A Role of Intravesical Capsaicin Instillation in Benign Prostatic Hyperplasia with Overactive Bladder Symptoms: The First Reported Study in the Literature

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Objective: To study the efficacy of capsaicin in treating overactive bladder symptoms in benign prostatic hyperplasia patients.

Material and Method: A prospective study of 20 benign prostatic hyperplasia patients whose overactive bladder symptoms were not improved by alpha1 blocker. Alpha1 blocker was taken about 22.9 ± 17.2 months before and continued throughout 6 months duration of the present study. All of them had undergone intravesical capsaicin instillation at the Faculty of Medicine Siriraj Hospital, Bangkok, from 2004 to 2006. Both clinical and urodynamic data were evaluated before and after treatment.

Results: Mean urgency decreased from 6.7 ± 5.1 at baseline to 2.0 ± 2.3 (p < 0.005), 1.4 ± 2.4 (p < 0.005), 1.3 ± 2.2 (p < 0.005) at 1, 3 and 6 months. Mean urge incontinence decreased from 1.7 ± 3.5 at baseline to 0.5 ± 1.3 (p = 0.148), 0.4 ± 1.2 (p = 0.114), 0.3 ± 1.1 (p = 0.085) at 1, 3 and 6 months. Mean urinary frequency decreased from 13.7 ± 3.3 at baseline to 10.5 ± 2.8 (p < 0.005), 9.6 ± 2.0 (p < 0.005), 9.5 ± 2.6 (p < 0.005) at 1, 3 and 6 months. Mean nocturia decreased from 4.7 ± 2.4 at baseline to 3.1 ± 2.2 (p < 0.005), 2.7 ± 1.2 (p < 0.005), 2.9 ± 1.6 (p < 0.005) at 1, 3 and 6 months. Mean first desire to void increased from 172.5 ± 100.4 ml at baseline to 210.6 ± 99.5 ml (p = 0.016) at 1 month. Mean maximal cystometric capacity increased from 350.3 ± 165.9 ml at baseline to 397.4 ± 165.7 ml (p = 0.012) at 1 month. Peak flow rate, detrusor pressure, and postvoid residual urine were not affected. No serious adverse effect occurred in the present study.

Conclusion: Intravesical capsaicin instillation is an effective treatment for overactive bladder symptoms in benign prostatic hyperplasia patients.

Keywords: Capsaicin, Benign prostatic hyperplasia, Overactive bladder

The overactive bladder (OAB) is commonly found in urological practice and causes a much disabling condition affecting heath-related quality of life. The overall prevalence is 16-29.9% in men(1,2). In the fact that benign prostatic hyperplasia (BPH) patients may have various degrees of lower urinary tract symptoms (LUTS) consisting of storage, voiding and post micturition symptoms. The storage symptoms are a common reason of BPH patients to look for medical treatment(3). OAB represents a recently defined constellation of storage LUTS that includes urinary urgency with or without urge incontinence, frequency and nocturia(4). Although OAB is undoubtedly associated with bladder outlet obstruction (BOO), the pathophysiological mechanism has not exactly been proposed(5). Detrusor overactivity (DO) is highly prevalent (52%) in patients with BOO and usually produces OAB symptoms(6). Many reports demonstrated the pathophysiology of DO in BPH and abnormally activated c-afferent fiber pathway, which seemed to be the one of primary etiology(7,9).
Although alpha1 blocker reduces obstructive symptoms to satisfaction in a majority of BPH patients, their OAB symptoms have been found persistent about 65% after treatment\(^\text{[30]}\). Capsaicin, 8-methyl-N-6-nonenamide, is extracted from hot pepper chili, available in many countries, and has been widely used in clinical practice\(^{11-13}\). Intravesical capsaicin instillation is an effective treatment for OAB, specifically targets the vanilloids receptor 1 in the urinary bladder wall in order to desensitize afferent c-fiber\(^{14,15}\). The authors prospectively studied the efficacy of capsaicin in treating OAB symptoms in BPH patients.

**Material and Method**

Twenty-five BPH patients treated with optimum dose alpha1 blocker for at least 1 month, whose OAB symptoms persisted, were recruited. They were enrolled between 2004 and 2006 at the Division of Urology, Department of Surgery, Siriraj Hospital, Mahidol University, Bangkok, Thailand. All of them were informed, which consent form had been approved by the Ethics Committee of the institute. None of them had received any drugs that influenced the bladder function for at least 2 weeks prior to the present study. The exclusion criteria were: patients with neuropathic bladder, urinary tract infection, bladder tumor, post surgery or radiation of prostate and/or bladder, bladder outlet obstruction from other conditions such as prostate cancer, urethral stricture or contracture bladder neck, and plan for prostate surgery. Patients with International Prostate Symptoms Score (IPSS) less than 8, maximal flow rate (Qmax) from uroflowmetry (UFM) less than 10 ml/s and prostate volume less than 20 ml were excluded from the present study. Before intravesical capsaicin instillation, complete history taking for OAB symptoms, physical examination and digital rectal examination, blood for serum BUN, creatinine, FBS and prostate specific antigen (PSA), urine analysis, IPSS score, three-days voiding diary, transrectal ultrasound (TRUS) prostate, urethrocystoscopy, UFM and postvoid residual urine (PVR), urodynamic study (UDS) (Dantec instrument) were completed.

Capsaicin for the present study was obtained from the Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The 14 F Foley catheter was inserted and the bladder filled with 2% xylocaine solution without adrenaline 40 ml for 30 minutes, and then evacuated out. Intravenous fentanyl 0.05-0.1 mg injection and oral etoricoxib 120 mg were given together to relieve pain during the instillation process. The bladder was filled with capsaicin solution 100 ml (concentration 1 m M/L in 30% ethanol) for 30 minutes and then washed out with normal saline. In addition to vital signs and side effect recording, the patients were asked to estimate pain score during capsaicin instillation in a visual analogue scale (0 was no discomfort and 10 was an intense pain requiring either more analgesic treatment or bladder emptying). The Foley catheter was removed at the end of the present study and 5-days of oral antibiotics were given to all patients.

Alpha1 blockers were continued throughout the study. Patients were reevaluated for OAB symptoms and UFM with PVR at 1, 3, and 6 months after treatment. UDS was performed at least one time after treatment in the first 3 months follow up. First desire to void (FDV), maximal cystometric capacity (MCC), detrusor pressure at MCC (PdetMCC), and detrusor pressure at Qmax (PdetQmax) were recorded for later analysis. DO was defined as an urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked\(^\text{[40]}\). Pre and post therapy data were presented as the mean value with standard deviation and compared for statistical purpose by analysis of variance (ANOVA) with repeated measurement and two-tailed t-test for means. The p-value < 0.05 was considered statistically significant.

**Results**

Twenty out of twenty-five patients completed the study and the data were analyzed. The patients’ characteristics are demonstrated in Table 1 and 2. All of the complications spontaneously resolved with symptomatic treatment. None of them had acute urinary retention in the present study (Table 3). Mean pain score was 8.8 ± 1.2 and no patients needed regional or general anesthesia to relieve pain during instillation.

**OAB symptoms**

Urgency symptoms decreased in 90% (18/20) of patients after instillation. Mean urgency decreased from 6.7 ± 5.1 at baseline to 2.0 ± 2.3 (p < 0.005) at 1 month, to 1.4 ± 2.4 (p < 0.005) at 3 months and to 1.3 ± 2.2 (p < 0.005) at 6 months. Urge incontinence was presented in 40% (8/20) of patients and mean incontinence was decreased or disappeared in 87% (7/8) of patients. Surprisingly, 5% (1/20) of the patients developed de novo urinary incontinence after capsaicin treatment. Mean incontinence decreased from 1.7 ± 3.5 at baseline to 0.5 ± 1.3 (p = 0.148) at 1 month, to 0.4 ± 1.2 (p = 0.114) at 3 months and to 0.3 ± 1.1 (p = 0.085) at 6 months.
Frequency was demonstrated in all patients, which decreased in 16/20 (80%) patients. Mean frequency decreased from $13.7 \pm 3.4$ at baseline to $10.5 \pm 2.9$ (p < 0.005) at 1 month, to $9.6 \pm 2.1$ (p < 0.005) at 3 months and to $9.5 \pm 2.6$ (p < 0.005) at 6 months. Nocturia was found in all patients and their degree decreased in 95% (19/20) of patients. Mean nocturia decreased from $4.7 \pm 2.4$ at baseline to $3.1 \pm 2.2$ (p < 0.005) at 1 month, to $2.7 \pm 1.2$ (p < 0.005) at 3 months and to $2.9 \pm 1.6$ (p < 0.005) at 6 months (Fig. 1).

Uroflowmetry and post void residual urine

Mean Qmax was $13.9 \pm 4.1$ ml/s at baseline. Post treatment mean Qmax was $15.3 \pm 5.8$ ml/s (p = 0.197) at 1 month, $14.8 \pm 5.6$ ml/s (p = 0.490) at 3 months and $14.6 \pm 5.0$ ml/s (p = 0.528) at 6 months. No significant differences between both results were found. PVR was measured after UFM and 10% (2/20) of patients had high residual urine (100 ml, 110 ml) before treatment. Mean PVR was $19.3 \pm 31.8$ ml at pre-treatment. Post treatment mean PVR was $23.3 \pm 30.7$ ml (p = 0.675) at 1 month, $18.4 \pm 24.0$ ml (p = 0.923) at 3 months and $16.3 \pm 32.9$ ml (p = 0.785) at 6 months. Mean PVR was not altered by capsaicin instillation.

Urodynamic study

FDV increased in 85% (17/20) of patients but decreased in the rest of the group. Mean FDV increased from $172.5 \pm 100.4$ ml to $210.6 \pm 99.5$ ml (p = 0.016) at 1-3 months. MCC increased in 75% (15/20) of patients and mean MCC increased from $350.3 \pm 165.9$ ml to
397.4 ± 165.7 ml (p = 0.012) at 1-3 months (Fig. 2). Both FDV and MCC increased, significantly. DO was observed in 15% (3/20) of patients and disappeared in all after capsaicin treatment. Mean PdetMCC was not changed at pre and post treatment (47.9 ± 20.4 cmH₂O vs. 48.2 ± 15.8 cmH₂O) (p = 0.873). Mean PdetQmax was 44.7 ± 15.3 cmH₂O and 42.7 ± 12.5 cmH₂O (p = 0.333) at baseline and post instillation, consecutively. There was no difference between both Pdet MCC and PdetQmax results.

Discussion

A few studies that supported activated c-afferent fiber pathway as an etiology of DO in BOO were conducted. Ice water test, a c-fiber trigger was evaluated by Chai et al in 1998(7). A positive ice water test (IWT) was found in 71% of subjects with BOO, which was significantly higher than 7% positive IWT rate in nonobstructed subjects. 47% positive bladder cooling reflex in 104 patients with BOO due to BPH was demonstrated by Gotho et al in 1999(8). Their study confirmed BOO may cause some alteration in the afferent neural function of the bladder, in particular of the c-afferent fibers. 27% positive IWT was observed in 127 BOO patients by Hirayama et al in 2003(9). Additionally, the patients who responded to IWT, had higher BOO indexes than did the nonresponders and had a smaller volume at MCC on UDS. The BPH patients clearly showed that DO was mainly due to active c-fiber stimulated by BOO and caused urgency and frequency-related symptoms. An experimental study was done by Schroder et al in 2003(10). After 7 days of BOO cystometry without anesthesia was performed with female MNRI mice, the majority of which had an overactive voiding pattern with increased nonvoiding DO and without increased bladder weight. This observation suggested that major disturbances caused by BOO might lie on the afferent arm of the signaling pathway.

In urologic practice, intravesical capsaicin instillation has been used for neurogenic DO and later introduced to idiopathic DO(11-13). In 2003, Soontrapa et al tested the efficacy of Thai capsaicin in management of 14 OAB and 11 hypersensitive bladder patients(17). Mean urinary frequency and incontinence statistically significant decreased after treatment. Bladder capacity increased without alteration in voiding pressure. They concluded that capsaicin efficacy was very high and had reasonable cost effectiveness, especially for developing countries.

To the best of the authors’ knowledge, this present study is the first study in the literature about capsaicin treatment for OAB symptoms in BPH patients. The presented patients had medium age and slightly enlarged prostate gland. Mean IPSS ranged in moderate symptom and was mainly due to storage LUTS. Although the authors tried to use potent analgesic agent before instillation, mean pain score was still high. General anesthesia is an alternative treatment for patients who cannot tolerate pain. Most common adverse event was dysuria, which was considered due to excitatory effects of capcaicin. The present results show that the blockade of c-fiber sensory input improves storage symptoms as long as 6 months after therapy. All OAB symptoms, except urge incontinence significantly, decreased from baseline after treatment. A statistically insignificant decrease.
in incontinence may be due to the too-small-studied population of patients. Qmax and PVR were not altered after treatment and these findings suggested that capsaicin affects only afferent fibers (sensory) not efferent fibers (motor) pathway. Although two patients had high PVR before therapy, AUR did not occur in any participants after capsaicin instillation. This finding supports the assertion that capsaicin is safe in men with BPH. Increasing of both FDV and MCC in the presented patients improves their OAB symptoms and decreases their bothersome. Only three patients had pretreatment DO, which was lower than the incidence in other studies\textsuperscript{6,10}. All of DO disappeared completely after treatment accompanied with improvement in OAB symptoms. This finding strongly supports the efficacy of capsaicin instillation for OAB in BPH patients. PdetMCC did not decrease in the same as the results from Soontrapa et al. Because PdetQmax was not affected so BOO is not altered by capsaicin instillation.

Resiniferatoxin (RTX), a substance isolated from some species of euphorbia (a cactus-like plant), was studied by Dinis et al in 2004\textsuperscript{18}. This non-pungent analogue has the mechanism of action, c-fiber desensitization the same as capsaicin but has less excitatory actions. They investigated RTX treatment in 12 BPH-associated storage LUTS patients. At 1, 3, and 6 months follow up, mean frequency and urge incontinence decreased after treatment. FDV and MCC increased from baseline after treatment. UFM and PVR were not altered. These results were the same as the present study but mean pain score was much lower. Incidence of DO was lower than the present study (8.3% vs. 15%) The cost expense and availability are the main disadvantages of RTX contrast to capsaicin.

Why didn’t all patients benefit from symptoms improvement in the present study? Because of the abnormal activated c-afferent fiber pathway was not the sole patho-physiology for OAB symptoms in BPH patients; therefore, we have to search for other etiologies and new treatment targets for better outcomes. A randomized, controlled trial will be arranged later to obtain the most accurate results regarding this challenging treatment.

Conclusion

In spite of BPH concomitant with OAB symptoms is quite common in urologic practice, its exact pathophysiology is unclear and has no standard treatment. Bladder c-fiber afferent desensitization seems to be a key for treatment in these disabling patients. Based on the present study, intravesical capsaicin instillation is an effective and safe treatment without long-term adverse events. It is cost-effective therapy and generally available in many countries. Because capsaicin has uncomfortable pain during administration, the authors generally recommend as an option for patients who have refractory symptoms after anticholinergic combination and do not have indication for prostate surgery.

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ประสิทธิภาพของแคพไซซินใส่ในกระเพาะปัสสาวะ เพื่อรักษาอาการกระเพาะปัสสาวะบีบตัวไวเกินในผู้ป่วยต่อมลูกหมากโตชนิดธรรมดา

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วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของแคพไซซินในการรักษาอาการกระเพาะปัสสาวะบีบตัวไวเกินในผู้ป่วยต่อมลูกหมากโตชนิดธรรมดา

วัสดุและวิธีการ: ผู้ป่วยต่อมลูกหมากโตจำนวน 20 ราย ซึ่งอาการกระเพาะปัสสาวะบีบตัวไวเกินไม่ดีขึ้นหลังจากได้รับยา alpha1 blocker ทางปาก ในขนาดที่เหมาะสม โดยเฉลี่ย 22.9 ± 17.2 เดือนก่อนการศึกษา ผู้ป่วยทุกรายจะได้รับการใส่แคพไซซินเข้าในกระเพาะปัสสาวะที่โรงพยาบาลศิริราช ในช่วงปี พ.ศ. 2547- พ.ศ. 2549 ผู้ป่วยทุกรายจะได้รับยา alpha1 blocker ต่อไปจนถึงระยะเวลา 6 เดือนที่ทำการศึกษา โดยตรวจสอบความผิดของอาการกระเพาะปัสสาวะในงดยา alpha1 blocker และการตรวจทางยูโรพลศาสตร์ระหว่างก่อนและหลังการรักษา

ผลการศึกษา: ค่าเฉลี่ยของอาการปัสสาวะรีบเร่งลดลงจาก 6.7 ± 5.1 ครั้งต่อวันเหลือ 2.0 ± 2.5 (p < 0.005), 1.4 ± 2.4 (p < 0.005) และ 1.3 ± 2.2 (p < 0.005) ครั้งต่อวันที่เวลา 1, 3 และ 6 เดือนหลังการรักษาตามลำดับ ค่าเฉลี่ยของอาการปัสสาวะเล็ดราดลดลงจาก 1.7 ± 3.5 ครั้งต่อวัน เหลือ 0.5 ± 1.3 (p = 0.148), 0.4 ± 1.2 (p = 0.114) และ 0.3 ± 1.1 (p = 0.085) ครั้งต่อวันที่เวลา 1, 3 และ 6 เดือนหลังการรักษา ค่าเฉลี่ยของอาการปัสสาวะบ่อยลดลงจาก 13.7 ± 3.3 ครั้งต่อวัน เหลือ 10.5 ± 2.8 (p < 0.005), 9.6 ± 2.0 (p < 0.005) และ 9.5 ± 2.6 (p < 0.005) ครั้งต่อวันที่เวลา 1, 3 และ 6 เดือนหลังการรักษา ค่าเฉลี่ยความจุกระเพาะปัสสาวะขณะที่เริ่มปวดปัสสาวะเพิ่มขึ้นจาก 172.5 ± 100.4 มิลลิลิตรเป็น 210.6 ± 99.5 มิลลิลิตร (p = 0.016) วันที่ 1 หลังการรักษา ค่าเฉลี่ยความจุกระเพาะปัสสาวะสูงสุดเพิ่มขึ้นจาก 350.3 ± 165.9 มิลลิลิตรเป็น 397.4 ± 165.7 มิลลิลิตร (p = 0.012) วันที่ 1 เดือนหลังการรักษา

สรุป: การใส่แคพไซซินเข้าในกระเพาะปัสสาวะมีประสิทธิภาพในการรักษาอาการกระเพาะปัสสาวะบีบตัวไวเกินในผู้ป่วยต่อมลูกหมากโตชนิดธรรมดา