BJU International (2001) 88(Suppl.2):23-26.

Clinical experience in lower urinary tract symptoms

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TITLE

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KEY WORDS:

BPH, LUTS, urodynamics, prostatectomy, BOO, detrusor instability

Introduction

Lower urinary tract symptoms (LUTS) are highly prevalent in elderly men. Population-based studies have shown that the prevalence of LUTS increases with age, and that moderate to severe LUTS occur in about 25% of men older than 50 years [1,2]. Thus, many elderly men visit physicians to seek relief from LUTS. The pathophysiology of LUTS is multifactorial [3-5]. Bladder outlet obstruction (BOO) is one of principal causes of LUTS. In addition to BOO, detrusor factors such as detrusor instability (DI) and impaired contractility (IC) can contribute to the development of LUTS. Urodynamic analysis has shown that of unobstructed male patients with LUTS, about 40% had DI alone, 31% had IC alone, and 11% had both [6]. These findings indicate that detrusor factors should be also targeted for treatment of LUTS.

Nowadays, α_1-adrenergic receptor (α_1-AR) antagonists are the most common first-line drugs in the management of LUTS [7]. About 80% of male patients receiving medical treatment for LUTS in the United States are prescribed α_1-AR antagonists by their primary care physicians [8]. Although the average improvement in overall symptom score is estimated about 40% for patients receiving α_1-AR antagonists, it is impossible to predict symptomatic outcome in each patient following treatment of LUTS with α_1-AR antagonists [9].

Urodynamic analysis can be used to predict the symptomatic outcome after TURP. TURP is still considered the gold standard in the surgical treatment of benign prostatic hyperplasia (BPH) [10]. However, not all patients have benefited from TURP. Several studies have shown that preoperative urodynamic findings can predict symptomatic outcome following prostatectomy. Jensen et al. reported lower success rate of symptomatic outcome for the unobstructed group of patients compared to those of obstructed group (78% versus 93%) [11]. Robertson et al. showed that 79% of patients with obstruction had good symptomatic outcome compared to 55% of those without obstruction [12]. These results indicate that patients without clear obstruction are less likely to have symptomatic improvement when compared to

those with obstruction. However the severity of LUTS does not correlate well with urodynamic obstruction and as many as one-third of men with LUTS are devoid of urodynamic obstruction [13]. Although TURP has been considered a procedure for relieving BOO, many patients without urodynamic obstruction benefit from the surgery. Thus assessment of BOO alone may not be accurate enough in predicting symptomatic outcome. On the other hand, it is recognized that unfavorable postoperative outcome is associated with persistent DI [14]. Taken together, preoperative DI might be a predictor of unfavorable symptomatic outcome in a particular group of patients. To assess this hypothesis, we evaluated the predictive value of preoperative urodynamic study with a special emphasis on DI relevant to BOO regarding symptomatic outcome after TURP

Predictor of unfavorable symptomatic outcome after TURP

Sixty-two male patients with LUTS who received TURP in our institution were analyzed. In each patient, International Prostate Symptom Score (I-PSS), I-PSS quality of life score (QOL score), uroflowmetry, conventional filling cystometry and pressure-flow study (PFS) were evaluated before and 3 months after TUR-P. DI was defined as involuntary detrusor contraction during filling phase with its amplitude of 15cmH_2O or more.

We examined prognostic value of preoperative PFS (with versus without urodynamic obstruction), or cystometry (with versus without DI), or combination of both to predict outcome after TUR-P. Of 62 patients, 28 and 34 were categorized to equivocally obstructed and obstructed, respectively, according to Abrams-Griffiths nomogram. There was no unobstructed patient. DI was noted in 28 patients before TUR-P. To combine data of PFS and cystometry, 62 patients were divided into 4 groups. Twenty-one patients with equivocal obstruction without DI were defined as group 1, 7 with equivocal obstruction and DI as group 2, 13 with obstruction without DI as group 3, and 21 with obstruction and DI as group 4. Except for detrusor pressure at maximum flow (Pdet at Qmax), preoperative patients characteristics including I-PSS, QOL score and Qmax were not significantly different

between patients with equivocal obstruction and those with obstruction (Table 1). After TUR-P, I-PSS and QOL score were reduced and Qmax was improved with similar magnitude in both groups of patients. Thus, there was no difference in outcome after TURP between patients with or without clear urodynamic obstruction.

Preoperative I-PSS, QOL score and Qmax were not significantly different between patients with or without DI (Table 2). Pdet at Qmax before TUR-P was significantly higher in patients with DI (Table 2). After TURP, I-PSS, QOL score were reduced and Qmax were improved with similar magnitude in both groups of patients, indicating no difference in outcome after TURP between patients with or without DI.

Except for Pdet at Qmax, preoperative I-PSS, QOL score and Qmax were not significantly different among 4 groups of patients (Table 3). After TURP, improvement of I-PSS was significantly worse in group 2 (equivocal obstruction together with DI) than other 3 groups. Improvement of QOL score and Qmax was not significantly different among 4 groups.

Since postoperative I-PSS (especially filling symptoms score) was the highest in group 2, we further analyzed a possible relationship between unsatisfactory symptomatic outcome and persistent DI. The incidence of persistent DI was higher in group 2 (60%) than in group 4 (27%). De novo DI was noted in 6% of group 1 patients.

Symptomatic outcome after TURP in men with LUTS was not different between groups of men with or without BOO, nor between men with or without preoperative DI, nor between men with normal detrusor contractility or those with IC (data not shown). However, symptomatic outcome of TURP was not favorable in unobstructed men with preoperative DI. Postoperative urodynamic characteristics in these patients with unfavorable symptomatic outcome were persistent DI in spite of having as good flow as those with favorable symptomatic outcome. Thus, persistent DI was associated with unfavorable symptomatic outcome after TURP. Interestingly, preoperative DI is not by itself an absolute predictor of postoperative outcome since in the majority of patients preoperative DI is improved after

TURP. DI associated with BOO is more likely to resolve after TURP than DI without BOO (73% versus 40% in our experience).

The pathophysiology of DI

In our study, persistent DI was noted in 60% of group 2 patients, in whom symptomatic outcome after TURP was significantly worse. Thus persistent DI might be the principle cause of unfavorable outcome. In accordance with our results, Seaman et al. detected 50% incidence of DI among non-neurological patients with persistent or recurrent LUTS after TURP [15]. General agreement exists as to the importance of postoperative cystometry in patients with persistent or recurrent LUTS after prostatectomy because of association between postoperative DI and unfavorable symptomatic outcome [14].

There are several factors contributing to the occurrence of DI. BOO is one of major causes of DI. As underlying mechanisms of DI associated with BOO, denervation supersensitivity [16], neuroplasticity [17], and myogenic origin [18] have been implicated. Subclinical neurogenic disorder and aging process have also been suggested as the underlying etiologies of DI other than BOO [19]. Thus, the pathophysiology of DI seems to be multifactorial.

Presently, there are few diagnostic methods to predict whether preoperative DI will resolve or persist after TURP or medical treatment. However, it seems that DI associated with BOO is more likely to resolve after relieving obstruction either by surgery or medical treatment than DI without BOO. Recent study has shown that persisting DI can be predicted by a careful analysis of preoperative cystometry (patterns and volume threshold for involuntary detrusor contractions) and single-photon emission computed tomography (SPECT) of the brain [20]. Although patient numbers were very small in the study, the presence of low regional cerebral blood flow detected on SPECT is highly predictive of persistent DI. Since coordinated micturition and continence is controlled by the brain, subtle abnormality in some parts of the brain might play a role in the pathophysiology of DI. The

central control of micturition and continence is now examined in human brain using positron emission tomography (PET) scan [21,22]. PET scan enables us to investigate human brain as an integrated center for urine storage (Fig. 1). Hopefully, possible involvement of human brain in the occurrence of DI will be clarified to create a new strategy for management of DI.

A strategy for the management of DI

There are several options for non-surgical management of DI. Anticholinergic (antimuscarinic) agents are often used for suppressing DI. However, significant side effects can occur in some patients, especially those with BOO. The principal action of α_1-AR antagonists is to relieve BOO by decreasing smooth muscle tone in the bladder neck and prostate. In addition, a direct effect of α_1-AR antagonists on detrusor has been proposed. A possible mechanism for this finding is that an obstructed detrusor may change from β-adrenergic dominant to α–adrenergic dominant innervation, being amenable to α_1-AR antagonists [9], although scientific evidence for the efficacy of α_1-AR antagonists in the management of DI has been still lacking. Cystometric bladder capacity increased more for patients receiving α_1-AR antagonists (prazosin or doxazosin) than for those receiving placebo in a few studies [23-25]. However, none of them noted a statistically significant improvement in cystometric parameters, nor was the volume threshold for inducing DI improved following treatment with doxazosin for 12 weeks [25]. Recent studies on expression of α_1-AR subtypes have shown that α_{1d}-AR subtype predominates in the human bladder and spinal cord [26,27]. These findings leave α_{1d}-AR subtype as a possible candidate for the treatment of DI [28].

Capsaicin and resiniferatoxin are specific neurotoxins that desensitize C fiber afferent neurons which may be responsible for signals that trigger DI [29]. Resiniferatoxin is approximately 1,000 times more potent than capsaicin but with minimal initial excitatory actions. Thus, resiniferatoxin has been arousing much attention as an effective therapeutic agent. Many clinical trials evaluating the efficacy of resiniferatoxin on overactive bladder are ongoing, and it needs a little more time before the efficacy of resiniferatoxin on DI is

established.

Conclusions

BOO as well as detrusor factors contribute to the occurrence of LUTS. Persistent DI might be a main cause of unsatisfactory symptomatic outcome after treatment of LUTS. Pathophysiology of DI seems to be multifactorial, and further studies are warranted to clarify etiology of DI and to establish effective treatment of DI.

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Figure

Fig. 1 Sagittal view of human brain on PET scan during maximal urine storage (anatomically standardized image of 10 healthy volunteers). Several parts of brain are significantly activated, including periaqueductal gray (PAG), anterior cingulate gyrus (ACG), thalamus and lentiform nucleus (putamen).

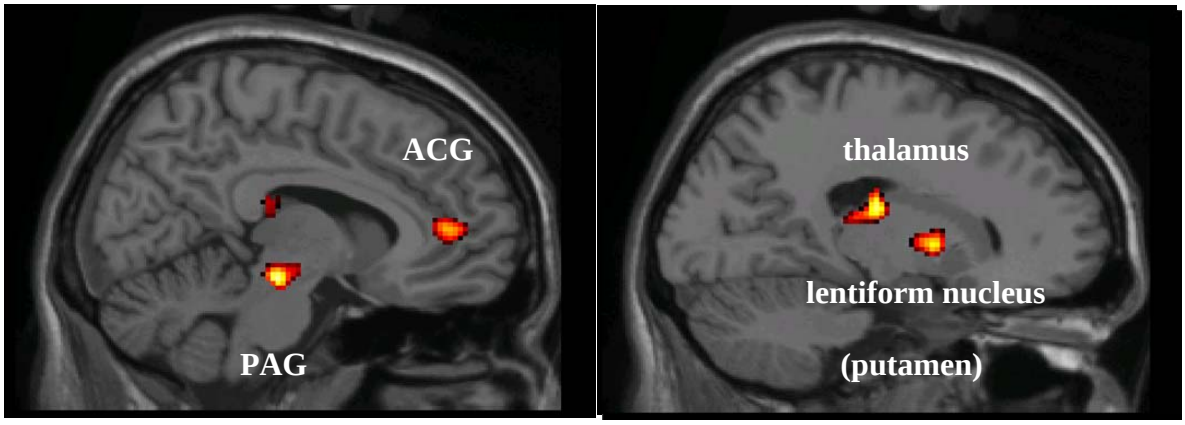

Table 1 Preoperative patients characteristics: equivocal obstruction versus obstruction

	Obstruction	Equivocal obstruction
Patients number	34	28
Mean age	70 ± 4.9	71 ± 6.0
I-PSS	18.5 ± 7.8	18.6 ± 6.2
QOL score	4.5 ± 1.1	4.7 ± 1.1
Pdet at Qmax (cmH_2O)	83 ± 23	47 ± 8
Qmax (ml/s)	8.3 ± 3.1	9.6 ± 4.5

Table 2 Preoperative patients characteristics: DI (-) versus DI(+)

	DI (-)	DI (+)
Patients number	34	28
Mean age	70 ± 5.7	71 ± 5.0
I-PSS	18.8 ± 6.6	18.1 ± 7.7
QOL score	4.5 ± 1.1	4.7 ± 1.1
Pdet at Qmax (cmH_2O)	57 ± 17	78 ± 29
Qmax (ml/s)	8.8 ± 3.7	8.9 ± 4.1

Table 3 Preoperative patients characteristics categorized by obstruction and DI

	Group 1	Group 2	Group 3	Group 4
Patients number	21	7	13	21
Mean age	70 ± 6.2	71 ± 5.6	68 ± 4.5	71 ± 4.9
I-PSS	18.4 ± 5.2	19.0 ± 9.0	19.5 ± 8.5	17.9 ± 7.5
QOL score	4.9 ± 0.8	4.1 ± 1.6	4.4 ± 1.4	4.6 ± 0.9
Pdet at Qmax (cmH_2O)	47 ± 8	48 ± 9	75 ± 13	88 ± 26
Qmax (ml/s)	9.2 ± 4.2	10.8 ± 5.4	8.4 ± 2.8	8.2 ± 3.3