to the ones of the active formulation.

Both treatments were provided by EMS Sigma Pharma, based in Hortolândia (SP), Brazil, and had the same characteristics. Two capsules were taken three times a day away from meals, for a 3 weeks period. Mood as well as physical and sexual activity were rated by 10 questions on a scale 0 to 6. The ratings were analyzed and the average for each patient in both groups Cystex[®] and placebo was determined as the quality of life index. The level of quality of life was assessed by a questionnaire (13, 14, 15) approved by the Ethical Committee for Human Research of The University of Alfenas, Alfenas, MG. This project was registered under number 685/99.

From the 22 patients enrolled, 11 were assigned to group Cystex[®] and 11 to group placebo. The physiological parameters (pulse rate, blood pressure and clinical history) were assessed with relation to the demographic characteristics (Table 1) and they were found to be similar in the groups enrolled. Also, there were no significant intergroup differences for obesity, arterial hypertension, renal and liver diseases or diabetes mellitus. No worsening of these pathologies was detected during the study. Adverse effects were recorded in the case report form and, if severe, were added to the discontinuation criteria, including pregnancy, interaction with others medications not allowed, as well as voluntary withdrawals or protocol violation.

This study used a randomized, placebo controlled, and double blind design and was conducted at one institution (University of Alfnas – Alzira Velano Hospital). The study protocol was approved by the Institutional Review Board of the Alzira Velano University Hospital and written informed consent was obtained from all patients.

The initiation of treatment with Cystex[®] occurs in the first day of one group while another takes the placebo. Patients eligible for the study were randomized into two groups in a 1:1 ratio. One group will start treatment with placebo and the other group will receive Cystex[®] for 21 days.

Patients were subsequently treated prospectively for 3 weeks with a selftitration protocol. The change from baseline in the O'Leary-Sant IC symptom and problem index was the primary outcome parameter for this study. This validated, self-administered index comprises 8 questions assessing major pain and voiding symptoms. The maximum index score-sum of 36 reflects maximum symptom and problem severity and the lowest possible score-sum is 0.5. Secondary outcome measures included patient reported symptoms of pain and urgency (visual analog scales, VAS), and changes in functional bladder capacity and frequency (48-hour voiding log). Additionally, patients were requested to rate satisfaction with the therapeutic outcome as excellent, good, fair or poor (Patient Global Assessment Form). Outcomes were evaluated at baseline and in 3-week intervals after randomization. The study sample size of 22 patients (11 per group) was powered for a difference of approximately 1 standard deviation between the Cystex[®] and placebo group with a 95%

confidence interval ($\alpha = 0.05$) and a statistical power of 85% ($\beta = 0.20$). Baseline factors were compared between the 2 groups using Fisher's exact and Mann-Whitney-U tests. Statistical comparisons were made using the Mann-Whitney-U test for changes in symptom score (primary outcome parameter), changes in pain and urgency intensity, and changes in voiding patterns (frequency, functional bladder volume). Chisquare statistics were calculated to compare proportion of responders between treatment groups, with $p < 0.05$ considered significant. All statistical tests were 2-tailed, and calculations were performed using Graph Pad Instat[®].

Results

No patients dropped out of the study because of adverse side effects. The data on 22 patients (11 patients in each group) were available for evaluation. Selected baseline characteristics are shown in table 1. For the primary outcome there was a highly statistically significant difference between the study groups. Mean symptom score-sum decreased from 28.4 to 20.5 in the Cystex[®] group compared with 29.5 to 26.8 in the placebo group ($p < 0.05$).

Table 1. Baseline patient demographic and clinical characteristics by treatment group

Characteristic	Cystex	Placebo
No. pts randomized	11	11
No. females (%)	9	9
No. males (%)	2	2
Mean age \pm SD (yrs)	54.9 \pm 5.1	55.3 \pm 5.8
Mean symptom duration before treatment \pm SD (yrs)	4.7 \pm 2.6	5.2 \pm 3.1
Mean age at onset of symptoms \pm SD (yrs)	49.3 \pm 3.4	47.8 \pm 4.3
Mean pain intensity \pm SD (mm on VAS)	58 \pm 26	55 \pm 29
Mean urgency intensity \pm SD (mm on VAS)	64 \pm 22	68 \pm 17
Mean 24-hr frequency \pm SD	14.2 \pm 6.4	1.5 \pm 6.3
Mean functional bladder volume \pm SD (ml)	134 \pm 68	126 \pm 71
Mean score-sum \pm SD	28.4 \pm 6	29.5 \pm 5

For the secondary end points, it can be noticed several outcome parameters statistically significant difference between the study groups (table 2). Pain

and urgency intensity improved statistically significantly in the Cystex[®] group compared with the placebo group ($p < 0.05$). The frequency and functional bladder capacity improved to a much greater degree in the Cystex[®] group. The differences were statistically significant for comparison of frequency ($p < 0.05$) and not for functional bladder capacity ($p > 0.05$). Of the 11 patients receiving Cystex[®], 4 (36%) rated satisfaction with the therapeutic outcome as excellent, 5 (45%) rated as good. Anticholinergic side effects were noted by all except 1 patient in the Cystex[®] group (91%) and by 9 patients in the placebo group (81%). A dry mouth was the most frequent side effect in the Cystex[®] group.

The treatment with Cystex[®] increased the quality of life compared to placebo treatment. At baseline, there was no significant difference between treatments groups. After 21 days of study, in visit 1, a significant difference between the treatments was observed, showing an increase in the group treated with Cystex[®] average scoring from 1.64 to 4.88 points. The statistical comparison found that every item the group treated with Cystex[®] had been better than with placebo (Table 3).

Discussion

Normal bladder function is the organ's competence to hold a sufficient volume of urine, a painless urge to void and finally almost complete emptying. This ability, which is impaired in patients with IC, is based on a mechanism of activation and maintenance of reflex mechanism involving parasympathetic, sympathetic and somatic control of the lower urinary tract (16, 17).

It was observed a significant change in the symptoms that accompany interstitial cystitis, prior and subsequent to treatment with Cystex[®]. It has also been noted a good tolerance of the treatment. It has been demonstrated that every single symptom was improved after 3 weeks of treatment by means of an analogue visual scale (18). The clinical and urodynamic benefit that we found may be explained by the property of the product composition with urinary antiseptics and parasympathetic drugs. Briefly, the patients with typical symptoms and urodynamic parameters of painful bladder syndrome associated with interstitial cystitis have been benefited from treatment with Cystex[®]. Likewise, we found evi-

Table 2. Changes in symptoms from baseline and within 21 days

Characteristic	Cystex	Placebo	P value
Mean score-sum \pm SD	- 7.9 \pm 7.2	- 2.7 \pm 5.8	< 0.05
Mean pain intensity \pm SD (mm on VAS)	- 25.2 \pm 23.3	2.4 \pm 13.9	<0.05
Mean urgency intensity \pm SD (mm on VAS)	- 47.8 \pm 21.5	1.4 \pm 3.2	<0.05
Mean 24-hr frequency \pm SD	- 5.8 \pm 6.1	1.1 \pm 5.4	<0.05
Mean functional bladder volume \pm SD (ml)	27.8 \pm 49.3	17.8 \pm 47.6	>0.05

Table 3. Mean ratings in each of the 10 items of the questionnaire in groups receiving Cystex[®] capsules or placebo at visit 0 (baseline) and at visit 1 (after 21 days from visit 1)

Item	Cystex [®]		Placebo	
	Baseline	Visit 1	Baseline	Visit 1
A	1.64	4.88*	1.59	1.92
B	1.58	4.73*	1.63	1.68
C	1.88	4.26*	1.90	2.01
D	2.07	4.32*	2.01	2.22
E	1.87	4.48*	1.86	2.05
F	1.96	5.16*	1.87	2.11
G	1.69	3.86*	1.93	1.96
H	1.34	3.95*	1.59	1.74
I	1.48	3.68*	1.63	1.99
J	1.78	5.42*	1.72	2.01

Compared to baseline. * $P < 0.05$.

dence that the said improvement is noticeable both in subjective parameters of the disease and in the objective parameters of urodynamics. The clinical use of intravesical hyaluronic acid in patients with painful bladder syndrome possibly associated with interstitial cystitis has demonstrated that the clinical improvement was related to a bladder's capacity and sensitivity increase (19).

In our study, Cystex[®] enhanced quality of life over the placebo showing a statistically significant improvement of any among ten items comprised in the assessment questionnaire. Therefore, it can be concluded that the composition of Cystex[®], increased the quality of life in treated patients.

No weight gain and increased physical activity were also observed in treated patients. The present study has shown that the daily use of Cystex[®], taking two capsules daily three times a day away from meals, has been effective in improving quality of life in patients suffering from interstitial cystitis. Moreover, its use has shown an undesired effects incidence similar to placebo among individuals in the groups. This trial have shown that the efficacy and safety of therapy with Cystex[®] in the treatment of interstitial cystitis and is an alternative for patients suffering from this pathology.

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