



A PROSPECTIVE STUDY OF CLINICAL PHENOTYPE DIRECTED MANAGEMENT OF BLADDER PAIN SYNDROME /INTERSTITIAL CYSTITIS (BPS / IC)

Urology

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ABSTRACT

Aims and Objectives:

Primary Objective

- To classify patients with Bladder Pain Syndrome/IC using clinical phenotype system using UPOINT classification system.
- To assess a therapeutic strategy for patients of interstitial cystitis/ bladder pain syndrome (IC/BPS) using an individualized phenotype-directed treatment plan based on clinically based categorization.

Secondary Objective

- To stratify the response after the treatment using O'Leary-Sant ICSI/ICPI questionnaire scores on clinical scale.

Materials and Methods:

It was a prospective observational hospital-based study where patients diagnosed with IC/BPS aged 18 years or older were considered in this study excluding all confusable diseases. All the patients according to their symptomatology, reports and clinical phenotype were classified into UPOINT system. All patients received treatment which were directed as per UPOINT system and O'Leary-Sant ICSI /ICPI questionnaire scores were collected as responses were achieved at 1 week, 1 month and 2 months of follow up. **Results:** Follow-up visit data were available for 52 patients mean age, 54.6±12.9 years and mean ICSI/ICPI, 23±3). Patients reported UPOINT domains with the following distribution: Urinary - 100%; Psychological – 73.1 %; Organic -100 %; Infection – 26.9 %; Neurogenic/Systemic- 55.8 %; and Tenderness- 25 %. The mean decrease in ICSI was 11±3 points. Significant clinical improvement (>30%-50% decrease in ICSI-26.9 and >50 % decrease in ICSI- 63.5 %) was observed in 91.4 % compared with initial baseline visit. Significant improvement was seen after UPOINT directed treatment with the symptoms of IC/BPS. **Conclusion:** Patients referred to a tertiary IC/BPS clinic, regardless of the complexity or severity of condition, experienced clinically significant improvement using an individualized UPOINT clinical phenotype-directed therapeutic approach.

KEYWORDS

Bladder pain, UPOINT, Interstitial cystitis, clinical phenotype.

INTRODUCTION:

Interstitial cystitis (IC)/Bladder Pain Syndrome is a heterogenous inflammatory bladder syndrome with symptoms that include pelvic and/or perineal pain, urinary frequency, urgency and nocturia 1,2. It is ten times more common among women than men (Hand, 1949; Oravisto 1975; Koziol et al, 1993)1-3. The diagnosis is made clinically, but currently there is no consensus on the specific findings required for this. The relative rarity if this syndrome and lack of objective findings have made epidemiological studies difficult and the prevalence of IC/BPS has also remained obscure. Many etiologies have been proposed and the pathogenesis has remained unknown.

Thirty years ago, it was believed that BPS/IC did not exist in India and it was a disease predominantly present in Western world. Symptoms of BPS/IC and tuberculosis are more or less same and as tuberculosis is common in India most of the patients of BPS/IC were diagnosed and treated as tuberculosis. In India there are no epidemiological studies, but even going by minimum population prevalence of 100 per 100,000, India has minimum 1.25 million patients with BPS/IC4.

Our goal, as urologists managing interstitial cystitis/bladder pain syndrome (IC/BPS) is to find the best treatment for our patients suffering from this painful and debilitating enigmatic condition. The

American Urological Association (AUA) IC/BPS guidelines⁵ provide a best evidence stepwise single therapy approach to treat patients with IC/BPS. Unfortunately, this approach does fail in some patients who continue to be impacted by this condition despite best efforts. On basis of analysis of the available evidence can only lead to conclusion that there is no single ideal therapy or a combination of therapies that will benefit all patients.

This necessity has been met with questionnaires, of which the O'Leary-Sant ICSI has emerged as predominant. Proposed in 1997, it has since been shown to be effective both as a screening tool⁶, and an outcome measure. ⁷It has four domains examining urinary urgency, frequency, nocturia, and pain, and gives a total score based on the sum (0–20).⁸

Lubeck et al. verified that the scale fulfilled established psychometric properties of variability, test-retest reliability, internal consistency reliability, construct validity, responsiveness, and clinically meaningful change.⁷ However, the scale has certain deficits that need to be considered. Lubeck et al. also noted weak correlations among ICSI scores and physical and emotional functioning, sleep, and sexual functioning. Phenotyping is process of grouping a set of organisms / individuals based on their easily discernible characteristics like

appearances, behaviour etc.

Clinical phenotyping will involve detailed history, examination and cystoscopic findings, according to which specific treatment strategies can be made.

In 2009, Shoskes et al 9 developed a 6-point clinical phenotyping system called UPOINT to classify patients with interstitial cystitis and subsequently direct appropriate therapy. UPOINT is a 6-point clinical classification system that categorizes the phenotype of patients with IC/BPS into 6 clinically identifiable domains including Urinary, Psychosocial, Organ Specific, Infection, Neurological/Systemic and Tenderness (muscle). This clinical classification system is not necessarily based on etiology, but remains flexible (will incorporate new epidemiology, therapeutic and biomarker research as it becomes available). Each domain has been clinically defined, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy.

The major finding of the first UPOINT retrospective study was the strong correlation between the number of UPOINT positive domains and the NIH-CPSI total score in each patient⁹, which was further verified by other studies.^{10,11} More recently, the UPOINT-guided multimodal therapy has been shown to significantly improve symptoms.¹²

MATERIALS AND METHODS:

A Prospective observational study was conducted at a tertiary care centre in the western part of India after obtaining ethical committee approval and patient consent for the study where a total of 52 patients of either sex presenting with suprapubic pain/frequency of urine / LUTS and diagnosed with IC/BPS who presented to urology department of the hospital were included in the study. The duration of the study was 1 year.

The inclusion and exclusion criteria for the study were as follows:

Inclusion Criteria:

1. Age group: 18 and above
2. Gender: Male and female patients will be included.
3. Patients who would voluntarily agree to sign informed consent form.

Exclusion Criteria:

1. Confusable diseases

Patients were assessed by taking a detailed history, examination, and routine urine analysis and ultrasound examination (if required) of urinary tract. As per clinical indications, further investigations were performed to exclude any confusable disease. In case of any doubt regarding diagnosis of BPS, an intravesical lignocaine test was performed to confirm. The diagnosis was based on chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. The patients thus diagnosed to have BPS were then enrolled in study, classified according to UPOINT classification system and treated accordingly. Further they were evaluated with the clinical scoring system. Patients were given questionnaire and scoring was done; Severity was then assessed and given a 0-35 score based on the proposed scale. The score thus obtained was plotted on "Clinical scale" and recommended treatment modality was adopted. Patients were grouped according to clinical phenotyping and treatment strategies were accordingly given.

Patients were categorized into clinical domains (UPOINT Classification) and treatment given as under:

The urinary domain included patients reporting bothersome urinary frequency, urgency, nocturia, incontinence and/or dysuria. It was expected that most if not all patients would be included in this domain due to criteria used to make clinical diagnosis of IC/PBS. Treatment: antimuscarinics, Pyridium, and bladder retraining.

The psychosocial domain included patients determined to be clinically depressed (or with a recent history of depression), those with identifiable maladaptive coping mechanisms (e.g., catastrophizing) or those who had problems with social interactions. This was a clinical assessment based on history and focused interview. Treatment: education, coping, Cognitive Behavioural Therapy, tricyclic antidepressants, and anxiolytics.

The organ specific domain included patients who reported pain with bladder recycling (typically pain with bladder filling and temporary relief with voiding), pain on bladder filling detected with low volumes of irrigation fluid, glomerulations and/or Hunner's ulcers noted during cystoscopy (under local or general anaesthesia), and/or those with typical inflammation confirmed on bladder biopsy. Treatment: Pyridium, lidocaine, PPS (pentosan polysulfate sodium), and quercetin.

The infection domain included patients who were confirmed to have significant bacteriuria with typical uropathogenic bacteria in the previous 2 years associated with exacerbation of baseline symptoms and return to baseline symptoms following appropriate antimicrobial therapy. Treatment: antimicrobials The neurological/systemic domain included patients with a concurrent diagnosis of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia or any other condition that suggested neuropathy or neural upregulation. Treatment: amitriptyline, gabapentinoids, system specific therapies, and referral.

The tenderness domain included patients with pelvic floor or lower abdominal muscle/ligament tenderness and or pain, including but not restricted to specific trigger points during standardized abdominal and pelvic examination. Treatment: physiotherapy, exercise, muscle relaxants, and injection therapy.

Follow up was done at 1 week, 1 month and 2 months. A 0-35 score was determined using the proposed scale at each visit in order to monitor improvement. Treatment was adjusted based on patient's response.

Responses were then stratified into three categories using the proposed scale:

1. Unsatisfactory response (decrease of < 30% of score),
2. Good response (decrease of > 30 to < 50% of score), and
3. Excellent response (decrease of > 50% of score)

All data thus obtained was thus tabulated and analysed. The change in clinical score from baseline to 1 week, from 1 week to 1 month and from 1 month to 2 months was analysed using Wilcoxon signed rank test. The number of patients whose values decreased or remained during the period was also noted from Wilcoxon signed rank test analysis. Also, the decrease in clinical score was calculated by subtracting the values at 2 months from values at baseline. $p < 0.05$ was considered to be statistically significant.

RESULTS:

A total of 52 patients were enrolled into the study which included 9 male and 43 female patients. The mean age of study participants was 54.6 ± 12.9 years. In terms of occupation, highest percentage of participants in the study were housewives (78.8%) followed by 15.4% being in business and 1.9% were retired and 3.8% were students. Almost all participants had complaints of frequency urination, urgency and nocturia. Suprapubic pain was observed in a little over 1/4th participants (28.8%) whereas haematuria was observed in 11.6% participants. Rest of the symptoms were observed in >10% participants which is shown in table 1.

The most commonly observed symptom on clinical examination was pelvic tenderness (9.6%). One participant each had grade 2 cystocele and prostate grade 2 respectively. Only 2 participants had pus cells on urine routine analysis. Table 2 depicts the clinical examination findings.

25% i.e., 1/4th of the total participant's urine culture report showed E-coli growth.

The mean haemoglobin was 11.4 g/dl, WBC count was 8325/mm³ and serum creatinine was 0.86 mg/dl.

UPOINT Score: (Table-3)

The UPOINT score frequency of participants is shown in Table 3 and Figure 1. Almost all participants had organ specific and urinary followed by 73.1% who had psychological. A little over 55% participants had neurological/ systemic whereas around 25 to 27% had infection and tenderness.

Treatment

Table 4 gives the type of treatment that participants in the current study

underwent. Most patients received B3 agonist, PPS, analgesic, behavioural modifications and pregabalin.

Clinical score:

Table 5 gives clinical scores of patients at baseline, at 1 week, at 1 month and at 2 months.

Response to treatment

Table 6 shows response to treatment in terms of it being unsatisfactory, good and excellent.

DISCUSSION:

The understanding of IC/BPS has evolved since the NIH classification. The major barrier in treating patient with IC/BPS is the heterogenous nature of this syndrome. The therapies discussed have had minimal or no success because they target a single mechanism for every patient with IC/BPS, whereas each patient should be evaluated individually to assess the nature of symptoms and then be treated appropriately.

In order to direct appropriate therapy, patients diagnosed with IC/BPS were easily categorized into UPOINT phenotype system using a traditional but standardized clinical assessment. The clinical domains are urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic, and tenderness of muscles, which produces acronym UPOINT. Each patient is evaluated clinically for involvement of each domain, and symptom severity is assessed using the NIH-CPSI. This is followed by a multimodal therapeutic approach toward positive domains.

In our study, we included 52 patients, in which 82.7 % patients were female and 17.3 % were male. Patients diagnosed with IC/BPS are more common among females than males with ratio of 4.8: 1 which is quite similar to study of Clemens et al, 2005 in which prevalence of IC/BPS of female to male ratio was 5:1. Out of these 174 patients, 19 (10.9%) were male in Taneja et al study.13,14

In study by Nickel et al, the age range was 45.2 +/- 17.4 (mean SD), while in our study it was 54.6±12.9 years. In our study, 78.8 % were doing household work.

In Taneja et al,2019 study the age group was 25-75 years.15 The diagnosis of IC/PBS by definition includes women with pain perceived to be localized to bladder, almost always associated with urinary frequency, urgency and nocturia. Almost 100 % of our patients were having urinary frequency, urgency and nocturia which is quite similar to studies done by Nickel et al in 2009 and 2014. Out of 52 patients in our study, 1/4th participants had suprapubic pain and 11.6 % had hematuria.16

Remarkably 100 % patients of our IC/BPS patients were included in Urinary and Organ specific domains, which is quite similar in Nickel et al, 2009 study. Unlike male CP-CPPS, in which approximately 52% and 61% were categorized in the urinary and organ specific domains, respectively, diagnosis of IC/PBS by definition includes women with pain perceived to be localized to bladder, almost always associated with urinary frequency and urgency. Treatment for these two domains were anticholinergics, alpha blockers, Beta-3 Agonist (Mirabegron) and Pentosan Polysulfate which included 32.7 %, 25% 96.2% and 92.3 %. This shows that most patients received Mirabegron and Pentosan Polysulfate as a part of multimodal phenotypically directed therapy for improvement of symptoms. With development of Mirabegron, which is selective for urinary bladder, it is safe and effective to control frequency, urgency and nocturia than usage of anticholinergics.16

Remarkably only 7.7 % of patients only had these 2 domains, and others were categorized into 3 (40.4 %), 4 (28.8), 5 (13.5%) or all 6 (9.6%) domains, while in contrary to this study Nickel et al, 2005 showed 13% of patients only had 2 domains. In fact, the other 87% were categorized into 3 (35%), 4 (34%), 5 (13%) or all 6 (5%) domains, this could explain failure of therapies directed against those domains to exclusion of other identified domains.16

In our cohort of 52 patients with IC/BPS 14 (26.9 %) patients were included in infection domain, which was comparable to study of Nickel, 2005 that included 35 % patients in infection domain. All 26.9% of patients were treated with short course of antibiotics directed against uropathogenic organism mainly E. coli according to culture report. It is generally conceded that cystitis associated with infection is

not compatible with a concurrent diagnosis of IC/BPS. We included patients with an IC/PBS diagnosis made at a time when urine was sterile, that more patients with IC may experience exacerbation secondary to uropathogenic bacteriuria than previously recognized. Patients with bacteriuria or recent documented bacterial cystitis are routinely excluded from most IC studies. However, in our cohort when assessment was performed when urine was sterile, we showed that being included in the infection domain did not impact any symptom parameter.16

The major psychosocial domain considerations identified in patients with IC/BPS include depression and social problems. In our cohort we had 73.1 % of patients with psychosocial domain. Aetiology and effect between IC/PBS symptoms and psychosocial parameters cannot be assessed in this study. IC/PBS symptoms, pain and psychosocial factors, showed that depression and greater catastrophizing were associated with diminished quality of life. Depression can be treated medically with cognitive behavioural therapy and social dysfunction can be treated with counselling. In our cohort 86.5 % received behavioural modifications in form of counselling that shows treatment not only focusing on psychosocial domain, but it helps in curing other domains and 38.5% received Amitriptyline acting as an anti depressant.

For patients to be included in neurological/systemic domain, clinician must first identify conditions outside bladder that imply chronic pelvic neuropathy, central sensitization and/or a diagnosis and symptoms of 1 of other associated conditions (the most prevalent would include irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome and possibly vulvodynia). We had 55.8 % of patients included in this cohort. Suggested therapy would include medical neuromodulation (amitriptyline, gabapentinoid therapy), surgical neuromodulation (implantable nerve stimulator) and/or therapy specifically directed toward an identifiable associated medical condition. In our cohort 75% received Pregabalin and 38.5 % received Amitriptyline. These two drugs other than neurological treats psychosocial and tenderness domain also.16

Patients identified in tenderness domain had pelvic, perineal and/or abdominal muscle (or ligament) pain/tenderness, and trigger points on physical examination, that included 25 % of patients in our cohort. Therapy for this domain would include counselling, analgesics and various forms of physical therapy.16

One of the difficulties for urologists using the UPOINT classification system is our lack of knowledge and experience in classifying patients into the psychosocial and neurological/systemic domains, and then describing actual individual patient phenotype within the domains. The group plans to develop clinically simple and applicable questionnaires to better quantify these domains, but until those are developed domain identification will be based on standard clinical assessment.

The UPOINT system of classifying patients according to phenotypes and then directing tailored therapies to individual patients really just formalizes and guides what many clinicians are already doing. Most importantly, UPOINT approach to IC/PBS is not static but rather is extremely flexible. It will easily incorporate new epidemiology and basic science finding

(Including biomarkers) as proposed in recently initiated NIH MAPP project. We cannot be sure if there should be other domains or whether some of the domains should incorporate more categories in such an enigmatic condition as IC/PBS. Future research in etiological mechanisms, epidemiology and biomarkers will allow subcategorization in the specific UPOINT domains.16

Another obvious major limitation is that there are no evidence-based indications for specific therapies directed toward the various phenotypes. Additionally, since a number of treatments have multiple modes of action that may benefit patients with IC/ PBS, specific treatments cannot be targeted exclusively to a particular phenotype. For example, amitriptyline has neuromodulatory, antinociceptive and antidepressant effects, mechanisms that could prove effective for more than 1 domain.

Researchers should consider phenotypically based inclusion and exclusion criteria to best match the specific treatment to related

UPOINT domains.

The marked correlation between UPOINT system and NIH symptoms score (NIH-CPSI) quality of life section was verified. All patients were given simultaneous questionnaires recommended by IC symptoms and problem questionnaire (similar to NIH- CPSI) scoring was done at the time of enrolment, 1 week, 1 month and 2 months of treatment.

Out of 35, minimum score was 18 at the date of enrolment and maximum score was 32 with mean +/- SD is 23±3. This suggest most of patients with IC/BPS were having high scores out of 35, which require treatment pertaining to particular symptoms of IC/BPS.10

Symptom reduction was seen after 1 week of treatment according to UPOINT phenotype in 51 patients out of 52 patients with a mean value of 19±2. After 1 week there is little reduction in symptom score after treatment. But mean values of symptom score after 1 month and 2 months symptoms were 16±3 and 12±4 respectively. So, there is significant reduction in symptom score after treatment, which improves patients' quality of life and satisfaction towards treatment.

Our result shows significant improvement in patients' response towards clinical UPOINT directed treatment and improves quality of life.

Though our cohort results are good, but it does not include quality of life and sexual dysfunction as a parameter of scoring system, which could be also included as described in study of Taneja et al. 2019. 13 The strength of this design lies in the fact that it most closely mimics real-life practice, and by our intention to treat design, we capture last visit outcome, that was for a few months.

Our experience is that of tertiary centre enrolling heterogeneous population without rigid inclusion and exclusion criteria. However, similar patient population was enrolled in Interstitial Cystitis Centres of Excellence in NIH-funded Interstitial

Cystitis Data Base Study and in that population, patients experienced no significant change in symptoms over an extended period of time despite standard therapy.

Based on this experience, we suggest that proposed scale is clinically useful assessment tool for BPS, with broad potential in diagnosis and care of these patients, and that it should undergo further evaluation to establish these utilities. We expect that it will not only incorporate desire for pain and voiding disturbance improvement but also expectations for improvement in quality of life, specific life activities as well as psychosocial (including relationship) improvement and satisfaction.

CONCLUSION:

Patients with IC/PBS with longer duration symptoms will have more UPOINT domains but ample amount of research is needed to clarify the time course of symptom development for the different domains. Most women with IC/PBS have UPOINT domains outside the bladder which likely is why bladder specific treatments often fail.


The results obtained in our study are relatively short term and might get altered over a period of time. The durability of the results over a period of time are a matter of debate and beyond the scope of this study as mentioned above. In our study, responses to the clinical phenotype directed treatment were excellent and satisfactory.

The aim of phenotyping patients with BPS/IC will improve understanding of the pathophysiological mechanisms of disease and to allow personalised treatment in order to get the outcomes. UPOINT directed therapy is an attractive approach that simplifies treatment in patients with the challenging diagnosis of IC/BPS.

This data justifies the development of a randomized Multiple Phenotype Intervention Trial, with validated patient-directed outcomes, perhaps comparing this phenotype multimodal directed strategy with the tiered stepwise approach advocated by tradition and the recent AUA guidelines.

Further studies should be addressed whether specific treatment for these domains will enhance the efficacy of traditional IC/PBS therapies.

Ethical committee approval:



Every Life Matters

Annexure - 3
Dated 22nd June 2020

Ref. No: No KDAH/DNB/THESIS/2020/11

To,

Deputy Director,
National Board of Examinations
Medical Enclave, Ansan Nagar,
Mahatma Gandhi Marg (Ring Road)
New Delhi-110029

Subject: - Thesis Protocol Approval Letter (Institutional Ethics Committee - Academics & Scientific Research Committee and its Composition)


Sir,

This is for your kind information that the research proposal/thesis protocols of below listed DNB candidates have been considered and reviewed by the Scientific Research Committee (SRC) of the Institute/hospital in its meeting held on 08th January 2020 and by the Institutional Ethics Committee-Academics (IEC-A) in its meeting held 22nd February 2020.

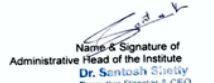
S.N.	Name of Candidate	Specialty	Session	Testing ID/Roll No.	Thesis Topic Title
1.	Asari Ashishkumar Narsinhbhai	DNB- Genitourinary Surgery	January 2018	1701200164	A prospective study of clinical phenotype directed management of bladder pain syndrome / interstitial cystitis (BPS / IC)

The IEC-A which reviewed the proposals is duly registered with the Drug Controller General of India (DCGI) and SRC of the hospital is composed as per guidelines prescribed by NBE for the enclosed purpose. The authenticated copies of composition of both the committees are enclosed herewith. Both the committees i.e. IEC-A and SRC have approved conducting the study on above listed research proposal(s) of DNB candidate(s) for the purpose of writing their DNB theses.

It is further certified that the proposed research protocol(s) have not been/shall not be submitted elsewhere for any degree, fellowship or any other titles for recognition. The minutes of aforesaid meetings of IEC-A and SRC are available with the hospital and can be reproduced before NBE, if so required, at any point of time.



Name & Signature of the Academic Head/DNB Coordinator



Name & Signature of Administrative Head of the Institute
Dr. Santosh Sinha

Encls: i. Composition of Institutional Ethics Committee - Academics
ii. Composition of Scientific Research Committee (SRC)

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CIN: U99999MH1999PLN127963

Patient Informed consent Form:

Informed Consent Form

Participant's Initials: _____ Participant's Name: _____
Date of Birth/ Age: _____

Please Initial Box

(I) I confirm that I have read and understood the information sheet dated [] for the study titled "A prospective study of clinical phenotype directed management of Bladder pain syndrome /Interstitial Cystitis (BPS / IC)" and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free [] free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the study investigator and study team, the Ethics Committee and [] the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand my identity will not be revealed in any information which may get published.

(iv) I agree not to restrict the use of any data or results that arise from this study provide [] such a use is only for scientific purpose(s).
(v) I agree to take part in the above study. []

Name of the Participant Sign/Thumb Impression Date

Name of LR Sign/Thumb Impression Date
(Legal Representative)

- Prevalence of interstitial cystitis symptoms in a managed care population. *J Urol.* 2005 Aug;174(2):576-80.
15. Nickel JC, Irvine-Bird K, Jianbo L, Shoskes DA. Phenotype-directed management of interstitial cystitis/bladder pain syndrome. *Urology.* 2014 Jul;84(1):175-9.
 16. Nickel JC, Shoskes D, Irvine-Bird K. Clinical phenotyping of women with interstitial cystitis/painful bladder syndrome: a key to classification and potentially improved management. *J Urol.* 2009 Jul;182(1):155-60.