Effect of Supplementation With Hydrogen-rich Water in Patients With Interstitial Cystitis/Painful Bladder Syndrome

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OBJECTIVE To investigate the efficacy of hydrogen-rich water for the treatment of patients with interstitial cystitis/painful bladder syndrome (IC/PBS).

METHODS We conducted a prospective, randomized, double-blind, placebo-controlled clinical trial of hydrogen-rich water in patients with IC/PBS. Inclusion criteria were stable symptoms of IC/PBS for ≥12 weeks after bladder hydrodistension, Interstitial Cystitis Symptom Index score of ≥7 and bladder pain (question 4 on Interstitial Cystitis Symptom Index) of ≥4. They were randomized by a 2:1 ratio to receive hydrogen-rich water or placebo water for 8 weeks. The symptoms were assessed using the Interstitial Cystitis Symptom Index, Interstitial Cystitis Problem Index, Parsons' Pelvic Pain and Urgency/Frequency Patient Symptom Scale, visual analog scale bladder pain scores, and a standard 3-day voiding diary. The primary outcome was improvement of patient-reported symptoms evaluated after treatment.

RESULTS A total of 30 participants (29 women and 1 man, age 64.0 ± 14.8 years) were enrolled in the present study, and 2 patients (both women) were withdrawn from the study. The score of bladder pain was significantly reduced in both groups. However, the effect of hydrogen-rich water on symptoms was not significantly different from that of placebo, although supplementation with hydrogen-rich water was extremely effective in improving the bladder pain score in 11% of the patients.

CONCLUSION The results of the present study do not support the use of supplementation with hydrogen-rich water for treating patients with IC/PBS. UROLOGY 81: 226–230, 2013. © 2013 Elsevier Inc.

Patients with interstitial cystitis/painful bladder syndrome (IC/PBS) present with a constellation of symptoms, including bladder pain, frequency, and urgency. The proposed etiology for the symptoms of IC/PBS includes bladder ischemia and reperfusion injury. Previous reports showed pathologic findings of IC/PBS focusing on ischemia and a reduction in bladder capacity owing to fibrosis of the bladder wall.[1-3] Hyperbaric oxygen therapy has been reported to be effective in patients with IC/PBS resistant to conventional treatment.[4,5] Oxidative stress due to free radicals, which are formed by reperfusion after bladder ischemia, can cause bladder damage. Reperfusion injury is more harmful than the damage caused by ischemia alone.[6] Previous studies using an experimental cystitis animal model revealed that free radical-mediated tissue damage is also involved in the pathogenesis.[7,8]

Recently, several investigators have shown that hydrogen has potential as an antioxidant in preventive and therapeutic applications. Ohsawa et al[9] reported that hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. These findings led us to consider the possibility that hydrogen-rich water might be useful as a therapeutic supplement for IC/PBS. We hypothesized that oxidative stress could be one of the causes of IC/PBS, because the disturbance of bladder blood flow has been suggested in IC/PBS. However, to our knowledge, no clinical data are available to prove the efficacy of hydrogen in patients with IC/PBS. In the present study, we assessed whether supplementation with hydrogen-rich water had beneficial effects on the symptoms in patients with IC/PBS.

MATERIAL AND METHODS

Study Protocol

We recruited 30 patients aged ≥50 years with IC/PBS, who fulfilled the diagnostic criteria for IC proposed by the clinical guideline for IC,[10,11] and obtained prospective approval of the trial protocol, informed consent forms, and other relevant

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Financial Disclosure: *The authors declare that they have no relevant financial interests.*

Funding Support: *This study was supported by the Public Health Research Foundation Comprehensive Support Project for Clinical Research Office on Lifestyle-related disease.*

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Submitted: August 24, 2012, accepted (with revisions): October 15, 2012

0090-4295/12/$36.00
http://dx.doi.org/10.1016/j.urology.2012.10.026

documents from the Public Health Research institutional review board (Tokyo, Japan). The present study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. All patients provided written, informed consent. The study was registered at the Japan Primary Registries Network (JPRN-UMIN000001253).

These patients were assessed using the O'Leary-Sant validated Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index,[12] Pelvic Pain and Urgency/Frequency Patient Symptom Scale,[13] visual analog scale (VAS) bladder pain scores, and a standard 3-day voiding diary. The primary outcome was patient-reported symptom improvement evaluated after treatment. The inclusion criteria were stable in the history of IC/PBS symptoms ≥12 weeks after bladder hydrodistension, total ICSI score of ≥7 and bladder pain (question 4 on ICSI) of ≥4. The exclusion criteria were as follows: >200 mL of an average voided volume; urinary tract infection and vaginitis; urolithiasis; significant hepatic, renal, cardiac, or cerebrospinal disease; neurologic bladder (eg, spinal cord injury, Parkinson's disease); surgery and/or radiotherapy to the pelvis; the use of any dietary and/or antioxidant supplement, initiation of bladder training in the preceding 12 weeks before the start of the study; the initiation or discontinuation or change of the dose of the following drugs within 4 weeks after the registration: antidepressant, anticholinergic drug, antihistaminergic drug, any drugs for lower urinary tract symptoms, and steroids.

All participants were randomized in a 2:1 ratio to receive the hydrogen-rich water 3 packs/d (1 pack, 200 mL; 20 patients) or the placebo water 3 packs/d (1 pack, 200 mL; 10 patients) for 8 weeks (Fig. 1). The randomization was performed by an independent statistician and was stratified by the Public Health Research Center. The participants were instructed not to change their comestibles or lifestyle during the study period.

Hydrogen-rich water was produced by the following process[14,15]: passage through a reverse osmosis/ultrafiltration unit, an ion-exchange resin, and an ultrafiltration membrane (pure water, pH 6.9 ± 0.05; electric conductivity 0.7 ± 0.2 μS/cm). Hydrogen-rich pure water then resulted from dissolving hydrogen gas directly into pure water and had the following physical properties: (pH 6.7 ± 0.1), low electric conductivity (0.9 ± 0.2 μS/cm), high content of dissolved hydrogen (1.2 ± 0.1 ppm), low content of dissolved oxygen (0.8 ± 0.2 mg/L), and an extremely negative redox potential (oxidation reduction potential): −600 ± 20 mV (for reference, tap water: +400 to +700 mV, mineral water: about +250 mV, natural water: +200 ~ +300 mV). The constitutions of hydrogen-rich water were as follows: energy, 0 calorie; protein, lipid, carbohydrate, 0 g; total hardness, 0 mg/L; mineral (sodium, potassium, magnesium, calcium), 0 mg/L (all free). To prevent the loss of hydrogen, the hydrogen-rich water was sealed in 200-mL aluminum pouches and stored at room temperature. The hydrogen-rich water and placebo water were obtained from I'rom Pharmaceutical Co., Ltd. (Tokyo, Japan).

From the data of the published clinical trial,[14] the percentage of success cases was presumed to be about 65%-75% for the hydrogen-rich water group and about 10%-15% for the placebo group. A sample size ratio of the hydrogen-rich water group to the placebo group was set 2:1 because of the paucity of study patients and eventual difficulty in recruiting patients for the present study. A total of 24 patients in a hydrogen-rich water group and 12 patients in a placebo group would be required supposing that the response rates for these groups was 65% and 15%, respectively, and 16 patients in a hydrogen-rich water group and 12 patients in a placebo group would be required, granting that the response rate for these groups was 70% and 10%, respectively. Therefore, the planned number of subjects was set to be a total of 30, 20 for the hydrogen-rich water group and 10 for the placebo group.

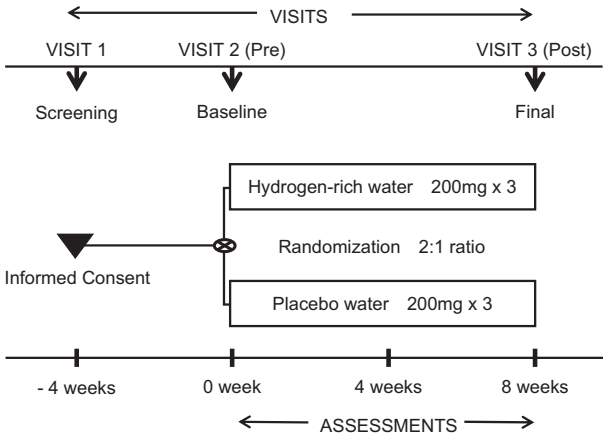

Figure 1. Study design with intervention schedule.

Statistical Analysis

The baseline demographic characteristics and symptoms measures were summarized and compared between both groups using descriptive statistics, including the mean and standard deviation. The efficacy parameters were compared between the 2 groups using 1-way analysis of variance. All analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC). The differences were considered to be significant at $P < .05$.

RESULTS

A total of 30 patients were recruited from April 2008 to July 2009. Two patients (both women) were withdrawn from the present study. The reason for withdrawal was self-judgment in 1 patient and concomitant use of other antioxidant supplements in 1 patient. Thus, 28 patients (27 women and 1 man) completed the full 8 weeks of treatment (Table 1). Their median age was 65 years. All baseline measures were comparable between the 2 groups.

The score of bladder pain (question 4 on the ICSI) was significantly reduced in both groups (Table 1). However, the effect of hydrogen-rich water on the score of bladder pain (question 4 on the ICSI) was not significantly different from that of the placebo control group. The overall treatment outcome was not significantly different statistically between the 2 groups. The change in the VAS in each patient is presented in Figure 2. The VAS bladder pain scores in 2 patients (11%) of hydrogen-rich water group showed remarkable improvement (VAS <1 point). All participants reported no adverse events.

COMMENT

To our knowledge, this is the first randomized clinical trial of hydrogen-rich water supplementation in patients with IC/PBS. The data in the present study showed no significant difference in each parameter between the

Table 1. Summary of measured variables at baseline and after 8 weeks of hydrogen-rich water or placebo

	Hydrogen-rich Water			Placebo Water		
Variable	Before	After	*P* Value	Before	After	*P* Value
Subjects randomized	18			10		
Sex						
Male	0			1		
Female	18			9		
Age (y)	65.2 ± 7.9			64.5 ± 4.5		
VAS (0-10)	6.0 (1.9)	4.9 (2.8)	.186	6.3 (1.5)	5.1 (2.4)	.182
24-h Voiding frequency	13.0 (3.9)	14.3 (5.4)	.402	13.1 (3.6)	12.5 (4.2)	.736
Voiding volume	124.0 (36.4)	138.7 (54.0)	.346	142.3 (27.3)	160.6 (48.7)	.313
ICSI (0-20)	13.2 (3.3)	11.4 (5.0)	.217	13.3 (2.0)	11.2 (3.8)	.141
Pain score (Q4; ICSI, 0-5)	4.3 (0.5)	3.1 (1.3)	.001*	4.4 (0.5)	3.2 (1.3)	.047*
ICPI (0-12)	10.1 (3.3)	9.4 (3.4)	.448	10.3 (2.6)	9.6 (3.2)	.595
PUF total score (0-33)	18.4 (4.1)	16.7 (5.8)	.298	19.4 (5.2)	15.9 (5.7)	.168
PUF symptom score (0-21)	12.4 (2.5)	11.6 (3.9)	.480	12.1 (2.8)	10.2 (3.2)	.177
PUF problem score (0-12)	6.1 (1.9)	5.0 (2.3)	.163	7.3 (2.6)	5.7 (2.8)	.203
Urgency score: Q8a in PUF (0-3)	1.7 (0.7)	1.7 (0.7)	.986	1.9 (0.7)	1.6 (1.0)	.493

ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; PUF, Pelvic Pain and Urgency/Frequency; VAS, visual analog scale.
* $P < .05$.

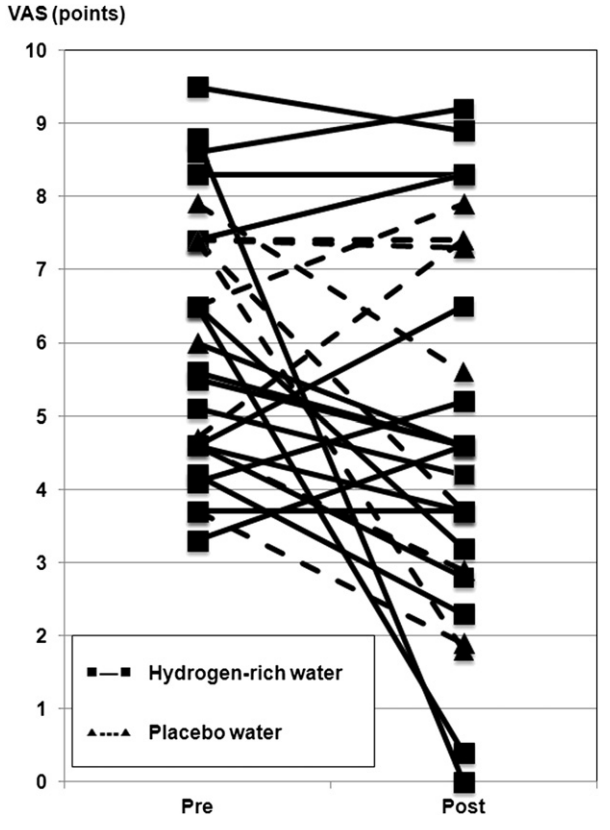

Figure 2. Change in visual analog scale bladder pain scores from baseline (Pre) to 8 weeks by treatment arm (Post).

hydrogen-rich water and placebo groups. However, the IC symptoms (especially bladder pain on the VAS) in some patients in the hydrogen-rich water group showed remarkable improvement.

Recently, increasing evidence has shown that ischemia, reperfusion, and the generation of free radicals are major etiologic factors in the progression of lower urinary tract symptoms.[16] We hypothesized that oxidative stress could be one of the causes of IC/PBS, because the disturbance of bladder blood flow has been suggested in IC/PBS. Irwin and Galloway[1] reported that the bladder is relatively ischemic during bladder filling in patients with IC compared with those without IC. Pontari et al[2] showed that bladder perfusion decreased and increased with bladder filling in patients with and without IC, respectively. Tamaki et al[3] showed that neovascularization in the IC bladder promoted by angiogenic growth factors has an important role in the pathogenesis of IC, inducing glomerulations during hydrodistension. Recently, hyperbaric oxygen therapy has been reported to be effective in patients with IC/PBS resistant to conventional treatment.[4,5] Hyperbaric oxygen treatment has clinical effects in different pathologic ischemic conditions, including impaired oxygen delivery or impaired oxygen metabolism.[17] Oxidative stress represents an imbalance between the production of reactive oxygen species and the activity of antioxidant defense systems.[18] Oxidative stress due to free radicals formed by reperfusion after bladder ischemia can cause bladder damage. Some studies have revealed that free radical-mediated tissue damage is also involved in the pathogenesis of the experimental cystitis animal model.[9,10] Previously, several trials were reported of L-arginine and quercetin that have a similar antioxidant mechanism.[9-25] L-Arginine supplementation is used to counteract the reduced production of nitric oxide. Nitric oxide is the oxidation product of L-arginine, a reaction catalyzed by nitric oxide synthase.[19] The decrease in nitric oxide synthase activity might play a role in the etiology of IC.[20] Cartledge et al[21] showed that oral L-arginine produced a statistically significant improvement in ICSI in patients with IC, but the effect was small. The effect of L-arginine might not be clinically significant, because no significant difference was seen between the responses to L-arginine and placebo.[21] In contrast, quercetin is a flavonoid molecule that is

ubiquitous in nature and functions as an antioxidant and anti-inflammatory agent, with little toxicity in vivo and in vitro.[22,23] The Cysta-Q complex (equivalent to 500 mg of quercetin twice daily) administered for 4 weeks to 20 patients in an open-label clinical trial improved IC/PBS.[24] Softgel CystoProtek (formulated with the natural GAG components chondroitin sulfate and sodium hyaluronate, together with the flavonoid quercetin; 6 capsules daily) administered for 6 months to 37 female patients with refractory IC in an open-label clinical trial significantly improved the ICSI and Interstitial Cystitis Problem Index scores and reduced the global assessment scale scores.[25] Thus, it seems that the dietary supplement with antioxidant mechanism have a possibility of treatment option for IC/PBS. In the present study, the supplementation with hydrogen-rich water was extremely effective in improving the bladder pain score in some patients. Increasing the intake of the hydrogen-rich water might have led to better results.

Several investigators have shown that hydrogen has potential as an antioxidant in preventive and therapeutic applications. Shirahata et al[26] reported that electrolyzed-reduced water, which has a high pH, high dissolved hydrogen, low dissolved oxygen, and extremely negative redox potential values, has the ability to scavenge reactive oxygen species and, therefore, protect deoxyribonucleic acid from oxidative damage. Recently, Kim and Kim[27] reported that administration of hydrogen water improved blood glucose control in animal models of insulin deficiency and insulin resistance. Kajiyama et al[14] reported that administration of hydrogen-rich water improved lipid and glucose metabolism in patients with type 2 diabetes. These findings led us to consider the possibility that hydrogen-rich water might be useful as a therapeutic supplement. However, it is not clear whether ingestion of hydrogen-rich water is able to provide hydrogen to the relevant bladder tissues. Also, the present study failed to show significant difference in each parameter between the hydrogen-rich water and placebo groups. According to the recommendation of conservative treatment in clinical guideline for IC,[10,11] dietary manipulation/diet therapy (recommendation grade b) by avoiding acidic beverages, coffee, tea, soda, spicy food, artificial sweeteners, and alcohol might be beneficial. We did not attempt to control comestibles and/or lifestyle differences, but instructed participants not to change their diet or lifestyle during the study period. The difference in comestibles and lifestyle among participants might have influenced the results of the present study. We speculated that enough fluid intake in the form of either hydrogen-rich water or placebo water might have contributed to stabilization of the urinary state and, therefore, led to significant improvement in the bladder pain score (question 4 on ICSI). The VAS bladder pain scores in 11% of the patients in the hydrogen-rich water group had markedly improved. However, it is not clear whether the dose chosen for the present study was adequate to provide a physiologic effect. On the basis of these findings, we would like to suggest that hydrogen-rich water might prevent bladder pain and other symptoms in patients with IC/PBS by providing protection against oxidative stress. However, because of the small sample size in our study, the results should be interpreted with caution. An appropriately designed, large-scale, prospective, clinical study is necessary to confirm the present findings.

CONCLUSION

To our knowledge, the present study is the first clinical trial of double-blind, placebo-controlled study of hydrogen-rich water supplementation in patients with IC/PBS. The effect of hydrogen-rich water was not significantly different from that of the placebo control in the present study, although the supplementation with hydrogen-rich water was extremely effective in relieving bladder pain in some cases. The results of the present study do not support the use of supplementation with hydrogen-rich water for treating patients with IC/PBS. An appropriately designed, large-scale, prospective clinical study would be advisable to confirm the present findings.

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