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Pilot Study on the Comparative Assessment of Maximum Bladder Capacity for the Diagnosis of Interstitial Cystitis: NaCl 0.9% Versus 0.2M KCl

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ABSTRACT

INTRODUCTION: A deficiency in the glycosaminoglycan (GAG) layer alters bladder urothelial permeability, mainly to potassium ions, in patients with interstitial cystistis (IC). The potassium sensitivity test (PST) causes bladder discomfort after instillation of a 0.2 molar potassium chloride solution (0.2 M KCl). The objective of the present study was to assess maximum bladder capacity (Cmax) using a 0.2 M KCl solution compared with 0.9% sodium chloride (NaCl) in patients with IC, in order to achieve diagnosis.

METHODS: The authors studied 17 female patients diagnosed with IC, based on criteria from the National Institute of Diabetes and Digestive and Kidney Diseases. Patients completed the *Pelvic Pain and Urgency/ Frequency* (PUF) questionnaire. Cystometry was performed first with a 0.9% NaCl solution, followed by 0.2M KCl soon after. The desire to void and Cmax were measured in both cystometries. After undergoing tests with each solution, the patients evaluated pain and urgency by using a visual numeric scale.

RESULTS: All patients presented a larger decrease in Cmax when using KCl, compared with NaCl. The median Cmax decrease was 32.8% (range, 7.69% - 57.8%). A decrease in Cmax > 30% was observed in 9 patients; the remaining 8 patients had a decrease < 30%. All patients reported greater discomfort with the use of 0.2M KCl solution. The visual numeric scale score for pain revealed a mean value of 2.41 for the NaCl solution and 4.52 for KCl, with 5 representing maximum pain. The average PUF score was 23.76 (range, 18-33). When the PUF score was compared between patients with a decrease in Cmax > 30% and < 30%, no statistically significant difference was found.

CONCLUSION: PST is a well-tolerated alternative when evaluating both the increased sensitivity to potassium and the diagnosis of IC, considering the reduction in Cmax. The PUF score has no direct correlation with the PST positivity.

KEYWORDS: Interstitial cystitis; Potassium sensitivity test; Cystometry; Urinary urgency; Nocturia; Painful bladder syndrome

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INTRODUCTION

Interstitial cystitis (IC) remains a challenge in the daily clinical practice of gynecologists and urologists [1]. The International Continence Society (ICS) defines interstitial cystitis as the presence of suprapubic pain related to bladder fullness in the absence of urinary tract infection (UTI) or other bladder dysfunction, accompanied by other symptoms such as increased urinary frequency and nocturia [2].

The lack of uniformity in available studies implies that it is very difficult to obtain accurate epidemiological data on IC. Prevalence is estimated at 865/100,000 women, with the sex ratio of women to men reaching 9:1. The distribution among age groups shows that it rarely affects people younger than 18 years old [2].

There are multiple etiological factors in the development of IC including recurrent urinary tract infections (UTI), sexually transmitted diseases, radiotherapy and chemotherapy, increased coffee intake, impairment of the urothelial layer coating, autoimmune disorders, continuous exposure to cold, and chronic pharmacological treatment [3]. The symptoms of interstitial cystitis are intermittent during the early stages of the disease. The pain may be described as occurring in various locations in the pelvis including the lower abdomen, vagina, urethra, and inguinal region in both women and men [4].

Current pathological patterns suggest that there is initial urothelial damage due to a decrease in the production of glycosaminoglycans (GAG) by the urothelial cells, because the presence of a full GAG layer will provide urothelial protection against direct contact with urine and its contents [5]. A deficiency in the GAG layer changes the urothelial permeability to urine compounds, mainly to potassium ions. An excess of potassium ions in the urothelial layer is responsible for an intense sense of urgency and/or bladder-related pain [3]. In healthy persons, the full epithelial bladder layer is relatively impermeable, not absorbing the potassium ions and thus not presenting urgency or pain. If the epithelium has undergone some injury, the potassium ions will be absorbed causing symptoms of pain and urgency [4].

In the initial presentation of IC there are only nonspecific symptoms, similar to those of other pelvic organ disorders (eg, urologic, gastrointestinal, gynecologic, pelvic floor, prostate), making the diagnosis challenging [5]. Even in more advanced stages of the disease, vague symptoms are frequent and other disorders may receive medical focus because IC is a diagnosis of exclusion [2].

The more characteristic symptoms of IC are voiding urgency or frequency and urethral, vaginal, suprapubic, pelvic, or perineal pain. The pain increases with the progress of bladder filling and can be present at an isolated point or a combination of locations. There is no criterion for pain severity and other causes of chronic pelvic pain should be excluded before diagnosing IC [2].

The potassium sensitivity test (PST) is a diagnostic tool that can help to identify the presence of bladder pain and urgency in cases of IC. This test detects abnormal permeability of the bladder epithelium, which is more common in individuals with IC. The PST has been shown to be positive in 70% - 90% of patients with IC [4]. Parsons et al [6] performed more than 1,500 PSTs in women with suspected IC, finding it positive in approximately 80% of patients [6]. These authors also claim that the test is valid at indicating abnormal epithelia permeability and that the false positives are extremely rare [4]. Asymptomatic persons are not affected by intravesical potassium because they present with an intact bladder urothelium, which is impermeable to ions. When an intended epithelium injury is created in healthy people, the PST is frequently positive because they absorb potassium, thereby deflagrating symptoms. Epithelial dysfunction leading to irritative symptoms shows that the PST is a generally useful diagnostic test in IC patients [7].

The PST can be considered as an indicator of bladder lining dysfunction and, if positive, can be regarded as defining the diagnosis of IC in certain conditions. The IC diagnosis can be based on symptoms; however, the use of the PST in the propedeutic supplement can increase the diagnostic accuracy, enabling early diagnosis of the condition and thus improving the quality of life of these patients [6].

According to literature, patients with IC present some abnormalities in their urothelium, allowing the passage of ions from urine and irritating the interstitial layer. Based on this information, it is hypothesized that patients with IC will present a decrease in Cmax and a higher intensity of bladder symptoms related to cystometry with 0.2 molar potassium chloride (0.2 M KCl) solution when compared with 0.9% sodium chloride (NaCl). It is also hypothesized that patients will have a good correlation between PST and clinical symptoms. Through evaluating the maximum bladder capacity (Cmax), irritative urinary symptoms, and pelvic symptoms in patients already diagnosed with IC and submitted to PST, the authors expect to define its role in the diagnostic armamentarium of this dysfunction.

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Table 1. Inclusion and Exclusion Criteria. doi: 10.3834/uij.1944-5784.2009.08.08t1

Inclusion Criteria	Age > 18 years
	Pain associated with bladder or urinary urgency
	Duration of symptoms > 9 months
Exclusion Criteria	Bladder capacity > 350 mL proven in urodynamic study (UD) performed with saline or gas
	Urinary frequency < 8 times/day
	Presence of involuntary detrusor contractions on cystometry
	Lack of intense urgency on bladder containing 150 mL of saline during cystometry, at infusion rate between 30-100 mL/min
	Presence of urethral diverticulum
	Urerine cervix, vaginal, or urethral cancer
	Active genital herpes
	Bladder tuberculosis
	Prior bladder radiation
	Benign or malignant bladder tumors
	Vaginitis
	Cyclophosphamide or any other type of bladder-instilled drugs
	Diagnosis of urinary tract infection in a period < 3 months
	Bladder or low ureter stone

METHODS

Participants

The study involved 17 female patients from the Urology Clinic of the Hospital das Clinicas at State University of Campinas – UNICAMP, selected from a database containing records of patients with the diagnosis of IC. The study was approved by the Ethics Committee of UNICAMP. The patients were invited to participate in the study and they signed an informed consent. The diagnosis of IC was based on clinical symptoms reported by the patients. Inclusion and exclusion criteria (Table 1) were based on the recommendations of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK - 1988).

The mean age of the patients was 50.6 years (range, 20-70 years). Fifty-nine percent of the patients had reached menopause; 41% had not. Previous anti-incontinence procedures had been performed in 41%. The mean body mass index was 27.02 (range, 18.75-37.65).

Procedures

All patients underwent clinical evaluation that included anamnesis focused on topics such as extent and duration of symptoms presented, associated gynecologic complaints, age, parity, history of vaginal and/or gynecological surgery, related medical disorders, medications that could affect IC, and hormonal status. Physical examination included a detailed gynecological exploration to assess the existence of conditions that could exclude the patient from the study, as stated previously. Cystoscopy, urinary cytology, urine culture, pelvic ultrasound, uterine cervix cytology, and evaluation of the intrauterine cavity were completed when a precise indication was present.

All patients completed the *Pelvic Pain and Urgency/Frequency* (PUF) questionnaire, which contains items related to symptoms such as urgency, frequency, and dysuria (the 3 main symptoms of IC). Patients use a scale to quantify their symptoms. The PUF questionnaire was developed over 2 decades ago and tested on 5,000 patients. It is currently recommended by ICS. The questionnaire is self-administered and requires approximately 5 minutes to complete [6].

Cystometry was performed using an 8Fr double lumen urethral catheter and a rectal catheter to determine the abdominal pressure. Cystometry by infusion of 0.9% NaCl solution in the bladder was performed first, followed immediately by

Table 2. Descriptive Statistics and Probability of Significant Differences Between Paired Comparisons for Variables From 0.9% NaCl and 0.2 M KCl, as Measured by Pressure-Flow Study and Cystometry (N = 17).
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Variable	Min	Max	Mean	SD	*P*
Cmax					
NaCl	25	196	83.18	52.77	.0312
KCl	25	110	59.12	22.87	
First desire to void					
NaCl	57	250	144.47	55.49	.0007
KCl	60	170	101.76	34.79	
Normal desire to void					
NaCl	94	290	205.41	54.54	.0005
KCl	80	250	148.53	48.74	
Strong desire to void					
NaCl	123	340	271.47	62.37	.0003
KCl	87	300	186.41	64.49	

Abbreviations: Min, minimum; Max, maximum; SD, standard deviation

the second cystometry using the 0.2M KCl solution, both at an infusion rate of 50 mL/min. Voiding desire, sense of urgency, and maximum bladder capacity (Cmax) were measured in both cystometries. The threshold of maximum bladder capacity was considered to be the point in which the patient demanded to interrupt the exam.

PST was considered positive when there was at least a 30% decrease in Cmax when compared to the cystometry performed with 0.9% NaCl solution. If the patients expressed pain or urgency during either cystometry, they were asked to indicate the degree of sensation or increase of these symptoms by using a visual numeric scale, where 0 represented no change and +1 to +5 represented the extremes of low and severe stimulation, respectively. Antimicrobial prophylaxis was performed by giving 500 mg of Ciprofloxacin to all patients.

Data were collected on an Excel 2000 spreadsheet and the R 2.6.0 system for statistical computation. Descriptive measures of mean, standard deviation (SD), and range were calculated and the data were presented in tables or graphs. The Shapiro-Wilk test was used to test the normality assumption of the variables involved in the study. The student *t* test was used for variables with normal distribution; the Wilcoxon test was used for the comparative analysis of quantitative variables when the assumption of normality was rejected. The Fisher's exact test was used for the comparative analysis of qualitative variables, and the Kendall correlation coefficient was used in the correlation analysis. All conclusions had a significance level of 5%.

Table 3. Kendall Correlation Between the *Pelvic Pain and Urgency/Frequency (PUF)* Questionnaire Variables and Cmax (N = 17). doi: 10.3834/uij.1944-5784.2009.08.08t3

Variable	Cmax Difference (*r*)	*P*
Symptoms	-0.3012	.1718
Emotion	0.0109	.9606
Total	-0.2059	.3341

RESULTS

Table 2 contains the descriptive statistics for variables from the use of 0.9% NaCl and 0.2 M KCl, as measured by pressure-flow study and cystometry. The table also contains the probability of significant differences between paired comparisons. All patients had a decrease in Cmax, measured by cystometry, with both KCl and NaCl solutions. Fifty-three percent of the total sample (9 patients) had a Cmax decrease > 30%; 35% had a Cmax decrease between 15% and 30%; 12% had a Cmax decrease < 15%. The mean Cmax with the 0.9% NaCl solution was 271.47 mL, which was significantly higher than the mean of 186.41 mL with the 0.2 M KCl solution ($P = .003$). Comparison of the means of the first desire to void (FD), normal desire (ND), and strong desire (SD) also resulted in significant differences between the 2 solutions (0.9% NaCl vs 0.2 M KCl) (Table 2).

The Kendall correlation coefficient was used for the correlation analysis between PUF variables and Cmax. It showed a low correlation with no statistical significance (Table 3).

The Kendall correlation coefficient was also used to evaluate the correlation between the 0.9% NaCl and the 0.2M KCl solutions and the degree that the patients were bothered by their symptoms. The comparison was not statistically significant ($r = 0.4230$; $P = .070$). However, it should be noted that the 0.2 M KCl solution was 18 times more likely to cause pain in IC patients than the 0.9% NaCl solution (Table 4).

DISCUSSION

Symptomatic reaction to the instillation of potassium into the bladder is not expected in healthy persons. Due to the integrity and impermeability of the bladder surface, it is expected that between 3% and 5% of patients will experience pain and a sense of urgency in response to the instillation of potassium into the bladder [6,8].

The bladder mucosa surface is formed by an impermeable layer of mucin, composed of sulfonated glycosaminoglycans

Table 4. Comparison of the KCl and NaCl Solutions and Intensity of Pain Using Fisher's Exact Test (N = 17). doi: 10.3834/uij.1944-5784.2009.08.08t4

Solution	Intense Pain		Moderate Pain		OR	CI 95%	*P*
	n	% N	n	% N			
KCl	14	82.35	3	17.65	18.47	3.58-136.69	.0004
NaCl	3	17.65	14	82.35	1.0	-	-

Abbreviations: OR, odds ratio; CI, confidence interval

(GAGs) and glycoproteins. If disturbance occurs in this surface leading to permeability alterations, the ions (mainly potassium) that may traverse the urothelium can cause depolarization of sensory and motor nerves, culminating with mast cells degranulation [5].

In the present study, intense pain was present in 82% of the patients and moderate pain in 18% during cystometry performed with 0.2 M KCl. These findings corroborated the Parsons et al studies from 2001 [4,7], in which the authors consider bladder pain as abnormal when above a moderate level. However, the authors of the present investigation found that the patients with IC were 18 times more likely to mention bladder pain during cystometry performed with 0.2 M KCl (Table 3). The results of the present study detected a significant difference (*P* = .0004) in the comparison of the numeric visual scale between cystometries using 0.9% NaCl and 0.2 M KCl solutions. There was a higher pain level with the 0.2 M KCl solution, which may be indicative of an impairment of the urothelial bladder layer. In another study, Parsons et al [8] found the PST effective in supporting epithelium disruption and K+, causing symptoms in patients that previously had experienced bladder radiation and urgency-frequency syndrome (UFS).

In the present study, the PUF questionnaire demonstrated a low correlation with the PST, which is not in agreement with the findings of Parsons et al [6]. These authors identified an 84% chance of positive PST when the PUF rate was ≥ 15. The authors of the present investigation found a mean PUF score of 23.76 (range, 18 to 33). When the PUF mean score was compared between NaCl and KCl, a significant difference was not found.

When comparing the 2 solutions, approximately 53% of the patients had a Cmax decrease > 30% and 35% of the patients had a decrease between 15% and 30%. These results are in accordance with Bernie et al [9]. These authors evaluated 551 patients with low urinary tract symptoms who had undergone urodynamic testing and PST. They found that Cmax in the patients with a positive potassium sensitivity test was significantly lower than Cmax in patients who have a negative test, and the findings were similar to characteristics of interstitial cystitis [9].

Daha et al [3] proposed that if the cutoff point of decrease in Cmax between KCl and NaCl is 15%, the sensitivity and positive predictive value of PST would be 91% and 87%, respectively. The findings of the present study (Table 2) are in agreement with this proposition, and are supported by the significant differences between all bladder sensitivity parameters used in cystometries with KCl and NaCl.

Gregoire et al [1] did not find a significant difference in Cmax in a retrospective study performed with 183 patients diagnosed with interstitial cystistis. However, they compared the 105 patients with positive tests to the 16 patients with negative tests, which may be considered a bias in their analysis. In the present study, the same patients had the Cmax compared in cystometric findings from the exam performed with saline and KCl, ensuring a more accurate test comparison.

One drawback of the present study is the relatively small number of patients. However, it is important to note that this is a pilot study and a larger cohort with symptomatic patients and controls is under development.

CONCLUSION

The potassium sensitivity test (PST) proved to be an alternative in the diagnosis of interstitial cystitis, especially regarding the comparative sensitivity during cystometry performed with 0.9% NaCl and 0.2M KCl. The difference between the 2 solutions in the degree to which the patients were bothered proved to be one more option in the diagnosis of IC. The PUF score had a low correlation with the cystometric results; however, the sample of the present study is small and further studies are necessary to determine if this finding is accurate.

Conflict of Interest: none declared

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