Potassium sensitivity test predicts hydrodistention efficacy in patients with bladder pain syndrome/interstitial cystitis

Ömer Gülpınar[1], Barış Esen[1], Çağrı Akpınar[1], Utku Baklacı[1], Mehmet İlker Gökce[1], Evren Süer[1], Yaşar Bedük[1]

Cite this article as: Gülpınar Ö, Esen B, Akpınar Ç, Baklacı U, Gökce Mİ, Süer E, et al. Potassium sensitivity test predicts hydrodistention efficacy in patients with bladder pain syndrome/interstitial cystitis. Turk J Urol 2020; 46(3): 231-5.

ABSTRACT

Objective: To determine the possible role of potassium sensitivity test (PST) in predicting the success of hydrodistention (HD) in patients with bladder pain syndrome/interstitial cystitis (BPS/IC).

Material and methods: Patients who underwent PST before diagnostic cystoscopy and HD were evaluated to collect data regarding the visual analog score (VAS) to assess pain, the voiding diary for frequency of urination/nocturia, mean urine volume per void, interstitial cystitis symptom index, and problem index before HD. Patients were requested to provide the VAS of pain at 1 month and 6 months post-HD. A reduction 2 or more on the VAS of pain was considered as a response adequate to be noted.

Results: The median age of the patients was 46 years. The PST was positive for 27 patients (27/39; 69.2%). At 1 month post-HD, out of the 27 patients with positive PST, 23 (85.2%) were found to have been responsive to HD and 4 (14.8%) were non-responsive. Of the 12 (12/39; 30.8%) patients who showed a negative PST, 7 (58.3%) were non-responsive and 5 (41.7%) were responsive to HD. A logistic regression analysis revealed that PST (p=0.009) was the only parameter that was able to predict HD efficacy at 1 month post-HD.

Conclusion: PST was found to be a predictive factor for the short-term efficacy of HD. BPS/IC patients with positive PST are likely to be more susceptible to the damage of mucosal afferent nerve endings, which results in them benefiting from HD to a greater degree.

Keywords: Bladder pain syndrome; hydrodistention; interstitial cystitis; potassium chloride test.

ORCID IDs of the authors:
Ö.G. 0000-0002-0869-708X;
B.E. 0000-0002-3117-4607;
Ç.A. 0000-0002-0288-8272;
U.B. 0000-0003-4599-3109;
M.İ.G. 0000-0002-2370-548X;
E.S. 0000-0002-1283-7903;
Y.B. 0000-0002-8567-4914

Department of Urology, Ankara University School of Medicine, Ankara, Turkey

Submitted:
07.05.2019

Accepted:
25.09.2019

Available Online Date:
14.11.2019

Corresponding Author:
Barış Esen
E-mail:
barsesen90@gmail.com

©Copyright 2020 by Turkish Association of Urology

Available online at
www.turkishjournalofurology.com

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is defined as the occurrence of persistent or recurrent pain that is experienced in the urinary bladder region, accompanied by at least one other symptom, such as worsening of pain with filling of the bladder and increase in the day-time and/or night-time urinary frequency, in the absence of a proven urinary infection or another obvious local pathology.[1] A wide spectrum of prevalence rates have been reported in the literature due to lack of reliable diagnostic tools and different definitions have been adopted in various studies, but BPS/IC seems to be a much more common entity than what has been conventionally reported. A recent prevalence study revealed that approximately 3.3 to 7.9 million women in the United States were affected by BPS/IC.[2] It is a debilitating medical condition that creates a major negative impact on the patients' quality of life. A previous survey indicated that 60% of the patients with BPS/IC were unable to enjoy usual activities or were excessively fatigued and 53.7% reported depression. In more than 80% of the patients, activities such as travel, employment, leisure activities, and sleeping were also found to have been adversely affected.[3]

The etiology of BPS/IC has not been clearly identified to date, however, strong evidence suggests that primary defective urothelium lining or damage of its glycosaminoglycan (GAG) component may play an important role in the pathogenesis of BPS/IC.[4] The loss of the watertight function of the urothelium may allow both the normal and abnormal constituents of urine to come in direct contact with the subepithelial lay-

Turk J Urol 2020; 46(3): 231-5
DOI:10.5152/tud.2019.19084

ers, resulting in inflammation and delayed healing of the damaged urothelial layer. Consequently, noxious substances in the urine may activate submucosal nerve filaments, leading to symptoms of pain, urgency, and urinary frequency.[5] The potassium sensitivity test (PST) is used to induce pain and other symptoms, which allows clinicians to detect patients with abnormal epithelial permeability or hypersensitivity of the sensory nerves.

Hydrodistention (HD) is a frequently used diagnostic and therapeutic tool in patients with BPS/IC. Significant improvement in symptom scores following HD has been reported in the literature with regards to short-term follow-ups.[6] Disruption of the sensory nerves of the bladder has been attributed as the mechanism of action of this disease.[7] HD is a safe and simple procedure but it does have some complications. Even if they are encountered rarely, complications such as bladder rupture, bladder necrosis, sepsis, prolonged retention, and postoperative severe hematuria have been reported in the literature.[8-10] Previous attempts to predict HD efficacy according to patient symptoms have failed.[11] The hypothesis investigated in this trial is that patients who show a positive PST have abnormal epithelial permeability or hypersensitivity of the sensory nerves, and HD in their case may result in a greater damage to the submucosal afferent nerves and also better relief from their symptoms. For this reason, PST can be a possible predictor of HD efficacy.

Material and methods

After receiving institutional ethical board approval (Research Ethics Committee of Ankara University, decision number: 04-290-19), prospectively collected data were evaluated retrospectively. Informed written consents forms were obtained from all patients. Patients with complaints of chronic pelvic pain related to bladder filling accompanied by either of the following symptoms were included in the study between June 2013 and August 2017: a voiding frequency of ≥8 times every 24 hours, nocturia occurence of ≥2 times per night, a persistent urge to urinate for at least 24 weeks continuously, an average pain score of ≥4 (VAS; 0 no pain, 10 unbearable pain), a negative pregnancy test, a sterile urine culture, and an inadequate clinical response after 6 months of conservative and medical treatment. Patients with a positive pregnancy test, current urinary infection or sexually transmitted disease, neurogenic bladder, chemical cystitis, tuberculous or radiation cystitis, urolithiasis, urological malignancy, endometriosis, urethral diverticulum, breastfeeding women, and patients who were uncompliant till at least 6 months of follow-up were excluded from the study. All patients were evaluated for individual VAS, voiding diary for frequency/nocturia, mean urine volume per void, interstitial cystitis symptom index score (ICSI), and problem index score (ICPI) before HD. During follow-up, patients were evaluated for VAS of pain at 1 month and 6 months post-HD. A reduction of 2 or more on the VAS for pain was considered an adequate response to the treatment.

Main Points:

- Hydrodistention (HD) is an effective treatment option for patients with BPS/IC but its efficacy decreases with time. (response rate; 71.8% at post-HD 1. Month and 28.2% at post-HD 6. Month).
- Potassium sensitivity test (PST) can accurately predict HD efficacy at 1. Month post-HD (p=0.009, OR: 8.050, 95% Cl: 1.686-38.442).
- PST was well tolerated in patients with BPS/IC when a local anesthetic solution was administered intravesically for 5 minutes after PST.
- Even if PST is not an ideal diagnostic test, it can be a valuable tool to determine a subgroup of patients with a urothelial abnormality or oversensitivity of sensory nerves and also to predict the HD efficacy.

In patients to whom HD was preoperatively planned; PST was performed before diagnostic cystoscopy in the operating theater to assess its potential role in predicting HD efficacy. An 8F urethral catheter was placed and the bladder was drained totally prior to instillations. Patients were not aware of the sequence of solutions instilled to their bladder during the procedure. Initially, 40 milliliters (mL) of 0.9% saline was instilled into the bladder slowly. After 5 minutes, patients were asked to report and grade their bladder sensations such as urgency and pain with a visual analog scale from 0 to 10. After 5 minutes, the bladder was emptied. Then 40 mL of 0.4 M potassium chloride solution was administered intravesically for 5 minutes. Patients were asked to grade their bladder sensations with the same scale. If a patient report intense pain suddenly, the test was considered positive and the bladder was emptied immediately. PST was considered positive if VAS score ≥4 and it was more provocative with KCL solution than saline. A local anesthetic solution (800 milligrams of prilocaine dissolved in 40 mL of saline) was administered intravesically in all patients to avoid pain after PST. Hydrodistention was performed after the diagnostic cystourethroscopy under sedation for 8 minutes at a pressure of 60 cmH_20. The dome of the bladder was visualized during hydrodistention procedure to detect any possible bladder rupture. After hydrodistention was completed bladder was drained totally. All procedures were performed by a senior surgeon.

Statistical analysis

Patients were categorized into two groups (PST-positive group and PST-negative group) according to PST results. Treatment response rates at post-HD 1. month and post-HD 6. month for each group were evaluated. Statistical analysis to compare proportions of responders between groups were calculated with the Fisher exact test. Logistic regression analysis was performed to define predictive factors of hydrodistention efficacy. A p-value

of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with Statistical Package for the Social Sciences, v.16.0 statistical software (SAS Institute, Cary, NC).

Results

The median age of the patients was 46 years (28-72 years). All patients were female (38/39; 97.4%), except for 1 patient who was male (1/39; 2.6%). The median time interval between the initiation of symptoms to HD was 60 months (6-238 months). PST was positive for 27 patients (27/39; 69.2%). None of the patients reported significant discomfort or pain after PST. Besides being recommended to follow dietary restrictions, patients in the PST-positive group had been treated with analgesics (n=11), hydroxyzine hydrochloride (n=4), amitriptyline (n=2), and oral pentosan polysulfate (n=8) previously. Similarly, in the PST-negative group, analgesics (n=3), amitriptyline (n=1), and oral pentosan polysulfate (n=5) were the treatment drugs that had been formerly administered. No patient had undergone intravesical GAG treatment previously.

The baseline results of the visual analog score (VAS), frequency/nocturia, mean urine volume per void, symptom index score (ICSI), and problem index score (ICPI) were comparable between the PST-positive and PST-negative groups (p>0.05) (Table 1). The median follow-up period after HD was 42 weeks (24-96 weeks). At 1 month post-HD, 28 patients were responsive (28/39; 71.8%) to treatment and 11 (28.2%) patients were non-responsive. Of 27 patients showing positive PST, 23 (85.2%) were responsive to HD and 4 (14.8%) were non-responsive. Of 12 patients with negative PST, 7 (58.3%) were non-responsive and 5 (41.7%) were responsive to HD (p=0.017). At 6 months post-HD, 11 patients (11/39, 28.2%) were still responsive to HD. Of these 11 patients, 9 (81.8%) were PST-positive and 2 (18.2%) were PST-negative (p=0.446) (Table 2). Univariate logistic regression analysis revealed that PST (p=0.009, OR:8.050, 95% Cl: 1.686-38.442) was the only parameter that could accurately predict HD efficacy at 1 month post-HD (Table 3). No further multivariate analysis was required due to the conclusive results of the univariate analysis. No severe adverse effects were noted.

Table 1. Baseline characteristics of PST-positive and PST-negative groups

Parameters	PST-positive (n=27)	PST-negative (n=12)	p
Age* (year)	46 (30-72)	47 (28-70)	0.708
VAS*	8 (6-10)	8.5 (7-10)	0.845
ICSI*	11 (5-19)	12 (7-20)	0.518
ICPI*	14 (4-16)	12.5 (5-16)	0.916
Frequency (24 hr)*	9 (5-30)	11.5 (5-22)	0.893
Nocturia*	2 (1-4)	2 (1-3)	0.599
Mean voided volume (mL)	148.93 (60-320)	135.42 (65-285)	0.313

*Median values. ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index; VAS: Visual Analog Scale; PST: potassium sensitivity test

Discussion

BPS/IC is a chronic syndrome that has a major negative impact on the quality of life of vast numbers of patients.[3] Although many treatment options were previously defined, it was proven that no single therapy was successful in a majority of the patients.[12] It is extremely challenging for practitioners to manage a disease correctly when its etiology is unknown. Therefore, it is critical to select patients who would most probably benefit from

Table 3. Univariate logistic regression analysis for HD efficacy at 1 month postoperatively

			95% Cl	
Factors	p	OR	Lower	Upper
Age (<50, ≥50) (year)	0.248	0.429	0.102	1.806
PST	0.009*	8.050	1.686	38.442
ICSI	0.932	0.992	0.823	1.195
ICPI	0.841	0.982	0.820	1.175
VAS	0.320	1.478	0.685	3.189
Nocturia	0.812	1.102	0.494	2.460
Frequency	0.804	1.013	0.917	1.118
Mean voided volume (mL)	0.309	0.994	0.983	1.006

*Statistically significant. ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index; PST: Potassium Sensitivity Test; VAS: Visual Analog Scale; HD: hydrodistention

Table 2. PST results and response of BPS/IC patients to hydrodistention at 1 month and 6 months post-HD

	Post-HD 1. month			Post-HD 6. month		
	PST (–) (n, %)	PST (+) (n, %)	p	PST (–) (n, %)	PST (+) (n, %)	p
HD responsive	5 (41.7)	23 (85.2)	0.017	2 (16.7)	9 (33.3)	0.446
HD non-responsive	7 (58.3)	4 (14.8)		10 (83.3)	18 (66.7)	

PST: potassium sensitivity test; HD: hydrodistention; BPS/IC: bladder pain syndrome/interstitial cystitis

Turk J Urol 2020; 46(3): 231-5
DOI:10.5152/tud.2019.19084

a specific treatment option. Herein, we propose the potassium chloride sensitivity test as an accurate predictor of the short-term efficacy of hydrodistention.

Hydrodistention, i.e., the hydraulic distention of the bladder under anesthesia, is commonly used as the first therapeutic modality for patients with BPS/IC as an adjunct to diagnostic cystoscopy. Hydrodistention has been reported to relieve the symptoms of patients with BPS/IC. Since Bumpus reported the first series, a wide range of efficacy and durability has been reported in the literature. [13] Cole et al.[11] reported efficacy rates ranging between 50%-61% at 1-month post-HD. At 6 months post-HD, the efficacy was found to have decreased to 0%-7%. Ottem et al.[14] also reported that 56% of patients improved with HD in a mean duration of 2 months. In a different trial, 12 patients (36%) showed at least 30% improvement in the UW score and 8 patients (24%) showed at least a 50% improvement.[15] Besides the studies that reported the short-lived efficacy of HD above, a more recent study reported that 60% of patients were relieved at 6 months and 43.3% at 1 year following the procedure.[10] Lack of standardization of the hydrodistention procedure and different patient characteristics are possible reasons for the differences between studies. Effect of distention volume and duration on the efficacy of hydrodistention has been investigated previously. Glemain et al.[10] had performed HD continuously for 3 hours without rest intervals, which had resulted in improved efficacy of 60% at 6 months and 43.3% at 1 year in patients who had undergone HD twice previously. Patients with a bladder capacity of less than 150 ml were found to be less likely to benefit from HD.

Hydrodistention is a safe and simple procedure but it can pose some potential complications. Mild to moderate hematuria is a common adverse effect following HD of the bladder. In 1978, Higson et al.[9] reported bladder ruptures in 5 of 34 distentions performed to treat interstitial cystitis. They concluded that bladder ruptures were more likely if the bladder wall was diseased, the distension pressure exceeded 145 cm H_2O, and the patient was more than 50 years of age. Currently, HDs are not performed at pressures as high as 145 cm H_2O and bladder ruptures are observed to have become much less likely than when they were reported in 1978. However, Glemain et al.[10] reported a bladder rupture following an HD procedure performed at a pressure of 80 cm H_2O in a patient with a bladder capacity of 70 mL.[10] Some case reports have described the catastrophic adverse effects of HD, such as bladder necrosis and sepsis.[8,10] It is also important to keep it in mind that HD is a surgical procedure performed under anesthesia. A large number of sedation- and anesthesia-related side effects including hypotension, desaturation, bradycardia, hypertension, arrhythmia, aspiration, respiratory depression, vomiting, cardiac arrest, respiratory arrest, angina, hypoglycemia, and/or allergic reaction, have been reported.[16] Considering the possible complications mentioned above and the fact that HD is a treatment that can relieve the symptoms in only half of the patients for a short duration, it is not reasonable to perform HD in all patients. It is crucial to determine the predictors of HD efficacy, however, most of the previous efforts to predict HD efficacy have failed.[11] This study provides the first evidence in literature that acts as a predictor of HD efficacy, the pottassium sensitivity test.

Potassium sensitivity test was proposed to identify a subset of patients with bladder epithelium abnormalities or oversensitive sensory nerves. PST was reported to predict the response to treatment with intravesical sodium hyaluronate.[17] In men, the high positivity rate was also reported in patients with classic prostatitis.[18] A recent trial reported 85.5% sensitivity and 81.6% specificity of PST.[19] However, the evidence on the sensitivity and specificity of PST is questionaable. A posititivity rate of 9.1% was reported in a group of asymptomatic female Turkish textile workers with pelvic pain, urgency, a frequency score of less than 6, and a 36% false-positive rate.[20,21] Parson has reported 78% positivity in patients with clinical IC who meet the NIDDK criteria, which are supposed to be a restricted and ideal group of patients meant solely for investigating sensitivity.[22] Based on the aforementioned data related to the sensitivity and specificity of the test, there are opposing views that question the clinical value of PST in patients with BPS/IC.[23] In our opinion, even if it is not an ideal diagnostic test, PST is a valuable tool that helps to determine patients with a urothelial abnormality or oversensitivity of sensory nerves. HD causes greater damage and adverse effects on the submucosal afferent nerves in PST-positive patients, but also results in better relief of symptoms, which explains the higher efficacy of HD in patients with positive PST.

The main limitation of our study is its retrospective nature. The small number of patients included in our study was also a drawback, but was comparable to other series in the literature.

In conclusion, PST was found to be a positive predictive factor for HD efficiency. BPS/IC patients with positive PST are more susceptible to damage of the mucosal afferent nerve endings, resulting inthem experiencing a greater benefit from HD. Further prospective studies with larger numbers of patients are required to define more and exact predictive factors.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara University (Decision number: 04-290-19).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ö.G.; Design – B.E., Ö.G.; Supervision – Ö.G., Y.B.; Resources – Ö.G., B.E.; Materials – B.E., Ç.A., U.B.; Data Collection and/or Processing – Ç.A., U.B.; Analysis and/or Interpretation – B.E.; Literature Search – B.E., M.İ.G., E.S.; Writing Manuscript – B.E.; Critical Review – Ö.G., Y.B., E.S., M.İ.G.; Other – Ç.A., U.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, et al. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol 2013;64:431-9. [CrossRef]
2. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 2011;186:540-4. [CrossRef]
3. Koziol JA, Clark DC, Gittes RF, Tan EM. The natural history of interstitial cystitis: a survey of 374 patients. J Urol 1993;149:465-9. [CrossRef]
4. Hurst RE. Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. World J Urol 1994;12:3-10. [CrossRef]
5. Han XM, Wu XH, Li B, Pan F, Li WC, Liu SL, et al. The effects of intravesical therapy with hyaluronic acid for painful bladder syndrome: Preliminary Chinese experience and systematic review. Taiwan J Obstet Gynecol 2015;54:240-7. [CrossRef]
6. Rigaud J, Delavierre D, Sibert L, Labat JJ. Hydrodistension in the therapeutic management of painful bladder syndrome. Prog Urol 2010;20:1054-9. [CrossRef]
7. Dunn M, Ramsden PD, Roberts JB, Smith JC, Smith PJ. Interstitial cystitis, treated by prolonged bladder distension. Br J Urol 1977;49:641-5. [CrossRef]
8. Zabihi N, Allee T, Maher MG, Mourtzinos A, Raz S, Payne CK, et al. Bladder necrosis following hydrodistention in patients with interstitial cystitis. J Urol 2007;177:149-52. [CrossRef]
9. Higson RH, Smith JC, Whelan P. Bladder rupture: an acceptable complication of distension therapy? Br J Urol 1978;50:529-34. [CrossRef]
10. Glemain P, Riviere C, Lenormand L, Karam G, Bouchot O, Buzelin JM. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. Eur Urol 2002;41:79-84. [CrossRef]
11. Cole EE, Scarpero HM, Dmochowski RR. Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? Neurourol Urodyn 2005;24:638-42. [CrossRef]
12. Rovner E, Propert KJ, Brensinger C, Wein AJ, Foy M, Kirkemo A, et al. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology 2000;56:940-5. [CrossRef]
13. Bumpus HC. Interstitial cystitis: its treatment by overdistention of the bladder. Med Clin North Am 1930;13:1495-8.
14. Ottem DP, Teichman JM. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005;66:494-9. [CrossRef]
15. Erickson DR, Kunselman AR, Bentley CM, Peters KM, Rovner ES, Demers LM, et al. Changes in urine markers and symptoms after bladder distention for interstitial cystitis. J Urol 2007;177:556-60. [CrossRef]
16. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. World J Gastroenterol 2013;19:463-81. [CrossRef]
17. Gupta SK, Pidcock L, Parr NJ. The potassium sensitivity test: a predictor of treatment response in interstitial cystitis. BJU Int 2005;96:1063-6. [CrossRef]
18. Parsons CL, Rosenberg MT, Sassani P, Ebrahimi K, Koziol JA, Zupkas P. Quantifying symptoms in men with interstitial cystitis/prostatitis, and its correlation with potassium-sensitivity testing. BJU Int 2005;95:86-90. [CrossRef]
19. Jiang YH, Jhang JF, Kuo HC. Revisiting the Role of Potassium Sensitivity Testing and Cystoscopic Hydrodistention for the Diagnosis of Interstitial Cystitis. PLoS One 2016;11:e0151692. [CrossRef]
20. Sahinkanat T, Guven A, Ekerbicer H, Aral M. Prevalence of positive potassium sensitivity test which is an indicator of bladder epithelial permeability dysfunction in a fixed group of Turkish women. Urologia Int 2008;80:52-6. [CrossRef]
21. Yilmaz U, Liu YW, Rothman I, Lee JC, Yang CC, Berger RE. Intravesical potassium chloride sensitivity test in men with chronic pelvic pain syndrome. J Urology 2004;172:548-50. [CrossRef]
22. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 2001;57:428-32. [CrossRef]
23. Hanno P. Potassium Sensitivity Test for Painful Bladder Syndrome/Interstitial Cystitis: Con. J Urology 2009;182:431-2. [CrossRef]