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Ueda T[1], Yoshida T[1], Tanoue H[1], Ito M[1], Yoshimura N[2]
1. *Kyoto Cityt Hospital, Kyoto, Japan,* ***2.*** *University of Pittsburgh, Pittsburgh, PA*

URINE ALKALINISATION BY CITRATES IMPROVES PAIN AND OTHER SYMPTOMS IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME. ASSESSMENT OF URINE PH USING COMPACT PH METERS AT EVERY VOIDING.

Hypothesis / aims of study
Acidic urine may play a role in the development of symptoms in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) because activation of afferent C-fibres can be triggered by excessive H^+ ions in acidic urine. In a previous study, which was presented at the AUA in 2009, we demonstrated that urine alkalinisation could be effective for reducing symptoms, especially pain at voiding and sleep disturbance, in patients with IC/BPS. Here, we report the result of the subsequent study that was designed to evaluate the precise data of urine pH value and pain intensity. A compact pH meter was used to measure the pH and the intensity of pain was recorded at every voiding. We also investigated sleep disturbance in this study.

Study design, materials and methods
Thirty-four participants who provided written consent were enrolled in this study, and thirty (twenty-five females, five males, age 56.6±15.8) were selected based on symptoms recorded in 2-day voiding diaries and urine pH of each voiding during the screening period. King's health questionnaire (KHQ), O'Leary & Sant IC symptom and problem indices (ICSI and ICPI) were also used to evaluate the symptoms. Sleep disturbance was also investigated using Pittsburgh sleep quality index questionnaire (PSQI) and Epworth sleepiness scale (ESS) . The intensities of pain and of discomfort were recorded by patients at each voiding using a 4-point (0 - 3) scale. Following the screening period, the participants were administered citrates (a mixture of potassium citrate and sodium citrate) for four weeks. Patient with insufficient alkalinisation of urine were administered higher dose of the citrates for four more weeks, and then changes in symptoms were evaluated.
Measurement of urine pH : Urine pH was measured by patients at every voiding using a compact pH meter (Twin pH B-212, HORIBA ltd., Japan), and was recorded in a voiding diary.

Results
Spot urine tests using the pH meter before treatment with the citrates revealed that many patients had urine pHs lower than 5.2, which is the lower limit of the urine pH test paper previously used. After the treatment, the urine pH at each voiding was increased, and the number of patients with urine with low pH was also decreased (Figure 1).
After the treatment with citrates, the mean urine pH was significantly increased from 5.6 to 6.0. Most symptoms were improved (Table 1). The volume per voiding and the maximum voided volume were increased significantly. For the KHQ, general health perception, incontinence impact, and physical limitations improved significantly, and the other domains also improved, though not significantly. The mean intensities of pain and discomfort at voiding were decreased significantly. The mean overall pain score on an eleven-point (0 - 10) numerical rating scale was also decreased significantly from 5.1 to 3.7 (P=0.0054, not shown in Table). The ICSI and ICPI were also decreased significantly.
With respect to sleep disturbance, a small improvement was observed in the PSQI and ESS, but the improvement was not significant.

Interpretation of results
The symptoms of IC/BPS may be related to an attack of H^+ ions to TRPV1 or the acid-sensing ion channels expressed at the termini of afferent C-fibres located underneath the bladder mucosa. This study demonstrated that the urine at every voiding was alkalinised, and the systemic acid-base balance was adjusted by the administration of citrates. As a result, most symptoms of IC/BPS were improved, suggesting that acidic urine and/or a disturbance in the systemic acid-base balance in the upper stream may cause some symptoms of IC/BPS.
Although a reduction of sleep disturbance was observed in the previous study, this effect was not clear in this study. Because the presence of a sleep disturbance was not one of the inclusion criteria of this study, a statistical power may be low.

Concluding message
In this study, the urine pH at every voiding was measured by patients using a compact pH meter, allowing us to evaluate precisely the elevation of urine pH after the administration of citrates throughout the day.
The results of this study suggest that urine alkalinisation could be an effective to reduce the symptoms of patients with IC/BPS.

Figure 1. The distribution of the spot urine pH values before and after treatment in thirty subjects.

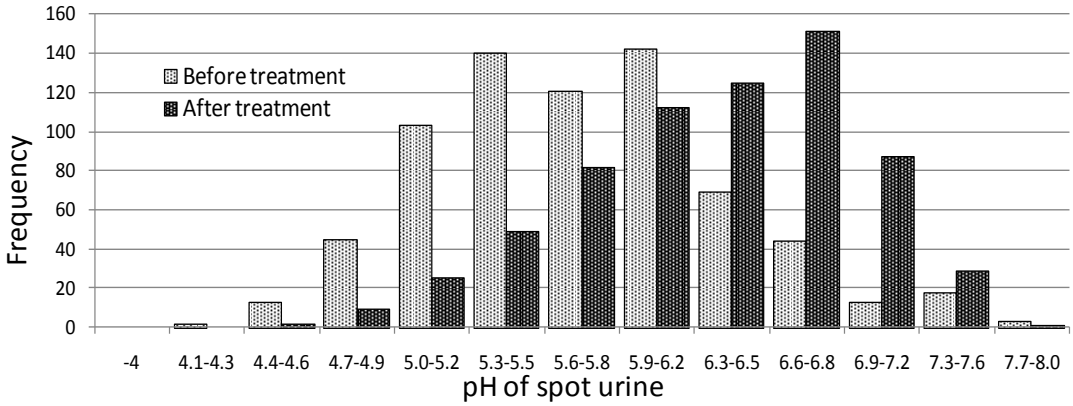

Table 1. Changes for symptoms and variables after treatment in thirty subjects.

	Before treatment		After treatment		Difference (after-before)		paired t-test
	Mean	SD	Mean	SD	Mean	SD	P value
Urine pH	5.6	±0.4	6.1	±0.4	0.5	±0.5	P<0.0001
Micturition per day	12.0	±5.8	11.4	±6.3	-0.6	±2.5	P=0.1784
Volume per voiding (mL)	164.0	±88.3	188.6	±96.0	24.5	±38.0	P=0.0014
Maximum volume per voiding (mL)	248.1	±125	283.2	±133	35.1	±47.5	P=0.0004
Intensity of pain at voiding (0-3)	1.0	±0.7	0.8	±0.8	-0.3	±0.5	P=0.0096
Intensity of discomfort at voiding (0-3)	1.1	±0.7	0.8	±0.9	-0.2	±0.5	P=0.0126
King's health questionnaire							
General health	49.2	±18.0	42.5	±22.9	-6.7	±17.3	P=0.0434
Incontinence impact	60.0	±29.6	50.0	±28.7	-10.0	±23.4	P=0.0264
Role limitations	42.8	±28.6	39.4	±27.2	-3.3	±19.8	P=0.3633
Physical limitations	51.1	±32.1	41.7	±30.9	-9.4	±19.9	P=0.0146
Social limitations	33.7	±28.8	29.6	±27.4	-4.1	±20.1	P=0.2762
Personal relationships	14.6	±23.2	13.9	±26.8	-0.7	±21.7	P=0.8767
Emotions	57.4	±30.1	48.5	±32.7	-8.9	±24.7	P=0.0579
Sleep /energy	51.1	±23.5	44.4	±31.1	-6.7	±19.9	P=0.0763
Severity	22.2	±13.6	19.1	±16.5	-3.1	±11.3	P=0.1427
O'Leary-Sant							
Symptom index	10.5	±4.8	9.0	±5.3	-1.6	±3.0	P=0.0072
Problem index	8.5	±3.8	6.6	±4.9	-1.9	±3.8	P=0.0109
Sleep quality							
Pittsburgh sleep quality index	7.8	±3.4	7.6	±3.4	-0.2	±1.7	P=0.6025
Epworth sleepiness scale	5.7	±4.8	5.2	±4.3	-0.5	±2.4	P=0.3019

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**UMIN CTR, UMIN000001761**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**The Ethics Committee of Kyoto City Hospital**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**