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

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Key Words: interstitial cystitis, painful bladder syndrome, questionnaires, supplementation, hydrogen-rich water
**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 or longer after bladder hydrodistension, total of interstitial cystitis symptom index (ICSI) of 7 or higher and bladder pain (Question 4 on ICSI) of 4 or higher. They were randomized by 2:1 ratio to receive hydrogen-rich water vs placebo water for 8 weeks. Symptoms were assessed using ICSI, interstitial cystitis problem index, the 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participants (29 female, 1 male, age 64.0 ± 14.8 years) were enrolled into the study and two cases (all females) were withdrawn from the study.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 placebo, although the supplementation with hydrogen-rich water was extremely effective in improving bladder pain score in 11% of the patients.

**Conclusions:** The results of the present study do not support the use of supplementation with hydrogen-rich water for treating patients with IC/PBS.
Introduction

Interstitial cystitis / painful bladder syndrome (IC/PBS) presents with a constellation of symptoms including bladder pain, frequency and urgency. Proposed etiology for the symptoms of IC/PBS includes bladder ischemia and reperfusion injury. Previous reports showed pathological findings of IC/PBS focusing on ischemia and a reduction in bladder capacity due to fibrosis of the bladder wall.\textsuperscript{1-3} Indeed, hyperbaric oxygen therapy has been reported to be effective in patients with IC/PBS resistant to conventional treatments.\textsuperscript{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.\textsuperscript{6} Previous studies using an experimental cystitis animal model revealed that free radical-mediated tissue damage is also involved in the pathogenesis.\textsuperscript{7,8}

Recently, several investigators showed that hydrogen (H2) has potential as an antioxidant in preventive and therapeutic applications. Ohsawa et al reported that hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals.\textsuperscript{9} 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, there are no clinical data that 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.

Materials and Methods

Study Protocol

We recruited 30 patients at least 50 years old with IC/PBS, who fulfilled the diagnostic criteria for IC proposed by the clinical guideline for IC,\textsuperscript{10,11} and obtained prospective approval of the trial protocol, informed consent forms, and other relevant documents from the Public Health Research institutional review board (Tokyo, Japan). This study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. Written, informed consent was obtained from each patient. The study was registered at Japan Primary Registries Network (JPRN) (JPRN-UMIN000001253).

These patients were assessed using the O'Leary-Sant validated Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI),\textsuperscript{12} the Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale,\textsuperscript{13} visual analog scale (VAS) bladder pain scores, and a standard 3-day voiding diary. The primary outcome was a patient reported symptoms improvement evaluated after treatment. The inclusion criteria were stable in the history of IC/PBS symptoms 12 weeks or longer after bladder hydrodistension, total of ICSI 7 or higher and bladder pain (Q4 on ICSI) 4 or higher. The exclusion criteria were as follows: more than 200 mL of an average voided volume; urinary tract infection and vaginitis; urolithiasis; significant
hepatic, renal, cardiac or cerebrospinal disease; neurologic bladder (e.g. spinal cord injury, Parkinson disease); surgery and/or irradiation to the pelvis; use of any dietary and/or antioxidant supplement, initiation of bladder training in the preceding 12 weeks before the start of the study; initiation or discontinuation or change of the dose of the following drugs within 4 weeks after the registration, (a) antidepressant, (b) anticholinergic drug, (c) antihistaminergic drug, (d) any drugs for lower urinary tract symptoms, (e) steroid.

All participants were randomized in a 2:1 ratio to receive the hydrogen-rich water 3 packs (1 pack 200 mL) per day (20 patients) or the placebo water 3 packs (1 pack 200 mL) per day (10 patients) for 8 weeks (Figure 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 comestibles or lifestyle during this study period.

Hydrogen-rich water was produced by the following processes \(14,15\): passage through (1) a reverse osmosis/ultrafiltration unit, (2) an ion-exchange resin, and (3) 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 ~ +700 mV, mineral water: about +250 mV, natural water: +200 ~
The constitutions of hydrogen-rich water are as follows: energy 0 calorie; protein, lipid, carbohydrate 0 g; total hardness 0 mg/L; mineral (Na, K, Mg, Ca) 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 the placebo water were obtained from I'rom Pharmaceutical Co. Ltd. (Tokyo, Japan).

From the data of the published clinical trial, the percentage of success cases was presumed to be about 65% to 75% for the hydrogen-rich water group and about 10% to 15% for the placebo group. A sample size ratio of the hydrogen-rich water group to the placebo group was set 2:1 on account of the paucity of study patients and eventual difficulty in recruiting patients for this study. Twenty-four 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 are 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 rates for these groups are 70% and 10%, respectively. Therefore, the planned number of subjects was set to be 30 in total, 20 for the hydrogen-rich water group and 10 for the placebo group.

**Statistical Analysis**

Baseline demographic characteristics as well as symptoms measures were summarized and compared between both groups using descriptive statistics.
including mean, standard deviation (SD). The efficacy parameters were compared between both groups using one-way ANOVA. All analyses were performed using SAS 9.1.3 (SAS Institute Inc, Cary, NC). Differences were considered to be significant at a $P$-value < 0.05.

**Results**

30 patients were recruited between April 2008 and July 2009. Two cases (all females) were withdrawn from the study. The reason for withdrawal was self-judgment in one case and concomitant use of other antioxidant supplement in another case. Twenty-eight patients (27 females and one male) completed the full 8 weeks of treatment (**Table**), and their median age was 65 years old. All baseline measures were comparable between the two groups.

The score of bladder pain (Q4 on ICSI) was significantly reduced in both groups (**Table**). However, the effect of hydrogen-rich water on the sore of bladder pain (Q4 on ICSI) was not significantly different from the placebo control. Overall treatment outcome was not statistically different between the two groups. The change of the VAS in each patient was presented in **figure 2**. The VAS bladder pain scores in two cases (11%) of hydrogen-rich water group showed remarkable improvement (VAS < 1 point). All participants reported no adverse event.

**Discussion**

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 hydrogen-rich water and placebo group. However, IC symptoms (especially VAS bladder pain) in some cases of hydrogen-rich water group showed remarkable improvement.

Recently, there is increasing evidence that ischemia, reperfusion, and the generation of free radicals are major etiological factors in the progression of lower urinary tract symptoms.\(^\text{16}\) 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 reported that the bladder is relatively ischemic during bladder filling in patients with IC compared to those without IC.\(^\text{1}\) Pontari et al. showed that bladder perfusion decreased and increased with bladder filling in patients with and without IC, respectively.\(^\text{2}\) Tamaki et al showed that neovascularization in IC bladder promoted by angiogenic growth factors has an important role in the pathogenesis of IC, inducing glomerulations during hydrodistension.\(^\text{3}\) Recently, Hyperbaric oxygen therapy has been reported to be effective in patients with IC/PBS resistant to conventional treatments.\(^\text{4,5}\) Hyperbaric oxygen treatment has clinical effects in different pathological ischemic conditions, eg impaired oxygen delivery or impaired oxygen metabolism.\(^\text{17}\) Oxidative stress represents an imbalance between the production of reactive oxygen species (ROS) and the activity of antioxidant defense systems.\(^\text{18}\) Oxidative stress due to free radicals that are formed by reperfusion after bladder ischemia, can cause bladder damage. In fact, some studies revealed that free radical-mediated tissue damage
is also involved in the pathogenesis of the experimental cystitis animal model.\textsuperscript{9,10} Previously, several trials were reported of L-arginine and quercetin that have similar anti-oxidant mechanism.\textsuperscript{9-25} L-arginine supplementation is used to counteract reduced production of nitric oxide (NO). NO is the oxidation product of L-arginine, a reaction catalyzed by NO synthase (NOS).\textsuperscript{19} The decrease in NOS activity might play a role in the aetiology of IC.\textsuperscript{20} Cartledge et al 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 may not be clinically significant as there was no significant difference between the responses to Larginine and placebo.\textsuperscript{21} On the other hand, Quercetin is a flavonoid molecule that is ubiquitous in nature and functions as an anti-oxidant and anti-inflammatory agent with little toxicity in vivo and in vitro.\textsuperscript{22,23} The Cysta-Q complex (equivalent to 500 mg of quercetin twice daily) administered for 4 weeks to 20 patients in an openlabel clinical trial improved IC/PBS.\textsuperscript{24} Softgel CystoProtek (formulated with the natural GAG components chondroitin sulfate and sodium hyaluronate, together with the flavonoid quercetin; six capsules per day) administered for 6 months to 37 female refractory IC patients in an open-label clinical trial was significantly improved ICSI and ICPI, and reduced global assessment scale.\textsuperscript{25} Thus, it seems that the dietary supplement with anti-oxidant 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 bladder pain score in some patients. Increasing the intake of the hydrogen-rich water may have led to
better results.

Several investigators have shown that hydrogen (H2) has potential as an antioxidant in preventive and therapeutic applications. Shirahata et al 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 ROS and therefore protect DNA from oxidative damage.26 Recently, Kim and Kim reported that administration of hydrogen water improved blood glucose control in animal models of insulin deficiency and insulin resistance.27 And, Kajiyama reported that administration of hydrogen-rich water improved lipid and glucose metabolism in patients with type 2 diabetes.14 These findings led us to consider the possibility that hydrogen-rich water may be useful as a therapeutic supplement. However, it is not clear if ingestion of hydrogen-rich water is able to provide hydrogen to the relevant bladder tissues. And, the present study failed to show significant difference in each parameter between hydrogen-rich water and placebo group. According to the recommendation of conservative treatment in clinical guideline for IC,10,11 dietary manipulation/diet therapy (grade of recommendation: b) by avoiding acidic beverages, coffee, tea, soda, spicy food, artificial sweetener and alcohol may be beneficial. We did not attempt to control comestibles and/or lifestyle differences, but instructed participants not to change comestibles or lifestyle during the study period. The difference in comestibles and lifestyle among participants may have influenced the results of the present study. We speculate that enough amount of fluid intake in either form of hydrogen-rich
water or placebo water might have contributed to stabilization of a urinary state, and therefore led to significant improvement of bladder pain score (Q4 on ICSI). Interestingly, VAS bladder pain scores in 11% of the patients of hydrogen-rich water group was markedly improved. However, it is not clear if the dose chosen for this study is adequate to provide a physiologic effect. Based on these findings, we would like to suggest that hydrogen-rich water may 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 this study, the results should be interpreted with caution. An appropriately designed, large-scale, prospective clinical study is necessary to confirm the present findings.

Conclusions

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 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.
References


scavenges active oxygen species and protects DNA from oxidative damage.


**Figure legends**

**Figure 1.** Study design with intervention schedule.

**Figure 2.** Change in the VAS bladder pain scores from baseline (Pre) to 8 weeks by treatment arm (Post).

**Table.** A summary of the measured variables at baseline (Pre) and after 8 weeks (Post) of hydrogen-rich water or placebo.
Figure 2

VAS (points)
<table>
<thead>
<tr>
<th>Mean (SD) variable</th>
<th>Hydrogen-rich water</th>
<th>Placebo water</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects randomized (M/F)</td>
<td>18 (0/18)</td>
<td>10 (1/9)</td>
</tr>
<tr>
<td>Age</td>
<td>65.2 (7.9)</td>
<td>64.5 (4.5)</td>
</tr>
<tr>
<td>VAS (0-10)</td>
<td>6.0 (1.9)</td>
<td>6.3 (1.5)</td>
</tr>
<tr>
<td>24-hr voiding frequency</td>
<td>13.0 (3.9)</td>
<td>12.5 (4.2)</td>
</tr>
<tr>
<td>Voiding volume</td>
<td>124.0 (36.4)</td>
<td>160.6 (48.7)</td>
</tr>
<tr>
<td>ICSI (0-20)</td>
<td>13.2 (3.3)</td>
<td>11.2 (3.8)</td>
</tr>
<tr>
<td>Pain score: Q4 in ICSI (0-5)</td>
<td>4.3 (0.5)</td>
<td>4.4 (0.5)</td>
</tr>
<tr>
<td>ICPI (0-12)</td>
<td>10.1 (3.3)</td>
<td>9.6 (3.2)</td>
</tr>
<tr>
<td>PUF total score (0-33)</td>
<td>18.4 (4.1)</td>
<td>15.9 (5.7)</td>
</tr>
<tr>
<td>PUF symptom score (0-21)</td>
<td>12.4 (2.5)</td>
<td>10.2 (3.2)</td>
</tr>
<tr>
<td>PUF problem score (0-12)</td>
<td>6.1 (1.9)</td>
<td>5.7 (2.8)</td>
</tr>
<tr>
<td>Urgency score: Q8a in PUF (0-3)</td>
<td>1.7 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
</tbody>
</table>

*; P<0.05.