

Efficacy of 0.4 mg tamsulosin monotherapy in patients with moderate-to-severe lower urinary tract symptoms

SAGE Open Medicine

Volume 9: 1–5

© The Author(s) 2021

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/20503121211047386

journals.sagepub.com/home/smo



Tae Wook Kang¹ , Jae Hung Jung¹, Dong Wook Kim², Kwang Ho Lee² and Hyun Chul Chung¹

Abstract

Purpose: To evaluate efficacy of 0.4 mg tamsulosin monotherapy in patients with benign prostatic hyperplasia with moderate-to-severe International Prostate Symptom Score.

Material and methods: From May 2015 to May 2017, 102 patients were analyzed, retrospectively. The patients were classified into three groups according to the combination of medication (tamsulosin 0.4 mg vs tamsulosin 0.4 mg + solifenacin 5 mg vs tamsulosin 0.4 mg + mirabegron 50 mg). Baseline characteristics (e.g. age, body weight, height, and underlying medical disease) were collected. International Prostate Symptom Score, prostate specific antigen, prostate volume, peak urinary flow rate (Q_{max}), voided volume, and post-voided volume before after treatment were evaluated.

Results: We classified and analyzed the patients into three groups depending on the medication. And there were no significant differences between all parameters among the groups. Voided volume at 3 months after treatment in each group was 170.54 ± 125.83, 121.55 ± 46.19, and 274.63 ± 132.30 ($p=0.019$). Differences of voiding symptom score and difference of post-voided volume among the groups before after treatment was 5.00 ± 5.42, 1.92 ± 3.92, and 0.11 ± 5.11 and 8.37 ± 34.32, 0.78 ± 14.86, -33.63 ± 28.58 ($p=0.037$, $p=0.007$).

Conclusion: We think tamsulosin monotherapy will be feasible as a first-line therapy for the patients with benign prostatic hyperplasia who has struggled with moderate-to-severe lower urinary tract symptoms.

Keywords

Lower urinary tract symptoms, mirabegron, prostatic hyperplasia, solifenacin, tamsulosin

Date received: 21 April 2021; accepted: 1 September 2021

Introduction

Lower urinary tract symptoms (LUTS) are most common urological symptoms in elderly men, and benign prostatic hyperplasia (BPH) is the most common cause in elderly men with LUTS. LUTS can be classified into storage, voiding, and post-voiding symptoms and often impress in a patient's quality of life (QoL) and daily activities, if not treated, it may cause lower urinary tract complications such as acute urinary retention (AUR), renal insufficiency, recurrent urinary tract infection or bladder stone, and so on, and require endoscopic surgery such as transurethral resection of prostate or Holmium enucleation of prostate.^{1,2}

According to a cross-sectional study, in a population of more than 100,000 middle-aged and older men, 18.3% of the cohort complained moderate LUTS and 3.6% severe LUTS. And the proportion of men with moderate-to-severe LUTS

tends to increase by age (10.6%; 45–49 years vs 35.4%; over 80 years) and 90% of severe LUTS patients had high voiding symptoms scores, 76% had high storage symptoms scores, while 66% had both high symptom scores.³ In a study of Korean men aged 40 years or older reported that the overall prevalence of LUTS was 83.4%, and storage LUTS were more prevalent than voiding or post-micturition LUTS (70.1% vs 60.4% vs 38.3%).⁴

¹Department of Urology, Wonju College of Medicine, Yonsei University, Wonju, Korea

²Department of Anesthesiology, Wonju College of Medicine, Yonsei University, Wonju, Korea

Corresponding author:

Hyun Chul Chung, Department of Urology, Wonju College of Medicine, Yonsei University, 20 Ilsan-ro, Wonju-si 26426, Gangwon-do, Korea.

Email: chc7174@yonsei.ac.kr



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

The European Urology Association (EAU) recommends a medical history, validated urologic symptom score questionnaire, frequency volume chart, bladder diary, a physical examination including digital rectal examination (DRE), a urinalysis, and a prostate-specific antigen (PSA) as an initial assessment of BPH.⁵ The International Prostate Symptom Score (IPSS) is the most commonly used assessment tool for patients complaining of LUTS and consists of seven questionnaires to evaluate voiding symptoms (feeling of incomplete emptying, intermittent, weak stream, and straining to urinate), storage symptoms (frequency, urgency, and nocturia) and QoL.⁵⁻⁹ Many of men with LUTS do not require medical or surgical intervention, but patients with moderate-to-severe LUTS have some indications for intervention.⁵ Alpha 1-adrenergic receptor blocker (A1B) is the most popularly prescribed drugs to improve LUTS in male BPH patients. However, storage symptom may persist even after treatment with A1B.¹⁰ The 2015 European Urologic Association Guideline recommends β 3-adrenergic receptor agonists (B3A) or antimuscarinic agents for the treatment of moderate-to-severe LUTS with the predominance storage symptoms in men with BPH. And if symptom relief is insufficient with both monotherapies, A1B and antimuscarinic agent combination therapy is recommended.⁵ Recently, many studies have been reported on the use of B3 agonists to control symptoms in patients with BPH, and a recent network meta-analysis comparing the use of tamsulosin 0.4 mg versus tamsulosin 0.2 mg to Asian BPH patients reported that the clinical effectiveness of using tamsulosin 0.4 mg is insufficient. Furthermore, according to previous studies, most of patients with BPH have low treatment compliance because of combined drug therapy.^{2,11-13}

We aimed to compare the clinical efficacy and safety of tamsulosin and solifenacin combination therapy and tamsulosin and mirabegron combination therapy versus tamsulosin monotherapy in patients with BPH complaining of moderate-to-severe LUTS.

Material and methods

We analyzed men over 40 years of age who visited our hospital with secondary LUTS due to BPH from May 2015 to May 2017. This is a retrospective observational study to confirm the clinical efficacy and safety of tamsulosin 0.4 mg. A total of 102 patients were evaluated and 5 patients with an IPSS symptom score of less than 7 were excluded from the study. We also excluded 13 patients requiring management for severe cardiovascular disease, patients requiring bronchodilator treatment for severe pulmonary disease such as asthma, patients with urinary tract infections, patients with a history of urethral injury, patients who previously had prostate surgery, and patients who receiving drugs for neurological causes. Baseline characteristics (e.g. age, body weight, height, and underlying medical disease) were collected at the first visit. And IPSS, prostate volume (PV), PSA, voided

volume (VV), peak urinary flow rate (Qmax), and post-voided volume (PVR) before and after treatment were evaluated.

According to the medication therapy, we divided the patients into three groups. Group A ($n=52$) was tamsulosin 0.4 mg monotherapy group, Group B ($n=15$) was tamsulosin and mirabegron combination therapy group (tamsulosin 0.4 mg + mirabegron 50 mg), and Group C ($n=17$) was tamsulosin and solifenacin combination therapy group (tamsulosin 0.4 mg + solifenacin 5 mg).

Clinical BPH is defined as having at least two of the following: (1) moderate-to-severe LUTS (IPSS ≥ 8), (2) decreased Qmax (<15 mL/s), and (3) enlarged prostate (total volume ≥ 30 mL).¹⁴ But in this study, we defined the BPH as a PV of 20 mL or greater as assessed by transrectal ultrasound (TRUS) or Computed Tomography (CT) scan. PV measured by TRUS or CT was calculated by the means of ellipsoid formula (PV = $\pi/6$ (width (cm) thickness (cm) length (cm))). We aimed the primary end point as change in total IPSS in each group, and secondary endpoints as changes in sub-score of urologic symptom score, change in QoL score, and change in Qmax. Changes in sub-score of urologic symptom score were measured by voiding and storage symptom score of IPSS. Also, we measured the changes in QoL by the changes of QoL score of IPSS. We measured the Qmax by the uroflowmetry (Urocap IV, Laborie, Minnetonka, MN, USA).

We statistically compared the baseline characteristics of the three groups using ANOVA and analyzed the differences between the three groups using the ANOVA method for the change of variables after 3 months of medication. And a p -value of less than 0.05 was considered statistically significant.

We used the Statistical Package for the Social Sciences (SPSS version 20.0 IBM, Armonk, New York, USA) for all statistical analyses in this study. All data were presented as mean value \pm standard deviation. This study was approved by the Ethics Committee of Yonsei University, Wonju Severance Christian Hospital (approval no. CR320023).

Results

Baseline characteristics of the patients were described in Table 1. The mean age for each group was 70.38 ± 9.37 , 67.67 ± 10.47 and 67.71 ± 9.74 , respectively. And mean PSA of three groups was 3.13 ± 8.64 , 1.21 ± 1.33 , and 2.14 ± 3.08 . Mean PV was 31.29 ± 18.04 , 25.43 ± 5.89 , and 30.48 ± 12.02 , respectively. The mean IPSS, QoL, and Qmax for each group were 21.85 ± 7.26 , 22.00 ± 6.07 , 19.64 ± 5.88 ; 4.54 ± 1.43 , 4.8 ± 1.42 , 4.07 ± 1.33 ; 9.16 ± 4.36 , 10.61 ± 4.56 , 10.06 ± 5.89 , respectively. There were no significant differences in the background characteristics in each group. We presented the results of the changes after 3 months of treatment in the three groups in Table 2. Three-months later, the mean variable changes of IPSS before and

Table 1. Baseline characteristics of patients according to medication.

	Group A (n=39)	Group B (n=15)	Group C (n=17)	p-value
Age	70.38 ± 9.37	67.67 ± 10.47	67.71 ± 9.74	0.464
PV	31.29 ± 18.04	25.43 ± 5.89	30.48 ± 12.02	0.457
PSA	3.13 ± 8.64	1.21 ± 1.33	2.14 ± 3.08	0.626
QoL	4.54 ± 1.43	4.8 ± 1.42	4.07 ± 1.33	0.374
IPSSv	12.27 ± 4.92	12.67 ± 4.03	10.14 ± 3.86	0.257
IPSSs	9.58 ± 3.42	9.33 ± 3.18	9.50 ± 2.77	0.968
IPSS	21.85 ± 7.26	22.00 ± 6.07	19.64 ± 5.88	0.539
VV	160.36 ± 130.76	154.54 ± 119.14	144.36 ± 86.79	0.915
PVR	52.30 ± 82.70	20.92 ± 28.57	27.00 ± 34.73	0.253
Qmax	9.16 ± 4.36	10.61 ± 4.56	10.06 ± 5.89	0.385

Group A: tamsulosin monotherapy; Group B: tamsulosin + mirabegron; Group C: tamsulosin + solifenacin; PV: prostate volume; PSA: prostate-specific antigen; QoL: quality of life; IPSS: International Prostate Symptom Score; IPSSv: voiding symptom score; IPSSs: storage symptom score; VV: voided volume; PVR: post-voided residual volume; Qmax: peak flow rate.

Values are presented as mean value ± standard deviation (range).

$p < 0.05$ compared with tamsulosin + solifenacin.

$p < 0.05$ compared with tamsulosin + mirabegron.

$p < 0.05$ compared with tamsulosin.

Table 2. Difference between groups in mean change at 3 months.

	Group A (n=39)	Group B (n=15)	Group C (n=17)	p-value
DQoL	1.41 ± 2.06	1.17 ± 1.75	0.00 ± 1.32	0.165
DIPSSv	5.00 ± 5.42*‡	1.92 ± 3.92	0.11 ± 5.11‡*	0.038
DIPSSs	1.30 ± 5.08	-2.00 ± 2.45	0.33 ± 6.66	0.364
DIPSS	7.82 ± 8.68	2.92 ± 8.40	1.44 ± 6.44	0.093
DVV	35.89 ± 184.84	-21.89 ± 126.68	149.50 ± 131.16	0.100
DPVR	8.37 ± 34.32*‡	0.78 ± 14.86	-33.63 ± 28.58‡*	0.007
DQmax	3.57 ± 8.20	2.07 ± 7.43	4.29 ± 4.69	0.813

Group A: tamsulosin monotherapy; Group B: tamsulosin + mirabegron; Group C: tamsulosin + solifenacin; D: changes in variables before and after treatment; QoL: quality of life; IPSS: International Prostate Symptom Score; IPSSv: voiding symptom score; IPSSs: storage symptom score; VV: voided volume; PVR: post-voided residual volume; Qmax: peak flow rate.

Values are presented as mean value ± standard deviation (range).

* $p < 0.05$ compared with tamsulosin + solifenacin.

‡ $p < 0.05$ compared with tamsulosin + mirabegron.

‡ $p < 0.05$ compared with tamsulosin.

after treatment among the groups were 7.82 ± 8.68 , 2.92 ± 8.40 , and 1.44 ± 6.44 , respectively. The mean variable change of IPSS was 1.30 ± 5.08 , -2.00 ± 2.45 , and 0.33 ± 6.66 , respectively. In Groups A and C, improvement of storage symptom score was observed, but in Group B, deterioration of storage symptom score was observed. But there were no significant differences statistically ($p=0.364$) (Table 2.)

In all three groups, an improvement of Qmax during voiding was observed after treatment as compared to pre-treatment. And the mean changes of Qmax among the groups were 3.57 ± 8.20 , 2.07 ± 7.43 , and 4.29 ± 4.69 . Among them, Group C showed the best improvement; however, there were no significant improvements statistically ($p=0.813$). In Group A and Group C, there were improvements of VV after treatment whereas in Group B, a decrease of VV was observed. However, this also did not show

statistically significant results ($p=0.1$). Improvements of QoL score of IPSS were observed in Groups A and B, but little improvement was observed in Group C ($p=0.165$). After 3 months medication, differences of voiding symptom score and difference of PVR among the groups before after treatment were 5.00 ± 5.42 , 1.92 ± 3.92 , and 0.11 ± 5.11 and 8.37 ± 34.32 , 0.78 ± 14.86 , and -33.63 ± 28.58 . And statistically significant difference was observed ($p=0.038$, $p=0.007$) (Table 2).

There were no reported adverse events in the tamsulosin monotherapy group and tamsulosin with mirabegron combination group. However, about 42% (7 of 17) of patients who medicated with anticholinergic combination therapy were complained about the adverse effect. Two (12%) patients complained of weak urinary stream, two (12%) patients complained of nocturia, two (12%) patients complained of dry mouth, and one (6%) complained of frequency.

Discussion

The purpose of this study is to evaluate the clinical effects of alpha-blocker monotherapy in patients with moderate-to-severe IPSS symptom score through comparison with combination therapy.

Alpha-blockers (ABs) have been considered as the first-line modality for treatment of BPH and previous studies have shown that 0.4 mg tamsulosin dose achieves a clinically significant effect without the requirement for dose titration, demonstrating a clear advantage over other approved ABs. However, even after taking this drug, one-third of men report LUTS did not improve, especially storage symptoms.^{15,16} Gacci et al.¹⁷ reported that AIBs show a 30%–40% reduction in IPSS and a 20%–25% increase in Qmax, but does not affect the increase in BPO and decreases the effect after 2 years.

According to the past studies, about 50% of men with BPH have struggled with storage symptom of BPH and for many years, the first-line treatment option for LUTS patients with storage symptom was lifestyle and behavior modifications.^{18,19} Therefore, anticholinergic combination therapy seems to be a good treatment options for LUTS, and there were several comparative studies of combination therapy with ABs and anticholinergic therapy versus ABs for LUTS patients.^{7,20}

Anticholinergic drugs, such as tolterodine propiverine solifenacin, bind to muscarinic receptors in the detrusor muscle cells of the bladder, which then blocks the action of acetylcholine and prevents the contraction of the bladder detrusor muscles. However, muscarinic receptors are also found in the body, including the brain, heart, intestines, salivary glands, and lacrimal ducts, so these drugs have several side effects such as dry mouth, constipation, tachycardia, lodging disorders, and cognitive dysfunction. A large-scale observational study indicates that anticholinergic drugs are not frequently recommended in clinical practice for the treatment of BPH. And they reported that only 3% of patients had an anticholinergic combination therapy.^{18,21} The reason for the low use of anticholinergics is because that clinicians tend to believe that combination of anticholinergics might aggravate the voiding symptom by decrease Qmax, increase PVR, thus leads side effects such as urinary retention. According to the European Association of Urology guidelines, combination therapy with AIB and muscarinic receptor antagonists should be prescribed with caution in men with a PVR >150 mL.^{6,22} Although there was no statistically significant difference, but improvements in IPSS (35.8%) and Qmax (31.1%) in this study showed similar results as in previous studies. However, the differences from previous studies are that the improvement of PVR and IPSSv was statistically significant in the tamsulosin monotherapy group (–26.1% vs –3.8% vs 124.5%) and (–40.8% vs –15.6% vs –1.1%). And Group C had the highest improvement on Qmax although not significant compared with Groups A and B;

however, the improvement of IPSS QOL was the lowest in Group C. In this study, due to adverse events, only 8 patients of 15 patients in the Group B maintained the previous treatment, and only 2 patients of 17 in the Group C maintained treatment.

However, this study has several limitations. First, we included small number of participants and could not perform the sample size calculation; therefore, careful interpretation for the results might be required. Further studies with large numbers of patients are asked for determine the detailed clinical relevance of our results. Second limitation relates to retrospective study design. These include unidentified confounding factors and the risk of missing data. Third, this study has a short-term follow-up period of 3 months. Therefore, we believe that well-designed long-term and multicenter trials of clinical efficacy and safety of these therapies are needed for further evaluation and a better understanding of the key prognostic determinants of the disease and treatment options.

Conclusion

As mentioned in section “Introduction,” patients under combination drug therapy abandon treatment more frequently than patients under monotherapy do. We found that 0.4 mg tamsulosin monotherapy improved the IPSSv and PVR in patients with BPH who complained of moderate-to-severe IPSS symptom score. However, an improvement in Qmax and an improvement in the IPSS symptom score were also observed in the tamsulosin monotherapy group, but there were not statistically significant. Therefore, we carefully recommended the 0.4 mg tamsulosin monotherapy would be feasible as a first-line therapy for the patients with BPH who has struggled with moderate-to-severe IPSS symptom score.

Author contributions

T.W.K. contributed to the draft original manuscript. J.H.J. contributed to the conceptualization. D.W.K. contributed to the data curation and analysis. K.H.L. contributed to the data curation and analysis. H.C.C. contributed to the review and edit manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Yonsei University, Wonju Severance Christian Hospital, Institutional Review Board (IRB) no. CR320023. Due to the retrospective nature of this study, the IRB determined that we did not require informed consent documents from the patients. During the entire period of this study, patient information was anonymized or in de-identified status. We performed all procedures associated with this study according to the Declaration of Helsinki guidelines.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

This study is a retrospective study of patients' medical records. When analyzing medical records of patients, this institution is provided to researchers so that important personal information of patients is not known. Therefore, the institution's IRB requires researchers to submit a reason for exemption from the process of obtaining consent for patients to participate in clinical trials. The study also submitted a reason for exemption from consent for participation in clinical trials and was approved by the institution's IRB.

ORCID iD

Tae Wook Kang  <https://orcid.org/0000-0003-4236-0664>

References

1. Stroup SP, Palazzi-Churas K, Kopp RP, et al. Trends in adverse events of benign prostatic hyperplasia (BPH) in the USA, 1998 to 2008. *BJU Int* 2012; 109(1): 84–87.
2. Tubaro A, Batista JE, Nitti VW, et al. Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies. *Ther Adv Urol* 2017; 9(6): 137–154.
3. Smith DP, Weber MF, Soga K, et al. Relationship between lifestyle and health factors and severe lower urinary tract symptoms (LUTS) in 106,435 middle-aged and older Australian men: population-based study. *PLoS One* 2014; 9(10): e109278.
4. Kim TH, Han DH and Lee KS. The prevalence of lower urinary tract symptoms in Korean men aged 40 years or older: a population-based survey. *Int Neurourol J* 2014; 18(3): 126–132.
5. Gratzke C, Bachmann A, Descazeaud A, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2015; 67(6): 1099–1109.
6. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992; 148(5): 1549–1557; discussion 1564.
7. Chapple C, Herschorn S, Abrams P, et al. Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers. *Eur Urol* 2009; 56(3): 534–541.
8. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011; 185(5): 1793–1803.
9. Jiang YH, Lin VC, Liao CH, et al. International Prostatic Symptom Score-voiding/storage subscore ratio in association with total prostatic volume and maximum flow rate is diagnostic of bladder outlet-related lower urinary tract dysfunction in men with lower urinary tract symptoms. *PLoS One* 2013; 8(3): e59176.
10. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 2003; 61(1): 37–49.
11. Kang TW and Chung HC. Add-on treatment with mirabegron may improve quality of life in patients with benign prostatic hyperplasia complaining of persistent storage symptoms after tamsulosin monotherapy. *Ther Adv Urol* 2020; 12: 1756287220974130.
12. Cindolo L, Pirozzi L, Sountoulides P, et al. Patient's adherence on pharmacological therapy for benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) is different: is combination therapy better than monotherapy? *BMC Urol* 2015; 15: 96.
13. Kim SJ, Shin IS, Eun SJ, et al. Evidence is enough? a systematic review and network meta-analysis of the efficacy of tamsulosin 0.2 mg and tamsulosin 0.4 mg as an initial therapeutic dose in Asian benign prostatic hyperplasia patients. *Int Neurourol J* 2017; 21(1): 29–37.
14. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349(25): 2387–2398.
15. Lepor H. Alpha blockers for the treatment of benign prostatic hyperplasia. *Rev Urol* 2007; 9(4): 181–190.
16. Djavan B and Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol* 1999; 36(1): 1–13.
17. Gacci M, Sebastianelli A, Spatafora P, et al. Best practice in the management of storage symptoms in male lower urinary tract symptoms: a review of the evidence base. *Ther Adv Urol* 2018; 10(2): 79–92.
18. Reynard JM. Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? *Curr Opin Urol* 2004; 14(1): 13–16.
19. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol* 2012; 188(Suppl. 6): 2455–2463.
20. Lee SH, Chung BH, Kim SJ, et al. Initial combined treatment with anticholinergics and α -blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multi-center, double-blind, placebo-controlled study. *Prostate Cancer Prostatic Dis* 2011; 14(4): 320–325.
21. Wei JT, Calhoun E and Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol* 2005; 173(4): 1256–1261.
22. Tehranchi A, Rezaei Y and Shojaee R. Tolterodine to relieve urinary symptoms following transurethral resection of the prostate: a double-blind placebo-controlled randomized clinical trial. *Korean J Urol* 2014; 55(4): 260–264.