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The role of prostaglandin E2 in children with lower urinary tract dysfunction

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ABSTRACT

Objectives: The objective of the study is to examine the effect of prostaglandin E2 (PGE2) in the etiology of children with lower urinary tract dysfunction (LUTD), we formed this prospective study. The role of PGE2 in children with LUTD has not been reported yet.

Materials and Methods: Between October 2010 and April 2012, a total of 91 children between 5 and 15 years age enrolled in this study. A total of 11 children were excluded from the study for active urinary tract infection. About 48 children from a nursery and a primary school were chosen as a control group. Nearly 32 of the children had LUTD.

Results: The median PGE2 was not statistically significant different between LUTD and control group ($P = 0.93$), but the PGE2 level was higher in control group. Although there was no statistically significant difference between genders and between the patients with overactive bladder (OAB) symptoms, postvoid residual (PVR), enuresis, and opposites, or according to voiding patterns; the PGE2 level was higher in the patients with OAB symptoms, enuresis, and tower voiding pattern. On the other hand, the PGE2 level was lower in the patients with PVR.

Conclusions: PGE2 may not be an etiological factor in children with LUTD. Higher PGE2 levels in control group and lower PGE2 levels in patients with PVR offers further examinations to understand the PGE2 effect.

Key words: Children, dysfunction, etiology, lower urinary tract, prostaglandin E2

INTRODUCTION

Children with significant lower urinary tract symptoms without associated neurological or anatomical abnormalities are considered to have non-neurogenic lower urinary tract dysfunction (LUTD). It represents a disturbance of the lower urinary tract dynamics affecting urine storage or emptying and can simply be categorized into two types in children. Problems related to the filling (storage) phase include overactive bladder (OAB) syndrome, functional urinary incontinence, and giggle incontinence. Disturbances of the emptying (voiding) phase include dysfunctional voiding, lazy bladder syndrome, Hinman syndrome, and post-void dribbling.[1,2]

Taking history, thorough physical examination, filling out a questionnaire (LUTD symptom score [LUTDSS]), and recording bladder and intestine diary, and sometimes urodynamic study are required to achieve correct diagnosis.[3] Within the confidence interval of 96.2%, the patients with LUTDSS threshold scores of 8.5 or greater had voiding abnormalities, with a sensitivity of 90% and a specificity of 90%.[4]

PGs play an important role in lower urinary tract function. PG synthesis in the bladder is enhanced by stimuli such as stretching of the detrusor muscle, injuries of uroepithelium, and inflammation.[5] These stimuli induce increases in prostaglandin E2 (PGE2), prostaglandin PGF2-alpha (PGF2-alpha), and prostacyclin (PGI2) concentrations.

In the urinary bladder, PGE2 is a cytoprotective eicosanoid which inhibits apoptosis of epithelial.[6] Intravesical instillation with PGE2 induces detrusor contraction, while topical application of PGE2 to the urethra causes urethral relaxation in rats.[7] In addition, PGE2 is associated with the activation of C-fibers in the bladder, and overexpression of PGE2 stimulates the micturition reflex through the activation of these fibers in a rat model.[8] In this way, they decrease the thresholds of the stimuli necessary to trigger bladder contraction through activation of these nerves.[9] We assumed that increased PGE2 level in the bladder is likely to be associated with long-standing storage dysfunction and bladder symptoms in children and alterations in its levels can be detected in the urine.

There have been some studies reporting the role of PGs in prostatitis, urogenital malignancies, OAB, and bladder outlet obstruction.[10-16] To the best of our knowledge, the role of PGE2 in children with LUTD has not been reported yet. This is the first study focusing on the role of PGE2 with the aim of identifying the possible diagnostic value of this substance in the evaluation of the children with LUTD.

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MATERIALS AND METHODS

This study was approved by the Ethical Committee of our university and followed the institution's Review Board of Human Subject Guidelines.

Between October 2010 and April 2012, a total of 91 children enrolled in this prospective, blinded, and controlled study after obtaining the consents from the parents. About 48 children from a nursery and a primary school who apply for routine body height and weight control and not suffer from any urinary symptoms were chosen as a control group.

For patient group, a thorough history was taken including diet, voiding habit, defecation habit, psychosocial problems, and constitutional urologic abnormalities. All patients underwent a complete physical examination including a neurourologic examination focusing on anal tone and voluntary control of the anal sphincter, the bulbocavernosus reflex, lower limb reflexes, and perineal sensitivity. After the physical examination, all patients were evaluated by urinalysis, urine culture, serum urea and creatinine, lumbosacral spine radiography, and urinary ultrasonography. Parents of the children were asked to use 3-day bladder diary for the recordings of voiding and bladder-related symptoms at their home under normal conditions. They were also asked to fill out the LUTD symptom score (LUTDSS).[4]

The uroflowmetry combined with perineal electromyographies (Uroflow-EMG) were performed by the same trained nurse with same uroflowmeter (MMS 5000) at our urodynamic laboratory. Before the Uroflow-EMG, bladder ultrasonography is used to ensure adequate volume and exclude patients with overdistention of the bladder. After Uroflow-EMG had been done, PVR was measured with BladderScan BVI 6100 (diagnostic ultrasound, Bothell, WA, USA). The UF-EMG was done two times and independently reviewed and determined under the agreement of two urologists at our center. The UF-EMG curves were classified as bell, staccato, tower, plateau, and interrupted.[15] Staccato voiding pattern was defined as continuous but fluctuating flow curve and larger than the square root of the maximum flow rate. Tower voiding pattern was defined as a sudden appearing curve like a tower and interrupted voiding pattern was defined as intermittent curves with stops and beginnings. Plateau voiding pattern was a low-amplitude and rather even flow curve.

The inclusion criteria for LUTD group were children between 5 and 15 years, LUTDSS ≥9 and/or abnormal voiding pattern and/or PVR >20 mL, and abnormal symptoms in bladder diary.[16] The exclusion criteria were any neurologic, constitutional, or infectious urologic abnormality detected by physical examination or laboratory tests. The children with active urinary tract infections were excluded from the study.

Collection of Urine Samples and Storage

5 ml first morning urine samples were taken from the study and control groups. Samples were placed and preserved in a refrigerator at −80˚C temperature till the end of study. At the same time, 3 mL of urine was taken to measure the urinary creatinine (Cr) level.

PGE2 Measurement

Urine PGE2 levels were measured blindly by a ELISA kit (Cayman Chemical Company, Michigan, USA) according to manufacturer's guide. Samples were diluted to 1:2. On plates for ELISA assay, first column's 1st and 2nd rows were designed as blank, 3rd and 4th rows were designed for non-specific binding, 5th, 6th, and 7th rows were designed for maximum blinding, and 8th row was designed for total activity. Second and 3rd columns were designed for standardization. Measurements were made by BioTek's Synergy HT (Vermont, USA) ELISA reader under 405 nm light. First column's 5th, 6th, and 7th rows' adsorbents were compared with other rows' and columns' absorbents and appropriate values of PGE2 were noted. The total urinary PGE2 level (mg/mol) was normalized by the urinary Cr, and the ratio of PGE2/Cr used as a normalized urinary PGE2 level. Urinary PGE2/Cr levels were compared among controls.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences 15.0 software (SPSS 15.0 for Windows) (Chicago, USA) by an expert biomedical statistician. Power analyze was done; however, for being the first study of PGE2 in children with LUTD, not enough statistical parameter had gotten from the previous studies. Descriptive statistics were noted with mean ± standard deviation, median (minimum-maximum), numbers, and percentiles. Kolmogorov–Smirnov test was used to assess the variables' normalization. Mann–Whitney U-test was used for comparing groups. $P < 0.05$ was accepted as the statistically significant difference.

RESULTS

A total of 91 children were evaluated on suspicion of LUTD. About 11 children with active urinary tract infections were excluded from the study. The remaining 80 children filled out the LUTDSS. Nearly 32 children with score ≥9 were diagnosed as LUTD and verified with 3-day bladder diary, 2-time Uroflow-EMG, and abnormal PVR. The LUTDSS of children in the control group was 0.

There were 25 girls and seven boys in the LUTD group and 22 girls and 26 boys in the control group ($P > 0.05$). The average age was 8.69 ± 2.41 in LUTD group and 9.26 ± 2.87 in control group ($P > 0.05$). About 21 (65.6%) of patients had daytime incontinence, 17 (53.1%) had enuresis, 13 (37.5%) had pollakiuria, and 26 (81.3%) had urgency. About 26 (81.3%) of the LUTD group had staccato voiding pattern, 4 (12.5%) had tower voiding pattern, and 2 (6.3%) had normal voiding pattern. All these patients had EMG activity while urinating. PVRs were >20 ml in 25 (78.1%) of the LUTD group. Mean PVR was 31 ml (range: 11.5–59 ml). The maximum flow rate was ≤10 ml/s for 9 and >10 ml/s for the other 23 patients. Only 3 (9.4%) of the LUTD group had bladder wall thickness. About 11 patients (37.5%) had a history of urinary tract infection, and seven patients (21.8%) had vesicoureteral reflux.

Urine PGE2 levels were compared between the LUTD and control groups. The median urine PGE2 level was 26.9 mg/mol Cr (range: 7.9–272.6) in the LUTD group and 27.7 mg/mol Cr (range: 9.8–346.4) in control group ($P = 0.93$). Despite no statistically significant difference, urine PGE2 level was higher control group [Table 1 and Figure 1].

Regarding gender difference, median urine PGE2 level was 20.40 mg/mol Cr (range: 12.00–54.00) in the male LUTD group

Table 1: PGE2 Levels

	Number patients	Mean±SD	Median	Minimum	Maximum	P*
LUTD	32	48.00±54.48	26.90	7.9	272.60	0.93
Control	48	47.92±56.84	27.7	9.8	346.4	
Male LUTD	7	29.78±18.36	20.40	12.00	54.00	0.66
Male Control	26	39.41±37.70	24.35	9.80	156.30	
Female LUTD	25	53.10±60.22	28.10	7.90	272.60	0.66
Female Control	22	57.98±73.10	30.05	12.40	376.40	
Male LUTD	7	29.78±18.36	20.40	12.00	54.00	0.35
Female LUTD	25	53.10±60.22	28.10	7.90	272.60	
LUTD with OAB	26	51.32±58.17	32.0	7.90	272.60	0.33
LUTD without OAB	6	33.60±34.31	21.7	12.2	103.0	
LUTD with PVR	25	44.36±39.08	30.5	11.2	172.0	0.68
LUTD without PVR	7	60.98±94.74	22.9	7.90	272.6	
LUTD with enuresis	17	56.74±62.63	39.7	12.0	272.6	0.18
LUTD without enuresis	15	38.08±43.5	22.9	7.9	172.0	
LUTD with normal void	2	35.55±34.43	35.55	11.2	59.9	0.18
LUTD with staccato void	26	44.79±54.36	25.1	7.9	272.6	
LUTD with tower void	4	75.05±66.95	52.8	22.6	172.0	

*Mann-Whitney-U Test. Mg/mmol creatinine. SD: Standard deviation, LUTD: Lower urinary tract dysfunction, PGE2: Prostaglandin E2, PVR: Postvoid residual

and 24.35 mg/mol Cr (range: 9.80–156.30) in the male control group [Table 1]. There was no statistically significant difference between these two groups (P = 0.66), but urine PGE2 level was lower in male LUTD group than male control group too.

In the female patients, median urine PGE2 level was 28.10 mg/mol Cr (range: 7.90–272.60) in the LUTD group and 30.05 mg/mol Cr (range: 12.40–346.40) in the control group [Table 1]. There was no statistically significant difference between these two groups (P = 0.66), but urine PGE2 level was lower in female LUTD group than female control group too.

Comparing male and female patients in the LUTD group, male patients' median PGE2 level was 20.40 mg/mol Cr (range: 12.00–54.00) and female patients' median PGE2 level was 28.10 mg/mol Cr (7.90–272.60) (P = 0.35) [Table 1].

In LUTD group, patients with OAB symptoms had 32.0 mg/mol Cr (range: 12.2–103.0) median urine PGE2 level (mean: 51.32 mg/mol Cr) and patients with without OAB symptoms had 21.70 mg/mol Cr (range: 12.2–103.0) median urine PGE2 level (mean: 33.6 mg/mol Cr) [Table 1]. There was no statistically significant difference between these two groups (P = 0.33), but urine PGE2 level was higher in OAB group than others.

The patients with PVR had 44.36 mg/mol Cr (range: 11.2–172.0) median urine PGE2 level (mean: 44.36 mg/mol Cr) and the patients without PVR had 22.9 mg/mol Cr (range: 7.9–272.6) median urine PGE2 level (mean: 60.98 mg/mol Cr) [Table 1]. There was no statistically significant difference between these two groups (P = 0.68), but urine PGE2 level was lower in patients with PVR [Figure 2].

The patients with enuresis had 56.74 mg/mol Cr (range: 12.0–272.6) median urine PGE2 level, and the patients without enuresis had 22.9 mg/mol Cr (range: 7.9–172.0) median urine PGE2 level [Table 1]. There was no statistically significant difference between these two groups (P = 0.18), but urine PGE2 level was higher in patients with enuresis.

When we examined the PGE2 levels according to voiding patterns, the patients with normal voiding pattern had 35.55 mg/mol Cr

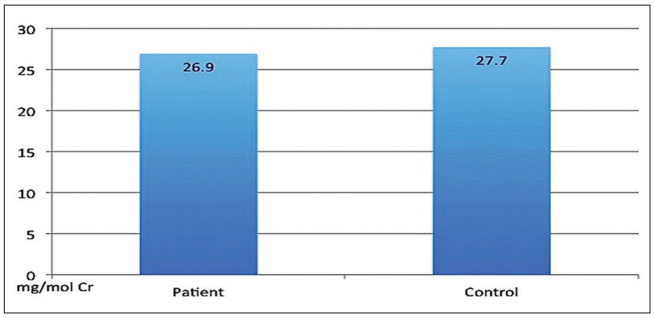

Figure 1: Urine prostaglandin E2 levels between patient and control group

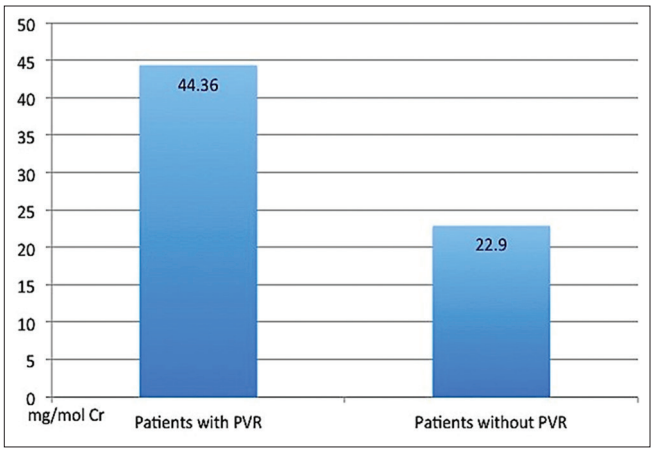

Figure 2: Urine prostaglandin E2 levels in lower urinary tract dysfunction group with and without postvoid residual

(range: 11.2–59.9) median urine PGE2 level, the patients with staccato voiding pattern had 25.10 mg/mol Cr (range: 7.9–272.6) median urine PGE2 level (mean: 44.79 mg/mol Cr), and the patients with tower voiding pattern had 52.8 mg/mol Cr (range: 22.6–172.0) median urine PGE2 level [Table 1]. There was no statistically significant difference between these groups (P = 0.32), but urine PGE2 level was higher in the patients with tower voiding pattern.

DISCUSSION

LUTD is an abnormally learned spectrum of voiding behavior often evolving from attempts to suppress impending or active bladder contractions by inappropriately contracting the pelvic floor muscles, thereby tightening the urinary sphincter complex.[17] LUTD in children is usually seen in females. The main complaints of children with LUTD are daytime incontinence, enuresis, urge incontinence, and weak urine flow. Our patients' main complaint was daytime incontinence, enuresis, and urgency. In our study, there were 32 patients in the study group, and 25 of them were female (78%), and these results were in accordance with the literature.

The etiology of LUTD in otherwise healthy, neurologically intact children remains a matter of debate. In the absence of any neurologic or anatomic findings, the voiding patterns in these children are often believed to originate from behavioral issues. These behavioral traits may evolve from adverse events that occur around or after the time of toilet training and/or personal stresses.[18,19] A mild delay in the maturation of the central nervous system (CNS) may also disrupt the ability of these children to learn true voluntary control over the micturition reflex.[20,21] In support of the belief that the roots of LUTD may be grounded in behavioral issues or CNS developmental delays, an association has been demonstrated between dysfunctional voiding and attention deficit hyperactivity disorder (ADHD). Higher rates of enuresis, urinary incontinence, constipation, and other voiding symptoms have been described in children with ADHD.[22,23] CNS effects the voiding in many ways, but sympathetic and parasympathetic imbalance may be the main cause of LUTD in children. A recent study has reported that central parasympathetic overactivity in children with LUTD and this may be a sign of CNS disorders.[24] In the present study, there was no statistically significant difference in urinary PGE2 levels among patients with LUTD and controls, so we may think that LUTD could be the consequence of CNS disorders, not the disorders of the end organs such as the bladder or external urethral sphincter.

There have been a lot of studies reporting the role of PGs in prostatitis, urogenital malignancies, OAB, and bladder outlet obstruction.[10-14] The causes and mechanisms of OAB remain poorly understood. PGs may affect bladder activity directly by effects on smooth muscle and/or indirectly through effects on neurotransmission.[25] Kim *et al*. reported that urinary PGE2 and PGF2-alpha in patients with OAB increased significantly, but urinary PGI2 was not significantly changed compared to the control group. Their results suggested that the bladder capacity is likely associated with changes in PGE2.[12] The pathophysiology of detrusor overactivity (DO) is not fully understood. It may represent a persistence of the normal infant voiding pattern after toilet training, or it may be caused by the transient obstruction.[19] Intravesical instillation with PGE2 facilitated micturition and increased basal intravesical pressure by releasing tachykinins, and contributed to urge and DO.[26] Thus, it is possible that increased PGE2 results in OAB symptoms. By contrast, Liu *et al*. compared urinary nerve growth factor (NGF) and PGE2 levels among adult female patients with OAB, interstitial cystitis/bladder pain syndrome (IC/BPS) and controls.[27] The patients with OAB were further classified into subgroups of DO or increased bladder sensation by urodynamic results. Urinary NGF levels were elevated in women with IC/BPS or DO, but not in those with IBS. However, urinary PGE2 levels showed no significant difference among patients with DO, IBS, IC/BPS, and controls. Urinary PGE2 levels were not significantly different among all subgroups. Our results are statistically similar to the study of Liu *et al*. In the present study, there was no statistically significant difference in urinary PGE2 levels between patients with LUTD and controls. On the other hand, although it is not statistically significant, the higher PGE2 level in control group may shows something different: PGE2 may be a relaxing agent for bladder, similar to blood vessels and contrary to most of our present urology knowledge, and with LUTD, its' level may show a decrease, or PGE2 receptors (especially EP3 and EP4) may play the main role of PGE2 activity rather than its level.

The other studies have not examined the gender difference for PGE2. In this study, we examined the gender difference and both male and female patients' PGE2 levels were lower than the control group. Both these finding still strengthens the thought of PGE2 is a relaxant agent.

Under the lower PGE2 levels in LUTD group, there lies a slight difference among some aspects of LUTD. The patients with OAB symptoms, enuresis, and tower voiding pattern have a higher PGE2 level, but patients with PVR have a lower PGE2 level. These findings show that the functionally normal bladder has more PGE2 synthesis.

CONCLUSION

PGE2 may not be an etiological factor in children with LUTD. Therefore, measuring urinary PGE2 mostly provides no further advantage in the diagnosis. The higher PGE2 levels in control group and lower PGE2 levels in the patients with PVR offers further examinations to understand the PGE2 effect.

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