POSSIBLE INVOLVEMENT OF PROSTAGLANDIN E2 IN THE PATHOPHYSIOLOGY OF INTERSTITIAL CYSTITIS

Hypothesis / aims of study
Interstitial cystitis (IC), non-specific inflammatory disease of the bladder, presents with a constellation of symptoms including urinary frequency, urgency and bladder pain. Prostaglandin E2 (PGE2) is known to be associated with inflammation or pain. There have been controversies about the involvement of PGE2 in the pathophysiology of IC. Urinary PGE2 in patients with IC was elevated in some reports, but not in other reports. Therefore the aim of this study was to examine the precise role of PGE2 in the pathophysiology of IC.

Study design, materials and methods
Study patients were those with IC who were diagnosed based on the presence of characteristic symptoms such as bladder pain or discomfort and cystoscopic findings including Hunner lesions or glomerulations. Patients recorded O'Leary-Sant Interstitial Cystitis Score/Problem Index and frequency volume chart (FVC). Voluntary urine was obtained from each patient and PGE2 level in urine was measured by enzyme immunoassay (EIA). Under anesthesia, the bladder was distented in a stepwise fashion (around 100ml as 1st step, around 200ml as 2nd, around 300ml as 3rd and maximum capacity as final). Irrigation solution at each step was collected and perfusate PGE2 level was measured. Then bladder biopsy was performed and PGE2 content in bladder tissue was measured by EIA after homogenization.

Patients with other urological disease who needed cystoscopic procedure and normal volunteers were set up as study controls. In control patients with other urological disease, irrigation solution only at 1st step was collected and bladder biopsy was also performed. This study was approved by institutional review board.

Results
Eighteen IC patients, 6 control patients (renal tumor in 3, isolated bladder tumor in 2 and ureteropelvic junction obstruction in 1) and 11 normal volunteers were enrolled in this study. However, one control patient and one normal volunteer were excluded from the analysis because of urinary frequency or bladder pain judged by FVC or symptom score. Symptom index and problem index of IC patients (12.8±4.5 and 12.1±3.7) were significantly higher than those of control patients (5.3±7.3 and 3.7±5.8) and normal volunteers (2.9±3.7 and 1.1±2.7). In IC patients, the number of daytime and nighttime voids was greater and average and maximum voided volume was smaller compared to normal volunteers.

Urinary PGE2 in IC patients, control patients and normal volunteers were 0.41±0.27, 0.31±0.20 and 0.26±0.15 ng/mg creatinine, respectively. Urinary PGE2 in IC patients tended to be higher than that in normal volunteers (P=0.08). Regarding PGE2 level in irrigation solution during bladder distention in a stepwise fashion, perfusate PGE2 level in IC patients increased in accordance with infusion volume (Figure 1). Perfusate PGE2 level at 1st step infusion (around 100 ml) was significantly higher in IC patients (2.14±3.70 ng/mg creatinine at mean volume of 112 ml) than that in control patients (0.27±0.33 ng/mg creatinine at mean volume of 144 ml) (Figure 1). PGE2 content in bladder tissue in IC patients was significantly greater than that in control patients (221±260 pg/mg versus 70±50 pg/mg, P<0.05) (Figure 2).

Interpretation of results
While urinary PGE2 level is influenced by not only regional secretion of PGE2 from the bladder but also PGE2 eliminated by renal excretion, perfusate PGE2 level is thought to reflect PGE2 almost entirely excreted from the bladder. Because perfusate PGE2 level and PGE2 content in bladder tissue were higher in IC patients than those in control patients, it seems likely that PGE2 is involved in the pathophysiology of IC. The increase in perfusate PGE2 level in accordance with infusion volume implies that PGE2 acts as causative factor of bladder pain associated with bladder filling in IC patients.

Concluding message
Overproduction of PGE2 in the bladder seems to have a significant role in the pathophysiology of IC. Blockade of the action of PGE2 may lead to relieving symptoms in IC patients.
Figure 1

Perfusate PGE2 level at 1st step distention

Control patients IC patients

Infusion volume 144±38 ml 112±27 ml

Perfusate PGE2 level in IC patients

1st step 2nd step 3rd step Final step

Infusion volume 112±27 ml 209±30 ml 307±31 ml 576±196 ml

P=0.09 P=0.07 P=0.03 P=0.07 P=0.05

Figure 2

PGE2 content in bladder tissue

Control patients IC patients

P<0.05

Disclosures

Funding: no Clinical Trial: No Subjects: HUMAN Ethics Committee: The ethical committee of Asahikawa Medical University Helsinki: Yes Informed Consent: Yes