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Evaluation of prostaglandin E2 and E-series prostaglandin receptor in patients with interstitial cystitis.

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TITLE PAGE**Prostaglandin E2 and E-series prostaglandin 1 and 2 receptor are involved in pathophysiology of ulcer-type interstitial cystitis/bladder pain syndrome**

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Runninghead: Involvement of prostaglandin E2 in interstitial cystitis

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ABSTRACT (250 words)

Purpose: To examine the precise role of prostaglandin E2 (PGE2) and E-series prostaglandin (EP) receptor in the pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS).

Materials and Methods: Twenty female patients with IC/BPS (11 ulcer-type and 9 non ulcer-type), 9 female controls with other urological diseases who needed cystoscopic procedure, and 10 normal female volunteers were enrolled. O'Leary-Sant Score (OSS) for symptoms and problems and voluntary urine for PGE2 analysis were obtained from all objectives. Under anesthesia, the bladder was distended by saline in a stepwise fashion (from 100 ml to maximum capacity) in patients with IC/BPS, and the infused saline was retrieved each time for PGE2 analysis. We also measured PGE2 and expression of EP receptors mRNA in bladder biopsy tissue in patients with IC/BPS.

Results: Symptoms and problems index in patients with ulcer-type was significantly higher than those with non ulcer-type. Urinary PGE2 in patients with ulcer-type was significantly higher than those with non ulcer-type and normal volunteers. PGE2 level in retrieved saline in patients with ulcer-type increased depending on infusion volume, but not in those with non ulcer-type. PGE2 content in bladder biopsy tissue was significantly higher in patients with ulcer-type than controls. In patients with ulcer-type, expression of EP1 and EP2 mRNA was significantly higher than controls.

Conclusions: Overproduction of PGE2 in the bladder seems to play a pathophysiological role in patients with ulcer-type IC/BPS via EP1 and EP2 receptors. Localized blockade of the action of PGE2 may lead to relieving symptoms in patients with ulcer-type IC/BPS.

TEXT

Interstitial cystitis/bladder pain syndrome (IC/BPS), non-specific inflammatory disease of the bladder, presents with a constellation of symptoms including urinary frequency, urgency and bladder pain. IC/BPS has 2 distinct subtypes based on cystoscopic evaluation. One is ulcer-type and another is non ulcer-type. Differences in age, bladder capacity, coexisting conditions, and responses to treatment have been noted between the subtypes.^{1,2} However, it is still unclear whether ulcer-type and non ulcer-type IC/BPS arise from two different reactions to a similar inciting factor or are different conditions from the outset.

Prostaglandins are synthesized from arachidonic acid via the cyclooxygenase (COX) pathway in response to various physiological and pathological stimuli. Among them, prostaglandin E2 (PGE2), one of naturally occurring prostanoids, is known to be associated with fever, inflammation, pain, blood circulation or gastric mucosal protection.³ Actions of PGE2 are mediated through activation of E-series prostaglandin (EP) receptor subtypes EP1, EP2, EP3, and EP4.³

Intravesical administration of PGE2 stimulated reflex micturition in human and rats, while administration of EP1 receptor antagonist improved bladder storage function in rats.^{4,6} These studies indicated the involvement of PGE2 via EP1 receptor in urinary frequency. There is a report that intravenous administration of EP1 antagonist relieved bladder pain in cystitis model rats.⁷ However, there have been few studies that investigated the pathophysiological role of PGE2 in patients with IC/BPS. To our knowledge, no single study has ever investigated the involvement of PGE2 and EP receptors in different subtypes of IC/BPS. Therefore the aim of this study was to examine the precise role of PGE2 and EP receptors in the pathophysiology of IC/BPS and its subtypes.

MATERIALS AND METHODS

This prospective pilot study was approved by Asahikawa Medical University Ethical Committee. Samples from patients were taken in Asahikawa Medical University Hospital (AMUH) and Hokkaido Memorial Hospital (HMH), and were examined in Minase Research Institute.

Study patients were female patients who had characteristic symptoms such as bladder pain or discomfort and were resistant to treatment for other urological, gynecological and intestinal diseases. They were finally diagnosed as IC/BPS based on cystoscopic findings including Hunner lesions or glomerulations. Patients with and without Hunner lesion were defined as ulcer-type and non ulcer-type IC/BPS, respectively. Female control patients with other urological disease who needed cystoscopic procedure and normal female volunteers were also enrolled in this study. Both control patients and normal volunteers had no bladder pain and no lower urinary tract symptoms (LUTS) requiring treatment. Written informed consent was obtained from each subject. O'Leary-Sant Score (OSS) for symptoms and problems, 2- or 3-day frequency volume chart (FVC), and voluntary voided urine were obtained from all subjects including patients with IC/BPS, controls and normal volunteers. Number of bladder pain per day were also estimated by FVC.

In patients with IC/BPS and controls, samples were taken by cystoscopic procedure under general or spinal anesthesia. In patients with IC/BPS, the bladder was distended in a stepwise fashion with a drip infusion of saline. Saline bottles were placed at 80cm height from the symphysis pubis. First, cystoscope was inserted and the bladder was emptied. Then 100ml of saline was infused into the bladder as first step and maintained for 5 minutes. All of the infused

saline was retrieved and sampled. Next, 200ml of saline was infused, maintained for 5 minutes, retrieved and sampled as second step. Third step and final step were similarly performed after 300ml saline infusion and maximum bladder capacity. Maximum bladder capacity was defined as bladder capacity at the time when saline infusion stopped after reaching 80cmH₂O. In control patients, infused saline only at first step (100ml infusion) was collected and sampled. In these 2 groups, bladder mucosa biopsy from 3 points of posterior bladder wall was finally performed. In patients with ulcer-type IC/BPS, bladder tissue from ulcer lesion was also additionally sampled.

Measurement of PGE2 concentration

After measuring the weight of mucosal tissue of the bladder, homogenization (300Hz/s, 3 min) was conducted with a mixer mill (MM300; Qiagen). The protein concentration in the supernatant was measured with the BCATM protein assay kit (Thermo Fisher Scientific). The urine and retrieved intravesical irrigation samples were centrifuged at 3000g for 10min at 4°C. The supernatant was separated into aliquots in 96 well plates and preserved in a freezer at -80°C. The level of PGE2 was measured by enzyme-linked immunosorbent assay (ELISA). To measure the amount of PGE2, a PGE2 EIA Kit-Monoclonal (Cayman Chemical) was used according to the methods described in the manual. The concentration was determined following absorbance measurement with a microreader (SpectraMax 250; Molecular Devices Japan). The total tissue PGE2 (pg/ml) was normalized by the weight of tissue and the ratio of PGE2/ the weight of tissue used as a normalized tissue PGE2 level. The total urinary PGE2 level (pg/ml) was normalized by the urinary creatinine and the ratio of PGE2/creatinine used as a normalized urinary PGE2 level.

Measurement of gene expression level by RT-PCR

Total RNA was extracted from the bladder mucosal biopsy specimens by the acid phenol-chloroform method using TRIzol reagent (Life Technologies) and RNeasy Mini Kit (Qiagen). With the extracted total RNA as a template, reverse transcription was conducted with High Capacity RNA-to-cDNA Kit and Corbett (Cosmobio) and cDNA was prepared. Measurement of expression for EP1-4, COX-1 and COX-2 mRNA was conducted by real time PCR method with ABI PRISM 7900HT Real-time PCR System and Power SYBR Green PCR Master Mix (Applied Biosystems). Validity of the primers specific to the genes measured (EP1-4, COX-1, COX-2 and GAPDH) was checked by performing PCR with the relevant primers, conducting agarose electrophoresis with the solution after reaction, and detecting the single-target amplified fragment.

Data were expressed as means \pm SD. For all statistical analyses, 2-group comparisons were performed with Wilcoxon matched-pairs signed-ranks test or Mann-Whitney test. P values of <0.05 were regarded as statistically significant.

RESULTS

We collected 20 female patients with IC/BPS (10 patients each from AMUH and HMH), and 11 and 9 of them were categorized as ulcer-type and non ulcer-type, respectively. We also collected 9 female control patients who needed cystoscopic procedure. The control patients underwent transurethral resection of small bladder tumor (5 patients), partial nephrectomy (3 patients) after placing ureteral catheter, and pyeloplasty (one patient) after retrograde pyelography. Eleven normal female volunteers were also enrolled. However, one of them was excluded because the number of daytime urinary frequency was more than 20 according to FVC,

and she was considered unsuitable as normal.

Symptoms and problems score of OSS in patients with ulcer-type IC/BPS were significantly higher than those with other 3 groups (Table 1). The number of daytime voids in ulcer-type IC/BPS was similar to that in those with non ulcer-type, but was significantly higher than controls and normal volunteers. The number of nighttime voids in ulcer-type and non ulcer-type was significantly higher than normal volunteers. Average and maximum voided volume in ulcer-type IC/BPS were significantly smaller than those with non ulcer-type, controls and normal volunteers. The mean number of bladder pain in patients with ulcer-type was significantly higher than those with other 3 groups.

Mean voluntary urine volume and urinary PGE2 in ulcer-type, non ulcer-type, controls and normal volunteers was 130ml, 210ml, 250ml, and 120ml, and 0.54ng/mgCre, 0.30ng/mgCre, 0.29ng/mgCre, and 0.26ng/mgCre, respectively (Table 1). Urinary PGE2 in ulcer-type was significantly higher than those with non ulcer type and normal volunteers.

Mean PGE2 in retrieved saline at first step bladder infusion (100ml) in ulcer-type, non ulcer-type and controls was 3.10ng/mgCre, 0.50ng/mgCre and 0.29ng/mgCre, respectively. PGE2 in retrieved saline at first step tended to be higher in ulcer-type than those with non ulcer-type ($P=0.09$) and controls ($P=0.07$) (Fig. 1). Mean actual infusion volume at maximum bladder capacity in patients with ulcer-type and non ulcer-type was 462ml and 688ml, respectively ($P=0.01$). All patients with IC/BPS could tolerate hydrodistention with more than 300ml under anesthesia and the minimum bladder volume at hydrodistention was 320ml. PGE2 at maximum capacity in patients with ulcer-type tended to be higher than those with non ulcer-type ($P=0.07$). PGE2 in retrieved saline in patients with ulcer-type increased in a volume-dependent manner, but not in those with non ulcer-type (Figure 2). PGE2 level in ulcer

lesion (19 to 1101pg/ml protein) and non ulcer lesion (12 to 547pg/ml protein) in bladder tissue from patients with ulcer-type was significantly higher than controls (0.1 to 151pg/ml protein) (Fig. 3). Expression of EP1, EP2 and COX2 mRNA was significantly higher in ulcer-type IC/BPS than controls (Fig. 4).

DISCUSSION

The present study showed that the patients with ulcer-type IC/BPS had different characteristics from those with non ulcer-type in terms of PGE2 level in voluntary voided urine and the increase of PGE2 production during bladder distention. PGE2 in ulcer lesion as well as in non ulcer lesion of the bladder tissue from patients with ulcer-type IC/PBS was significantly higher than controls. Furthermore, expression of EP1 and EP2 receptor mRNA in the bladder was significantly higher only in patients with ulcer-type IC/BPS than controls. These data suggest that overproduction of PGE2 during bladder filling play a significant pathophysiological role via EP1 and EP2 receptors in patients with ulcer-type IC/BPS.

There are some studies that examined urinary PGE2 in patients with IC/BPS.^{8,9} They showed that PGE2 in voluntary urine was not significantly different among patients with overactive bladder (OAB), IC/BPS and controls. However, they did not divide the patients with IC/BPS into ulcer-type and non ulcer-type. Because urinary PGE2 is secreted not only from the bladder but from the kidney, urinary PGE2 does not necessarily reflect the production of PGE2 in the bladder per se. To overcome these concerns, we divided the patients with IC/BPS into ulcer-type and non ulcer-type, and examined PGE2 level in retrieved saline from the bladder after 5 min distention of bladder in a stepwise fashion. Urinary PGE2 in non ulcer-type IC/BPS was similar to that in controls and normal volunteers as shown in the previous study. However,

in ulcer-type IC/BPS urinary PGE2 was significantly higher than that in non ulcer-type or normal controls. Although it is a controversial issue whether urinary PGE2 is a useful biomarker for patients with IC/BPS, urinary PGE2 seems to have such a potential at least for patients with ulcer-type IC/BPS. During the stepwise bladder distention, PGE2 secreted by the kidney could be ignored and PGE2 in retrieved saline could be considered to express PGE2 secreted only from the bladder. In ulcer-type IC/BPS, PGE2 level in retrieved saline even at first step bladder infusion (100ml) tended to be higher than that in non ulcer-type or controls. Furthermore PGE2 level in retrieved saline in patients with ulcer-type IC/BPS increased in a volume-dependent manner in contrast to patients with non ulcer-type. PGE2 in retrieved saline after maximum bladder distention tended to be higher in ulcer-type despite a significantly smaller maximum bladder capacity compared to those with non ulcer-type. When combined with severer bladder pain and lower voided volume in ulcer-type, it is assumed that PGE2 secreted from the bladder might trigger pain that is associated with bladder filling.

PGE2 is generated locally in both detrusor muscle and mucosa and its synthesis is initiated by various physiological stimuli such as stretch of the detrusor muscle.¹⁰ In the present study, PGE2 increased in a volume-dependent manner after stretch of the detrusor muscle by bladder distention in ulcer type IC/BPS but not in non ulcer-type. Although the stepwise bladder distention was not performed in controls, it seems that PGE2 level in the bladder remains at a low level during bladder distention in usual circumstances except ulcer-type IC/BPS. PGE2 content in both ulcer and non ulcer lesion in bladder tissue from patients with ulcer-type was significantly higher than controls. Taken together, we believe that PGE2 is obviously involved in the pathophysiology of ulcer-type IC/BPS. Actions of PGE2 are mediated by specific receptors on cell membranes.³ The present study showed increased expression of EP1 and EP2

mRNA in the bladder tissue from patients with ulcer-type IC/BPS.

The role of EP receptors in lower urinary tract function has not been well established. The EP3 and EP4 receptors are widely distributed throughout the body. In contrast, the distribution of EP1 is restricted to several organs and EP2 is the least abundant among the EP receptors.³ EP1 receptor is known to play a major role in processing of pain. EP1-deficient mice exhibit reduced nociception, and intrathecal administration of EP1 antagonist reduces hyperalgesia.^{11,12} Systemic administration of EP1 antagonist attenuates esophageal hyperalgesia in human and bladder pain in cystitis model mice.^{7,13} Regarding EP1 receptor and bladder function, it is suggested that intravesical PGE2 promotes micturition reflex by stimulating C-fiber afferent nerves via EP1 receptor.^{14,15} These previous studies and the present study indicate that the action of PGE2 via EP1 receptor has an important role in the development of bladder pain and urinary frequency in ulcer-type IC/BPS.

EP2 receptor is expressed in the urothelium and muscle interstitial cells of guinea pig bladder.^{16,17} A previous study demonstrated that non-selective EP1/EP2 receptor antagonist decreased detrusor contraction in human isolated bladder.¹⁸ However, the role of EP2 receptor in bladder function remains to be clarified. To our knowledge, the present study is the first report showing an involvement of EP2 receptor in the pathophysiology of IC/BPS. EP2 receptor has been reported to regulate tumor angiogenesis through the effect on endothelial cell motility and survival in the field of cancer research.^{19,20} Possible involvement of EP2 receptor in progression and angiogenesis of prostate cancer has been suggested.^{20,21} Also in IC/BPS, angiogenic factors were shown to be involved in the inflammatory process to induce symptoms such as bladder pain.²² Angiogenesis is an important mechanism for inflammatory reactions and subsequent repair processes. New capillary formation or glomerulation of the bladder is considered to be an

important feature of IC/BPS. Some studies suggest that PGE2 might promote wound healing and play a cytoprotective role through angiogenic factors in gastrointestinal or esophageal damage.^{23,24} Rastogi et al demonstrated the loss of PGE2 release from immortalized urothelial cells obtained from IC/BPS patient bladders, suggesting a cytoprotective role of PGE2 in IC/BPS.²⁵ It is speculated that the action of PGE2 via EP2 receptor might have an important role in angiogenesis and healing from bladder damage in ulcer-type IC/BPS.

Limitations of the present study include a small sample size and a lack of data on PGE2 in controls after stepwise bladder distention. The results of the present study should be verified by recruiting more number of patients with IC/BPS, especially those with ulcer-type. Another limitation is inclusion of patients with bladder tumor as controls. Although the activity of bladder cancer was also related to elevation of urinary PGE2,²⁶ urinary PGE2 in ulcer-type IC/BPS was higher even compared to patients with bladder tumor. Despite these limitations, we believe that the present study provide valuable information on the involvement of PGE2 via EP1 and EP2 receptors in the pathophysiology of ulcer-type IC/BPS.

CONCLUSIONS

Overproduction of PGE2 in the bladder seems to play a significant role in the pathophysiology of ulcer-type IC/BPS via EP1 and EP2 receptors. Localized blockade of the action of PGE2 may lead to relieving symptoms in patients with ulcer-type IC/BPS.

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Figure legends

Figure 1: PGE2 level in retrieved saline after first step bladder infusion (100 ml): PGE2 in ulcer-type tended to be higher than non ulcer-type ($P=0.09$) and controls ($P=0.07$).

Figure 2: PGE2 level in retrieved saline after stepwise bladder distention (100, 200, 300 ml and maximum bladder capacity) in patients with IC/BPS.: There was a significant difference in maximum bladder capacity between patients with ulcer-type (462 ± 99 ml) and non ulcer-type (688 ± 205 ml). PGE2 level in retrieved saline after stepwise bladder distention increased in a volume-dependent manner in patients with ulcer-type IC/BPS (\blacktriangle). PGE2 level at maximum capacity in patients with ulcer-type tended to be higher than those with non ulcer-type ($P=0.07$).

Figure 3: PGE2 content in bladder biopsy tissue: PGE2 in both ulcer lesion and non ulcer lesion in bladder tissue of ulcer-type IC/BPS was significantly higher than controls.

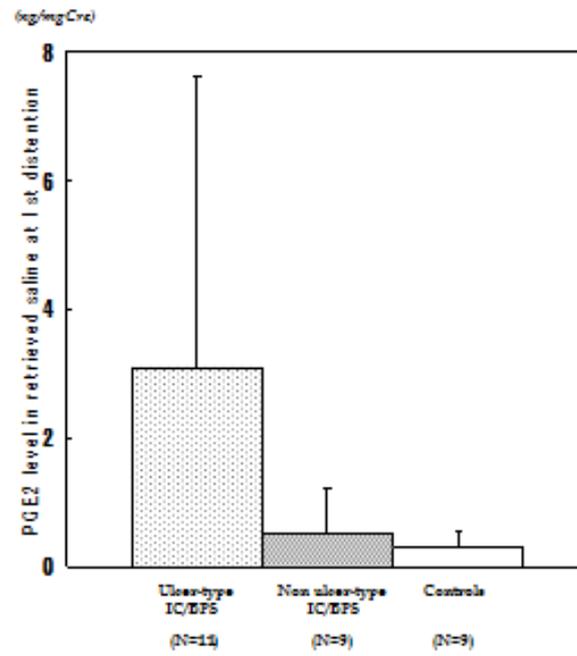
Figure 4: Expression of EP receptors and COX mRNA: Compared to controls, mRNA expression of EP1 (A), EP2 (B) and COX2 (F) was significantly higher in patients with ulcer-type IC/BPS.

Table 1 Characteristics in patients with IC/BPS, controls and normal volunteers

	Ulcer-type IC/BPS	Non ulcer-type IC/BPS	Controls	Normal volunteers
No.	11	9	9	10
Age (yrs)	66±12	60±15	68±11	60±6
O'Leary-Sartt Score				
Symptoms score	14.9±2.7	10.2±5.8 *	3.7±3.2 *†	1.9±1.7 *†
Problems score	13.7±1.6	9.6±5.3 *	2.8±4.0 *†	0.3±0.5 *†
Frequency volume chart				
24-hour urine volume (ml)	1500±700	1800±600	2100±800	1500±500
Number of daytime voids	11.6±3.8	9.9±3.6	7.1±1.5 *	6.3±1.3 *†
Number of nighttime voids	2.1±0.8	2.2±2.0	1.6±0.9	0.5±0.7 *†
Average voided volume (ml)	110±50	170±80 *	260±120 *	220±40 *
Maximum voided volume (ml)	170±60	320±160 *	400±190 *	380±80 *
Number of bladder pain (per day)	9.0±4.5	2.8±2.6 *	0 *†	0 *†
Urinary PGE2 (ng/mgCre)	0.54±0.34	0.30±0.16 *	0.29±0.22	0.26±0.15 *

* P<0.05 versus ulcer-type IC † P<0.05 versus non ulcer-type IC

Figure 1



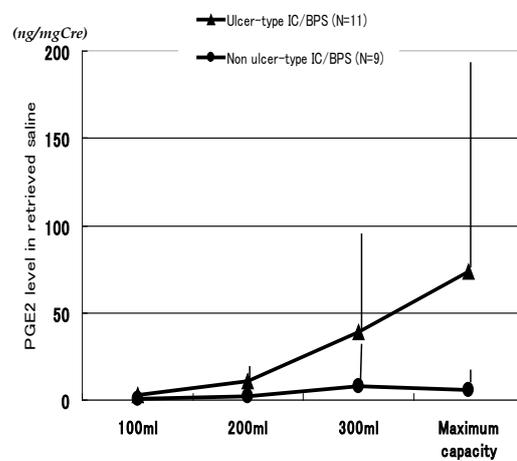


Figure 3

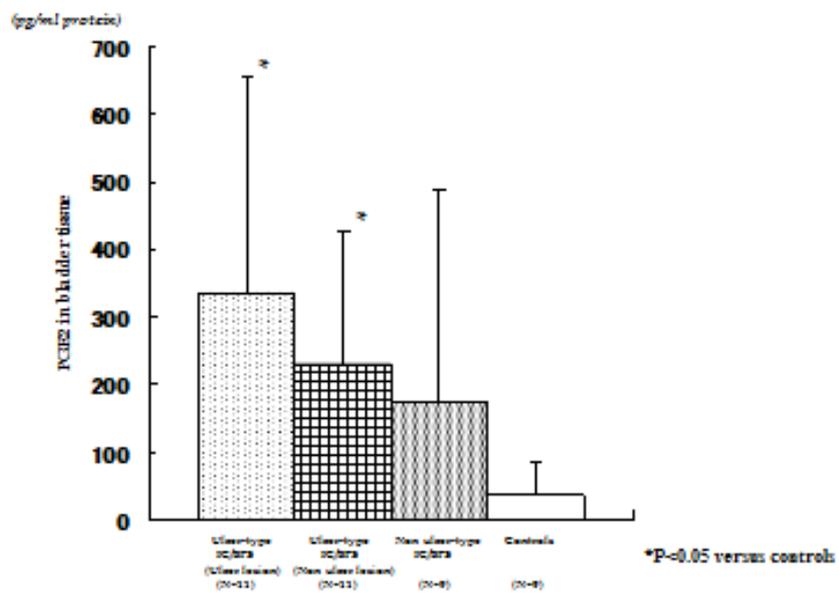


Figure 4

