Medical & Surgical Urology

ISSN: 2168-9857

Park et al. Med Surg Urol 2012, S:1
DOI: 10.4172/2168-9857.S1-001

Research Article Open Access

# The Effects of Tamsulosin Dose Escalation in Benign Prostate Hyperplasia Patients with Lower Urinary Tract Symptoms

**Park JS, Lee SW, Choi HY and Moon HS***

*Department of Urology, Hanyang University College of Medicine, Seoul, Korea*

## Abstract

**Purpose:** To investigate the efficacy and adverse effects of escalating the dose of tamsulosin in Korean benign prostate hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS).

**Materials & methods:** From March, 2010 to February, 2011, we prospectively enrolled 120 BPH patients who complained of LUTS. We evaluated the prostate specific antigen (PSA) levels, transrectal ultrasonograms (TRUS), International Prostate Symptom Scores (IPSS), International Index of Erectile Dysfunction Questionnaire-5 (IIEF-5) responses, uroflowmetry measurements and post-voided residuals (PVR) of these patients. At first, tamsulosin 0.2 mg was prescribed for 8 weeks. After 8 weeks, we prescribed tamsulosin 0.4 mg for a further 8 weeks to those patients who had not responded to tamsulosin 0.2 mg. After another 8 weeks we re-evaluated the variables, and assessed side effects. Patients prescribed tamsulosin 0.4 mg were divided into two groups; those whose total IPSS were reduced by more than 3 were assigned to the responder group (n=31), those whose total IPSS were reduced by less than 3 were assigned to the non-responder group (n=29). We then compared the variables and frequencies of adverse effects in the two groups.

**Results:** 60 patients completed the study. Mean age, prostate volume and PSA were 67.3±7.9 years, 31.0±7.7 ml and 1.8±2.3 ng/ml, respectively. Baseline prostate volume, maximal urine flow rate and IPSS score were higher in the responder group ($p<0.05$). There was no significant difference in baseline PVR or IIEF-5 between the two groups. Maximal urine flow rate increased in both groups but PVR did not improve in the non-responder group, and IIEF-5 scores decreased slightly in the non-responder group but not in the responder group. Numbers of adverse effects such as orthostatic hypotension, ejaculatory dysfunction, erectile dysfunction, dizziness and gastrointestinal discomfort were not significantly different in the two group (n=5 vs. 8, $p=0.430$).

**Conclusions:** Dose escalation of tamsulosin is effective in improving the urinary symptoms of patients with large prostate volumes and high IPSS scores. The incidence of adverse effects is unaffected by tamsulosin dose escalation.

**Keywords**: Prostatic hyperplasia; Tamsulosin

## Introduction

Benign prostatic hyperplasia (BPH) is an age-related medical condition, particularly prevalent in those aged 40–80 years [1], that can interfere with quality of life specific to urinary symptoms. There are several treatment options for BPH, such as watchful waiting, lifestyle modification, medical treatment and surgical treatment. Medical treatment is the first option for symptomatic BPH patient [2]. Currently, alpha-adrenergic receptor blockers and/or 5-alpha-reductase inhibitors (5-ARIs) are used in the medical treatment of BPH [3]. Selective alpha 1-adrenergic antagonists, such as tamsulosin, relax the smooth muscle of the prostate and bladder neck, thus decreasing resistance to urine flow [1]. In Asian countries, such as Korea, Japan, Taiwan and Singapore, tamsulosin 0.2 mg is prescribed to treat patients with BPH, unlike in Western countries, where tamsulosin 0.4 mg is prescribed as the initial dose [2]. Studies in Japan in 1990 and 2000 showed that tamsulosin 0.2 mg was an adequate therapeutic dose for Asian men [3], and had the same effect as tamsulosin 0.4 mg has for Western BPH patients [4]. However many BPH patients did not respond to tamsulosin 0.2 mg, and in June 2008 the Korea Food and Drug Administration approved prescription of tamsulosin 0.4 mg for BPH patients who did not respond to tamsulosin 0.2 mg. However there are few studies of the beneficial and adverse effects of tamsulosin 0.4 mg in Korea and other Asian countries. In this study, we investigated the effects of tamsulosin 0.4 mg in symptomatic Korean BPH patients.

## Materials and Methods

From March, 2010 to February, 2011, we prospectively enrolled 120 BPH patients. To diagnose BPH, we made transrectal ultrasonograms (TRUS) and evaluated International Prostate Symptom Scores (IPSS), uroflowmetry, post-voided residuals (PVR) and PSA. Responses to International Index of Erectile Dysfunction Questionnaire-5 (IIEF-5) were also investigated. Inclusion criteria were age over 50 years, men with prostate volume over 20 ml, IPSS scores over 8 or maximal urine flow rates of less than 15 ml/sec without a history of BPH medication in 3 months. Excluded patients were those who had PSA levels over 4.0 ng/ml or PVR over 150 ml, or prostate cancers, bladder tumors, or bladder stones, urethral disorders, urinary tract infections, histories of prostate operations, neurogenic bladder, hypersensitivity to tamsulosin, or disorders of the liver or kidney. The study was made up of 3 sessions. In the first session, after baseline studies, tamsulosin 0.2 mg for 8 weeks was prescribed for all the enrolled patients. In the second session, tamsulosin 0.4 mg was prescribed for an additional 8 weeks for those patients whose total IPSS had not fallen by at least 3 in response to the tamsulosin 0.2 mg. In the third session, at the end of the 8 weeks of tamsulosin 0.4 mg, we re-evaluated IPSS, IIEF-5, uroflowmetry, and PVR, and examined adverse effects (Figure 1). The patients who had received tamsulosin 0.4 mg were divided into two

***Corresponding author:** Hong Sang Moon, M.D, Department of Urology, Hanyang University Guri Hospital, 249-1,Gyomun-dong, Guri 471-701, Korea, Tel: +82-31-560-2374; Fax: +82-31-560-2372; E-mail: Moonuro@hanyang.ac.kr

**Received** December 09, 2011; **Accepted** January 09, 2012; **Published** January 11, 2012

**Citation:** Park JS, Lee SW, Choi HY, Moon HS (2012) The Effects of Tamsulosin Dose Escalation in Benign Prostate Hyperplasia Patients with Lower Urinary Tract Symptoms. Medical & Surgical Urology S1:001. doi:10.4172/2168-9857.S1-001

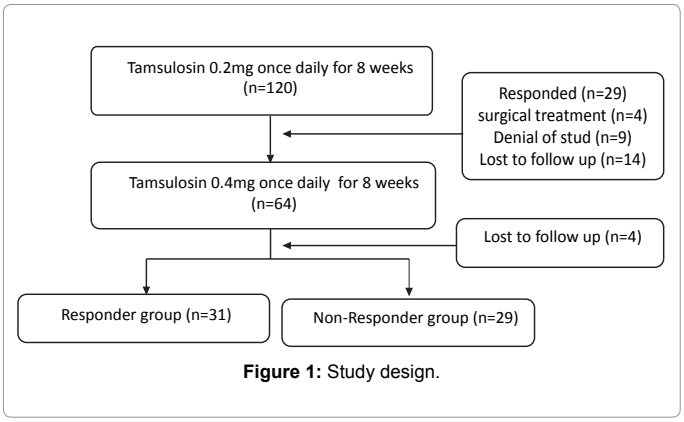


**Figure 1:** Study design.

groups. Those whose total IPSS was reduced by more than 3 fold after tamsulosin 0.4 mg were assigned to the responder group, and those who's total IPSS had fallen by less than 3 fold into the non-responder group, and we compared the variables and numbers of adverse effects in the two groups. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0. for Windows; SPSS Inc., Chicago, IL, USA). Continuous data are reported as means ± standard deviation. A 5% level of significance was used for all statistical tests. The study protocol was approved by the Institutional Review Board, and all subjects gave written informed consent before being enrolled.

## Results

120 BPH patients were enrolled in this study. By the end of the 8 weeks of tamsulosin 0.2 mg, 29 patients had responded, 4 others requested surgical treatments such as transurethral prostatectomy, 9 did not have improved IPSS scores but wanted to remain on the tamsulosin 0.2 mg medication, and 14 were lost to follow up. Tamsulosin 0.4 mg was therefore prescribed for 64 patients. By the end of the 8 weeks of tamsulosin 0.4 mg, 4 more patients were lost to follow up, leaving 60 patients who were finally analyzed (Figure 1). The IPSS scores of 31 of these patients had increased by more than 3 and they were assigned to the responder group while the remaining 29 patients, whose IPSS scores had not increased by more than 3, were assigned to the non-responder group. The general characteristics of the patients in the two groups were similar with respect to age and PSA. Mean age was 67.3±7.9 years and mean PSA 1.8±2.3 ng/ml. Prostate volume was significantly larger in the responder group (33.0±8.7 ml vs 28.7±6.0 ml, p=0.032) (Table 1). IPSS score and maximal urine flow rate were also significantly higher in the responder group (22.4±7.4 vs 11.0±5.0, and 12.4±3.8 ml/sec vs 9.6±4.2 ml/sec, respectively, p< 0.001; p=0.010) (Table 2). Baseline IPSS subscores were also significantly higher in the responder group. After the tamsulosin 0.4mg medication, IPSS irritative subscores and maximal urine flow rates were significantly improved in both groups (p<0.001). In the responder group, both obstructive symptom score and irritative symptom score had improved (11.4±3.3 to 8.2±4.3, 11.0±5.0 to 7.6±3.8, p<0.001), as had PVR (32.1±27.9 to 22.7±23.2, p=0.004). In the non-responder group, only irritative symptom score had improved (6.1±2.5 to 4.8±2.8, p<0.001), whereas end point IPSS obstructive subscore and PVR had not (4.6±2.9 to 4.9±2.4, 28.6±43.0 to 28.4±34.1, p=0.245, p=0.556). IIEF-5 score did not decrease in the responder group, whereas in the non-responder group there was a slight but significant decrease in IIEF-5 score. There were 5 adverse effects in the responder group and 8 in non-responder group (n=5 vs. 8, p=0.427). The adverse effects were orthostatic hypotension, dizziness, erectile dysfunction, ejaculatory dysfunction and gastrointestinal discomfort (Table 3).

## Discussion

Alpha-adrenergic blockers are the main treatment options for patients with LUTS/BPH. Tamsulosin, which was used in our study, antagonizes alpha-1A- and alpha-1D-adrenergic receptors and is considered alpha-1-adrenergic-receptor-subtype selective [5]. Previous studies indicated that treatment with alpha-blockers results in 15–30% improvements in total IPSS score and peak urinary flow rate within 8–12 weeks, and is safe [6-8].

There are many reports of treatment of BPH with multiple doses of the alpha-blockers terazosin or doxazosin. In 2005, Chung et al. [9], reported the results of an experiment with doxazosin with upward titration (2, 4, or 8 mg/day) at 2-week intervals, which showed that doxazosin reduced total IPSS by 48 % without significant adverse effects in Korean BPH patients. In 2007, Kwak et al. [10], reported on high-dose terazosin therapy (5mg), which reduced total IPSS and QoL scores, without significant adverse antihypertensive effects on patient who received antihypertensive medication. In 2010, Hisamatsu et al. [11], reported that increasing the loading dose of tamsulosin from 0.2 mg to 0.3 mg, led to a significant reduction in total IPSS, especially of urinary storage symptoms. Most recently, in Korea, Chung et al reported that tamsulosin 0.4 mg once daily was effective without serious adverse effects [12].

In our study, 29 of 120 patients (29/120, 24.2%) responded to tamsulosin 0.2 mg and 64 of the other patients (64/120, 53.3%) received tamsulosin dose escalation. After tamsulosin 0.4 mg, there was a significant improvement in maximal urine flow rate in all patients. The mean total IPSS score of the 31 patients (31/60, 51.7%) who responded to tamsulosin 0.4 mg increased by more than 3, and in those patients both the obstructive subscore and the irritative subscore, and PVR, improved significantly. But total IPSS score, and especially obstructive subscore, did not improve in about half of the patients (29/60, 48.3%) after tamsulosin dose escalation. Therefore we compared the variables in the responder and non-responder groups. According to Steele et al, the combination of IPSS score, maximal urine flow and prostate volume reliably predicts bladder outlet obstruction [13]. In our study the responder group had a significantly larger prostate volume (33.0±8.7 vs 28.7±6.0) and higher IPSS score (22.4±7.4 vs 11.0±5.0) than the non-responder group, which implies that the responder group had more severe bladder outlet obstruction, and that tamsulosin dose escalation is more effective in patients with more severe in such patients.

The incidence of adverse effect did not increase with tamsulosin 0.4 mg. There were 4 cases of orthostatic hypotension (6.7%), 2 of dizziness (3.3%), 2 of erectile dysfunction (3.3%), 3 cases of ejaculatory dysfunction (5%), 1 of gastrointestinal discomfort (1.6%) and 1 of leg edema (1.6%) (Table 3). Schulman et al. [14], reported on the adverse effects of tamsulosin as part of a long-term study of the effects of tamsulosin 0.4 mg in Western countries. They reported a 2.7 % incidence of orthostatic hypotension, 5.8 % of dizziness, 2.9 % of impotence and 4.3 % of abnormal ejaculation. Our data show that tamsulosin 0.4 mg in Korea does not lead to a greater incidence of adverse effects than in the West.

In our study, the incidence of adverse effects in the 0.4 mg responder group (16.1%) was lower than in the non-responder group (27.6%) but the difference was not statistically significant (p=0.427). Even though the IIEF-5 score decreased in the non-responder group after tamsulosin 0.4 mg treatment, the effect was also not statistically significant (8.3±8.1 to 7.6±8.3, p=0.231).

| | Total (n=60) | Responders group (n=31) | Non-responders group (n=29) | p-value |
|---|---|---|---|---|
| Age, years | 67.3±7.9 | 66.4±8.5 | 68.5±7.4 | 0.311 |
| HTN, n (%) | 38 (63.33) | 18 (58.06) | 20 (68.97) | 0.528[a] |
| Duration of illness, years | 2.93±2.78 | 3.32±3.72 | 2.52±1.06 | 0.266 |
| Prostate volume, ml | 31.0±7.7 | 33.0±8.7 | 28.7±6.0 | 0.032 |
| PSA, ng/ml | 1.8±2.3 | 2.2±3.1 | 1.3±0.8 | 0.127 |

**Table 1:**

| | Total | Responder Group (n=31) | Non-responder Group (n=29) | p-value[a] |
|---|---|---|---|---|
| IPSS total score | | | | |
| Baseline | 16.1±9.2 | 22.4±7.4 | 11.0±5.0 | <0.001 |
| Endpoint | 13.5±6.6 | 15.8±7.3 | 9.4±5.5 | <0.001 |
| p-value[b] | <0.001 | <0.001 | <0.001 | |
| Endpoint-baseline | | -6.6±2.9 | -1.7±2.2 | <0.001 |
| IPSS irritative subscore | | | | |
| Baseline | 8.0±5.1 | 11.0±5.0 | 6.1±2.5 | <0.001 |
| Endpoint | 6.9±3.3 | 7.6±3.8 | 4.8±2.8 | 0.002 |
| p-value[b] | 0.007 | <0.001 | <0.001 | |
| Endpoint-baseline | | -3.4±2.2 | -1.3±1.6 | <0.001 |
| IPSS obstructive subscore | | | | |
| Baseline | 8.1±4.6 | 11.4±3.3 | 4.6±2.9 | <0.001 |
| Endpoint | 6.6±3.8 | 8.2±4.3 | 4.9±2.4 | 0.001 |
| p-value[b] | <0.001 | <0.001 | 0.245 | |
| Endpoint-baseline | | -3.3±2.1 | 0.3±1.6 | <0.001 |
| Qmax (ml/sec) | | | | |
| Baseline | 11.0±4.2 | 12.4±3.8 | 9.6±4.2 | 0.01 |
| Endpoint | 14.2±4.7 | 15.3±4.8 | 13.1±4.4 | 0.08 |
| p-value[b] | <0.001 | 0.003 | <0.001 | |
| Endpoint-baseline | | 2.87±4.9 | 3.6±3.4 | 0.536 |
| PVR (ml) | | | | |
| Baseline | 30.6±35.6 | 32.1±27.9 | 28.6±43.0 | 0.391 |
| Endpoint | 24.2±28.2 | 22.7±23.2 | 28.4±34.1 | 0.509 |
| p-value[b] | 0.034 | 0.004 | 0.556 | |
| Endpoint-baseline | | -9.4±16.7 | -3.0±27.4 | 0.286 |
| IIEF-5 | | | | |
| Baseline | 8.3±8.1 | 7.2±7.6 | 9.4±8.5 | 0.456 |
| Endpoint | 7.6±8.3 | 7.4±8.1 | 8.0±8.7 | 0.342 |
| p-value[b] | 0.231 | 0.842 | 0.02 | |
| Endpoint-baseline | | 0.2±4.5 | -1.4±3.2 | 0.112 |

**Table 2:**

| Side effects | Total (n=60) | Responder Group (n=31) | Non-responder Group (n=29) | p-value |
|---|---|---|---|---|
| Ejaculatory dysfunction | 3 ( 5.0% ) | 1 ( 3.2% ) | 2 ( 6.8% ) | |
| Erectile dysfunction | 2 ( 3.3% ) | 1 ( 3.2% ) | 1 ( 3.4% ) | |
| Orthostatic hypotension | 4 ( 6.7% ) | 1 ( 3.3% ) | 3 ( 9.7% ) | |
| Dizziness | 2 ( 3.3% ) | 0 ( 0% ) | 2 ( 6.8% ) | |
| GI trouble | 1 ( 1.7% ) | 1 ( 3.2% ) | 0 ( 0% ) | |
| Leg edema | 1 ( 1.7% ) | 1 ( 3.2% ) | 0 ( 0% ) | |
| Total | 13 ( 21.6% ) | 5 ( 16.1% ) | 8 ( 27.6% ) | 0.427 |

**Table 3:**

There were limitations to this study. First, we did not perform a urodynamic study because that is too invasive to perform on all LUTS/BPH patients. Moreover, the number of enrolled and analyzed patients was small and our study was not blind, controlled, or randomized. Also there was no placebo group for comparison. A randomized, large scale and controlled study of longer duration is needed to establish the effect of tamsulosin dose escalation in LUTS/BPH patients. We believe that our findings together with those of the earlier study of tamsulosin dose escalation in Korea [12], provide the basis for further investigation of tamsulosin dose escalation in Korean LUTS/BPH patients.

## Conclusion

In LUTS/BPH patients with high maximal urine flow rates, we may expect escalation of tamsulosin dose from 0.2 mg to 0.4 mg to be effective in improving the urinary symptoms of those patients with large prostate volumes and high IPSS scores. There is no significant effect of tamsulosin 0.4 mg on the incidence of adverse effects. Our findings could provide the basis for further investigations of tamsulosin dose escalation, such as determination of the criteria for such escalation. Further large scale and comparative studies with a control group are needed.

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This article was originally published in a special issue, **Benign Prostatic Hyperplasia** handled by Editor(s). Dr. Hong-sang Moon, Hanyang University, Korea, Democratic People's Republic Of