

SELF-ADMINISTERED INTRAVESICAL HYALURONIC ACID IMPROVES SYMPTOMS AND QUALITY OF LIFE IN A PATIENT-CENTRED APPROACH TO BLADDER PAIN SYNDROME MANAGEMENT

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ABSTRACT

Background and Objectives

Bladder pain syndrome (BPS) is an uncommon and potentially debilitating spectrum of chronic pain typically accompanied by lower urinary tract symptoms. Intravesical hyaluronic acid (HA) is a commonly used treatment option, but requires multiple follow-up clinic appointments. We introduced a novel patient-led ‘at-home’ pathway of self-administered HA treatment to reduce the number hospital visits required by patients.

We assessed and compared patient-reported outcome measures (PROMS) from patients receiving nurse-administered ‘in-hospital’ and patient-led self-administered ‘at-home’ intravesical HA (Cystistat® and Hyacyst®, respectively). Secondary outcome measures included differences between waiting times for treatment, frequency of treatments, number of clinician and nurse clinic appointments, and estimated financial costs.

Patients and Methods

Sixty consecutive patients commencing intravesical HA for BPS symptoms between 1st January 2016 and 31st March 2019 were included. O’Leary-Sant Interstitial Cystitis Symptom Index questionnaires were completed prior to, and following, six treatments. Relevant clinical and demographic data were also collected.

Results

Overall, 76.6% of the patients had improvement in symptoms after HA treatment. Mean O’Leary-Sant questionnaire symptom and problem scores were significantly improved following HA treatment (11.8 (range 6–17) to 8.5 (range 4–13) ($p=0.00005$) and 11.4 (range 4–16) to 7.9 (range 4–14) ($p=0.0002$), respectively. There were no significant differences in symptom improvements between patients on either pathway.

Mean waiting time for treatment and number of treatments were lower in the patient-led pathway, and number of hospital visits was significantly lower in the patient-led at home pathway. The patient-led pathway could ‘save’ approximately 76 nurse clinic and 11 outpatient clinic appointments per year, and confer cost-savings of more than £1,500 per patient, per year.

Conclusions

Our case series analyses suggest that patient-led ‘at-home’ intravesical HA administration (Hyacyst®) is acceptable to patients and confers similar symptomatic benefit to ‘in-hospital’ nurse-led HA (Cystistat®). In addition, it appears that BPS sufferers established on the patient-led pathway require fewer HA treatments and fewer hospital visits, and as such, the patient-led pathway may also confer financial cost savings, and relieve some pressures on clinic appointment availability.

Key words: *Bladder pain syndrome; intravesical hyaluronic acid; patient-reported outcome measures*

Bladder pain syndrome (BPS) is an uncommon, heterogeneous, and potentially debilitating spectrum of chronic pain, perceived by the sufferer to originate from the bladder.¹ BPS predominantly affects women with peak age of onset at 45–60 years, and has an estimated worldwide prevalence of 3–6%.^{2,3} In addition to chronic pain, BPS is typically associated with lower urinary tract symptoms such as urgency, frequency, dysuria, nocturia (increasing with age of patient), and pain on filling and/or voiding, and non-urinary symptoms such as genital pain and dyspareunia.^{1,3,4} BPS is associated with a significant reduction in quality of life, and may impact psychological (low mood, depression, anxiety and sleep disturbance), relationship and sexual, and work/employment functions.^{4–6}

Although the aetiology of BPS is incompletely understood, it is thought that loss of glycosaminoglycans (GAGs) is a key step in pathogenesis.^{7,8} GAG loss may contribute to bladder mucosal surface disruption, exposing the underlying urothelium to noxious stimuli; the resultant immune and inflammatory responses causing the range of symptoms observed.^{7–9} Multiple studies have demonstrated that the exogenous administration of hyaluronic acid (HA), a member of the GAG family, improves patient outcomes in BPS.^{10–12} Therefore, and following lifestyle/fluid advice and holistic management steps,^{13,14} the mainstay of current treatment at our University Teaching Hospital is GAG replacement with intravesical HA (Cystistat® 40 mg).

Historically, we used a predefined schedule of nurse-led clinic visits for HA instillation. However, feedback from patients and increased demand for our nurse-led clinics (particularly for intravesical therapies for bladder cancer patients) necessitated the introduction of a novel patient-led ‘at-home’ pathway, comprising teaching intermittent self-catheterisation

(ISC) and self-administration of HA (Hyacyst® pre-filled syringe 40 mg).

As a novel and unique treatment pathway, we sought to assess and compare patient-reported outcome measures (PROMS) from patients receiving scheduled nurse-administered ‘in-hospital’ and patient-led self-administered intravesical HA. As secondary outcome measures, we assessed the differences between treatment pathways in waiting times for treatment, frequency of treatments, number of clinician and nurse clinic appointments (hospital visits) required, and potential financial costs on a per-patient basis.

PATIENTS AND METHODS

All patients commencing intravesical hyaluronic acid (HA) treatment for Bladder Pain Syndrome (BPS) symptoms between 1st January 2016 and 31st March 2019 were included for analyses as a consecutive case series ($n=60$). All patients were invited to complete O’Leary-Sant Interstitial Cystitis Symptom Index questionnaires¹⁵ (Supplemental Figure 1.) prior to, and following six intravesical treatments (in the absence of urinary tract infection). Where questionnaire data were not available, patient symptoms documented in medical notes were recorded. Clinical and demographic data were collected alongside the patient-reported outcome measures (PROMS). The number of treatments and number of hospital visits (either clinician or specialist nurse) were also recorded.

Microsoft Excel (Microsoft Corporation, USA, v16.0, 2016) and online Social Science Statistics software¹⁶ were used for statistical analyses. Paired-sample and standard T tests were used to compare pre- and post-treatment questionnaire scores, and differences between outcomes of nurse-led and patient-led pathways ($p<0.05$ considered significant).

RESULTS

Patient Demographics

A total of 60 patients were included. 55 (91.7%) were female. Mean age was 50.4 years (range 18 to 86). Predominant symptoms were urinary tract infections ($n=29$), pain ($n=24$) and refractory bothersome lower urinary tract symptoms (LUTS) ($n=7$).

Of the 60 patients included, 28 chose to start on the nurse-led pathway and 32 chose to start on the patient-led pathway. 14/28 successfully moved from the nurse-led Cystistat® to the patient-led at-home Hyacyst® pathway. Two patients were unsuccessful in moving to the patient-led pathway (did not want to self-catheterise), 6 patients declined self-administration as they had no benefit from HA treatment, 2 patients discontinued during pregnancy, and 4 patients had not yet been approached.

Patient-Reported Outcome Measures Following Intravesical Hyaluronic Acid (HA) Treatment

Completed pre- and post-treatment questionnaires were available for 31/60 patients (51.7%). As shown in Figure 1. (panel a.), mean IC symptom index (ICSI) scores pre-treatment were 11.8 (range 6–17), and 8.5 (range 4–13) following HA treatment ($p=0.00005$). Mean IC problem index (ICPI) scores pre-treatment were 11.4 (range 4–16), and 7.9 (range 4–14) following HA treatment ($p=0.0002$). Symptomatic improvement was reported/observed in 46/60 (76.6%) patients overall.

Stratifying the ICSI further into component questions (**Figure 1.** panel b.), mean urgency scores (Question 1 (Q1)) were 3.5 and 2.5 pre- and post-treatment, respectively ($p=0.001$), frequency scores (Q2) were 3.3 and 2.4 pre- and post-treatment ($p=0.008$), nocturia scores (Q3) were 2.0 and 1.7 pre- and post-treatment ($p=0.172$), and pain and burning scores (Q4) were 3.1 and 1.9 pre- and post-treatment ($p=0.00004$).

Separating the ICPI (**Figure 1.** panel c.), mean frequency scores (Q1) were 3.1 and 2.1 pre- and post-treatment, respectively ($p=0.001$), nocturia scores (Q2) were 2.1 and 1.5 pre- and post-treatment ($p=0.019$), urgency scores (Q3) were 2.9 and 2.0 pre- and post-treatment ($p=0.003$), and pain and burning scores (Q4) were 3.3 and 2.3 pre- and post-treatment ($p=0.0003$).

Patient-Reported Outcome Measures of Nurse-Led and Patient-Led Pathways

There were no differences in the nurse-led Cystistat® and the patient-led at-home Hyacyst® pathway populations (age, gender, comorbidity, predominant symptom or questionnaire scores).

As shown in Figure 2. (panel a.), in the nurse-led pathway patients, mean ICSI pre-treatment scores were 11.9 (range 8–17), and 8.2 (range 5–16) following treatment ($p=0.002$), and mean ICPI scores were 11.6 (range 4–16) pre-treatment, and 7.6 (range 4–13) following treatment ($p=0.003$). In the patient-led pathway, mean ICSI scores pre-treatment were 11.8 (range 6–17) and 8.7 (range 4–16) following treatment ($p=0.005$), and mean ICPI scores were 11.3 (range 6–16) pre-treatment and 8.2 (range 4–14) following treatment ($p=0.001$).

There was no significant difference in overall symptom or problem score reduction between the nurse-led and patient-led pathway ($p=0.131$).

Mean reduction in ICSI and ICPI scores for the nurse-led and patient-led pathways across all questions are shown in Figure 2. panels b. and c., respectively. Mean reduction in symptom scores for the nurse-led and patient-led pathways for urgency (Q1) were 1.3 and 0.8, ($p=0.114$), frequency (Q2) were 1.3 and 0.9 ($p=0.184$), nocturia (Q3) were 0.4 and 0.1 ($p=0.134$), and pain and burning (Q4) were 1.1 and 1.4 ($p=0.175$), respectively. Mean reduction in problem scores for the nurse-led and patient-led pathways for frequency (Q1) were 1.4 and 0.7, respectively ($p=0.068$), nocturia (Q2) were 0.9 and 0.3 ($p=0.058$), urgency (Q3) were 1.2 and 0.8 ($p=0.173$), and pain and burning (Q4) were 0.9 and 1.2 ($p=0.198$), respectively.

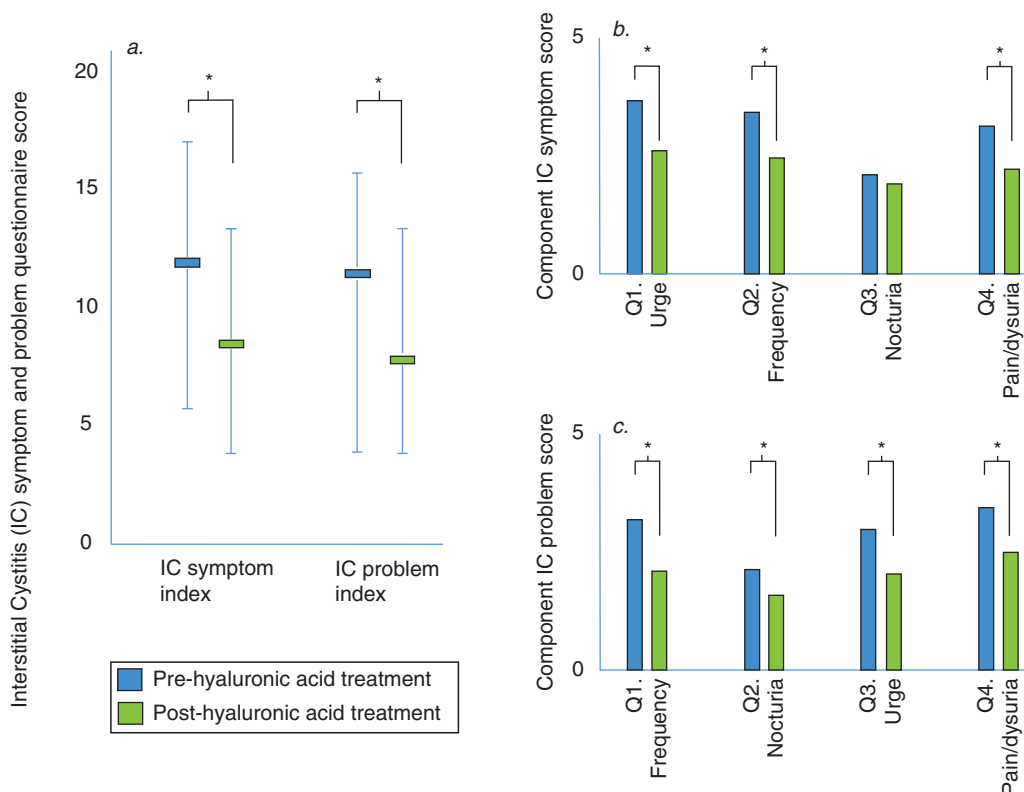
Patient-Reported Outcome Measure Scores in Relation to Clinical and Demographic Factors

Multivariate regression analyses suggested that patient age, gender, number of comorbidities, predominant symptom, and treatment type, were not independently associated with improvement in IC symptom or problem scores ($p>0.05$, data not shown).

Potential Implications of Establishing the Patient-Led Pathway for Intravesical HA

In addition to PROMS, we also evaluated other possible benefits to patients and to our service provision

FIG. 1 IC symptom and problem questionnaire scores prior to and following intravesical hyaluronic acid. **Panel a.** shows the pre- and post-treatment O’Leary-Sant questionnaire symptom and problem scores. Pre-treatment mean is represented by the solid blue bar; the post-treatment mean is represented by the solid green bar. Significant differences in scores are denoted by ‘*’, where $p < 0.05$ by T Test. Panels b. and c. show the pre- and post-treatment scores for the specific symptom areas that comprise the symptom and problem questionnaire scores, respectively. The blue bars represent mean pre-treatment score and the green bars represent post-treatment mean scores.



gained by using the patient-led pathway. As shown in Figure 3. (in the nurse- and patient-led pathways, respectively) average waiting time to start treatment was 16.7 and 14.9 weeks ($p=0.169$) (panel a.); mean number of treatments were 12.0 and 10.4 ($p=0.062$) (panel b.), mean number of nurse clinic appointments were 12.0 and 7.1 ($p=0.0001$) (panel c.), mean number of clinician outpatient appointments were 1.0 and 0.3 ($p=0.001$) (panel d.), and estimated cost per patient was £4,860 and £3,350 (all per year).

DISCUSSION

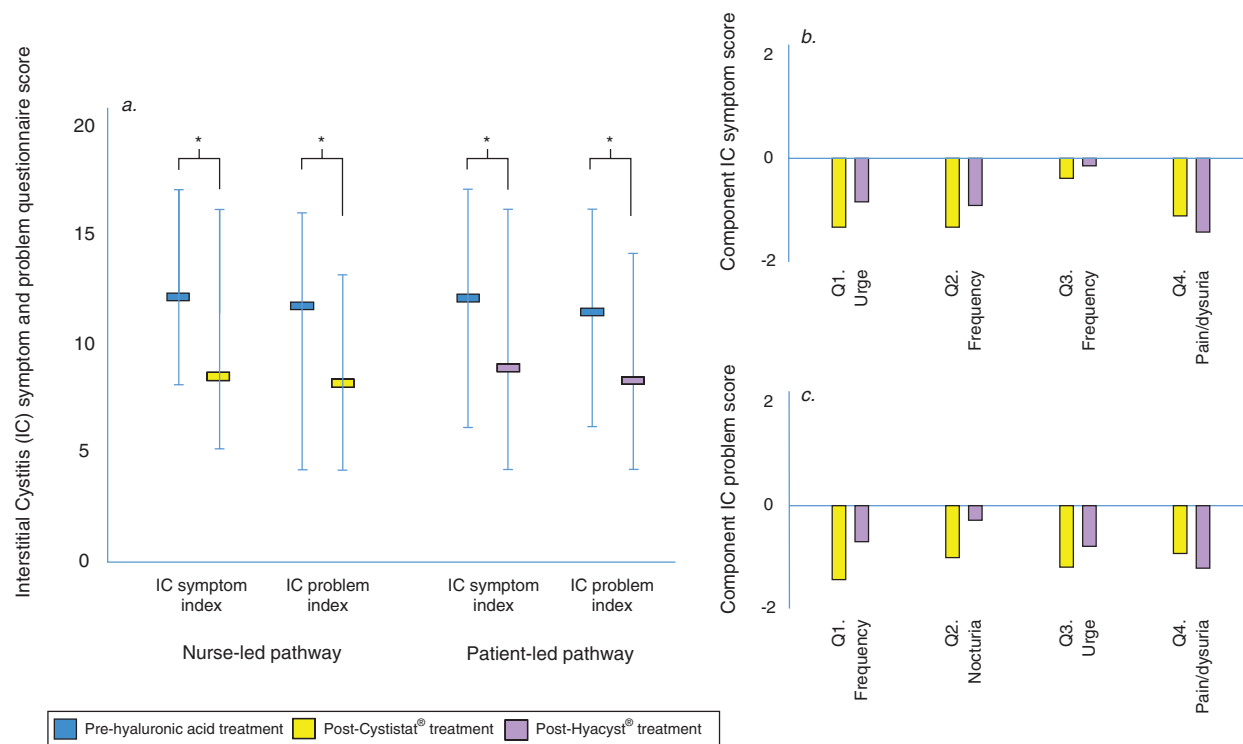
Painful bladder syndrome (PBS) is associated with a broad range of symptoms and significant reduction

in quality of life.⁴⁻⁶ Although no treatment option provides reliable and significant improvements, exogenous hyaluronic acid (HA) administration has been shown to reduce symptom severity and improve quality of life for PBS patients.¹⁰⁻¹²

Hitherto, our BPS patients received regular nurse-led clinic appointments for intravesical HA instillations (Cystistat® 40 mg)(once per week for 6 weeks, then monthly thereafter), with regular nurse and outpatient clinic review. Patient feedback regarding inconvenience of multiple hospital visits, combined with pressures on service provision, necessitated the introduction of an ‘at-home’ patient-led pathway, comprising self-catheterisation teaching and self-administration of

FIG. 2 IC symptom and problem questionnaire scores in the nurse-led and patient-led intravesical hyaluronic acid pathways.

Panel a. shows the pre- and post-treatment O’Leary-Sant questionnaire symptom and problem scores for the nurse-led and patient-led pathways. Pre-treatment mean is represented by the solid blue bars, the post-treatment mean is represented by the solid yellow bars (nurse-led) and purple bars (patient-led). Significant differences in scores are denoted by ‘*’, where $p < 0.05$ by T Test. Panels b. and c. show the reduction in symptom and problem scores following hyaluronic acid treatment. For each, the yellow bars represent mean improvement with the nurse-led pathway, and the purple bars represent mean improvement in the patient-led pathway.



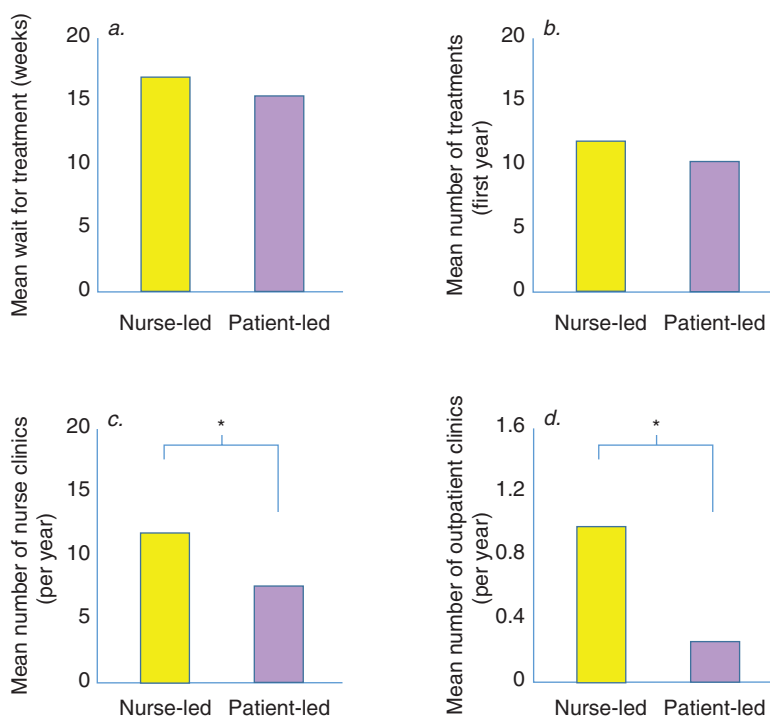
HA (Hyacyst® 40 mg) (once per week for 6 weeks then patient-led thereafter). Patients were given the option of the nurse- or patient-led pathway at the start of treatment and given the option to continue or change at each nurse clinic visit. Although, to our knowledge, there are no previous reports of similar treatment pathways for comparison, successful patient-delivered non-oral medication/treatments for chronic pain are described.¹⁷⁻¹⁹

Anecdotally, we observed that our patient-led pathway PBS patients were using fewer HA instillations and were requesting fewer clinic appointments, a finding substantiated by our study. Patient feedback suggested that empowerment and control over

treatment timing and frequency was a driving factor in symptom control and perhaps led to the need for fewer treatments, a finding similar to that reported in other conditions causing chronic pain.¹⁹⁻²² Reassuringly, this empowered population also reported a significant improvement in symptoms despite fewer treatments. Indeed, the majority of our patients receiving intravesical HA had symptomatic benefit, in keeping with previous reports,^{11,12,22} and therefore supporting the validity of our data. No patients had problems performing intermittent self-catheterisation in the community. Interestingly, conversely to previous studies, nocturia was a difficult symptom (and problem) to improve in our case series. Although we

FIG. 3 Comparison of treatment time and number, and number of hospital visits required, between the nurse-led and patient-led intravesical hyaluronic acid pathways.

Panel a. shows the mean waiting time to start intravesical hyaluronic acid on the nurse-led (yellow bar) and patient-led (purple bar) pathways. Panel b. shows the mean number of intravesical hyaluronic acid treatments received in the first year, on the nurse-led (yellow bar) and patient-led (purple bar) pathways. Panel c. shows the mean number of nurse clinic appointments used in the first year of treatment, on the nurse-led (yellow bar) and patient-led (purple bar) pathways. Panel d. shows the mean number of clinician outpatient appointments used in the first year of treatment, on the nurse-led (yellow bar) and patient-led (purple bar) pathways. Significant differences in scores are denoted by ‘*’, where $p < 0.05$ by T Test.



did not collect separate patient satisfaction scores, we considered improvements in ICS symptom and problem scores, and the fact that most of the patients continued HA treatment as surrogates for symptom improvement and satisfaction.

Although patient symptom benefit, empowerment and convenience are the primary reasons for this pathway, an important additional consideration is the potential benefit to service provision. In this regard, we observed that fewer nurse clinic appointments were required, fewer outpatient appointments were required, and fewer treatments were needed. Assuming, on average, 17 new patients commence (and

continue) self-administered HA per year, we estimate that 76 nurse clinic appointments and 11 clinician outpatient appointments can be ‘saved’ per year over the nurse-led pathway. These appointments could be used for new urgent and cancer referrals and for patients requiring intra-vesical therapies for bladder cancer. Furthermore, based upon NHS National Tariff 2018/2019 figures,²³ and assuming treatment continues with a constant number of hospital visits per year, we estimate that the patient-led pathway could save approximately £1,500 per patient in the first year, and approximately £3,200 for subsequent years.

Whilst these initial analyses are promising, we do advocate caution in interpretation of our results, as we present a retrospective analysis of our (single-centre) case series. Our patients were not randomised, the nurse-led and patient-led pathway patients were not matched nor controlled, and we recognise the possibility of inherent responder and recall bias in symptom score questionnaires. Nevertheless, given that our patient outcomes are broadly in keeping with previous reports, and the O’Leary-Sant questionnaire used is widely accepted for BPS patients,^{15,24} we believe our methods to be robust, and our preliminary data to be reliable and reflective of a typical UK BPS patient population.

We will continue to provide this novel service to support our local PBS patient community, and furthermore, it is our intention to develop our nursing service to offer (patient-initiated) telephone consultations, nurse-led ‘at-home’ community review. We hope this will be more convenient for our patients, contribute to empowerment, patient-decision making and symptom control, and relieve pressures on hospital outpatient services.

CONCLUSIONS

To our knowledge, this is the first reported case series in the UK to evaluate the use of a novel patient-led at-home self-administer pathway for intravesical hyaluronic acid (HA) treatment. We have shown, in this potentially debilitating and difficult to manage spectrum of disease, that self-catheterisation and self-administration of HA is well tolerated, improves symptoms for most patients, reduces the number of patient hospital visits (and therefore the burden on nurse and outpatient clinics), and is cost-effective. Despite the limitations of our study, and although we recognise that further evaluation in greater patient numbers is required, the use of such a patient-led at-home treatment pathway should be advocated and encouraged.

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SUPPLEMENTAL FIG. 1

Interstitial Cystitis Symptom and Problem Questionnaire

Identifying IC

To help your clinician determine if you have IC, please put a check mark next to the most appropriate response to each of the questions shown below. Then add up the numbers to the left of the check marks and write the total below.

IC Symptom Index

During the past month:

Q1. How often have you felt the strong need to urinate with little or no warning?

- 0. Not at all
- 1. Less than 1 time in 5
- 2. Less than half the time
- 3. About half the time
- 4. More than half the time
- 5. Almost always

Q2. Have you had to urinate less than 2 hours after you finished urinating?

- 0. Not at all
- 1. Less than 1 time in 5
- 2. Less than half the time
- 3. About half the time
- 4. More than half the time
- 5. Almost always

Q3. How often did you most typically get up at night to urinate?

- 0. None
- 1. Once
- 2. 2 times
- 3. 3 times
- 4. 4 times
- 5. 5 or more times

Q4. Have you experienced pain or burning in your bladder?

- 0. Not at all
- 2. A few times
- 3. Almost always
- 4. Fairly often
- 5. Usually

Add the numerical values of the checked entries; total score: _____

IC Problem Index

During the past month, how much has each of the following been a problem for you?

Q1. Frequent urination during the day?

- 0. No problem
- 1. Very small problem
- 2. Small problem
- 3. Medium problem
- 4. Big problem

Q2. Getting up at night to urinate?

- 0. No problem
- 1. Very small problem
- 2. Small problem
- 3. Medium problem
- 4. Big problem

Q3. Need to urinate with little warning?

- 0. No problem
- 1. Very small problem
- 2. Small problem
- 3. Medium problem
- 4. Big problem

Q4. Burning, pain, discomfort, or pressure in your bladder?

- 0. No problem
- 1. Very small problem
- 2. Small problem
- 3. Medium problem
- 4. Big problem

Add the numerical values of the checked entries; total score: _____