



Is Tamsulosin 0.2 mg Effective and Safe as a First-Line Treatment Compared with Other Alpha Blockers?: A Meta-Analysis and a Moderator Focused Study

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Purpose: Tamsulosin 0.2 mg is used widely in Asian people, but the low dose has been studied less than tamsulosin 0.4 mg or other alpha blockers of standard dose. This study investigated the efficacy and safety of tamsulosin 0.2 mg by a meta-analysis and meta-regression.

Materials and Methods: We conducted a meta-analysis of efficacy of tamsulosin 0.2 mg using International Prostate Symptom Score (IPSS), maximal urinary flow rate (Qmax), post-voided residual volume (PVR), and quality of life (QoL). Safety was analyzed using adverse events. Relevant studies were searched using MEDLINE, EMBASE, and Cochrane library from January 1980 to June 2013.

Results: Ten studies were included with a total sample size of 1418 subjects [722 tamsulosin 0.2 mg group and 696 other alpha-blockers (terazosin, doxazosin, naftopidil, silodosin) group]. Study duration ranged from 4 to 24 weeks. The pooled overall standardized mean differences (SMD) in the mean change of IPSS from baseline for the tamsulosin group versus the control group was 0.02 [95% confidence interval (CI); -0.20, 0.25]. The pooled overall SMD in the mean change of QoL from baseline for the tamsulosin group versus the control group was 0.16 (95% CI; -0.16, 0.48). The regression analysis with the continuous variables (number of patients, study duration) revealed no significance in all outcomes as IPSS, QoL, and Qmax.

Conclusion: This study clarifies that tamsulosin 0.2 mg has similar efficacy and fewer adverse events compared with other alpha-blockers as an initial treatment strategy for men with lower urinary tract symptoms.

Key Words: Prostatic hyperplasia, alpha blockers, tamsulosin

INTRODUCTION

Benign prostatic hyperplasia (BPH) with lower urinary tract

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symptoms (LUTS) is common in older men. Medical treatment with alpha blocker is the first recommended option for patients with BPH/LUTS.¹ Alpha blockers could improve BPH/LUTS by relaxing the prostatic urethra and bladder neck through alpha-receptor block.² As a result of its prostate selectivity, tamsulosin may improve LUTS with fewer side effects. Many studies have shown that tamsulosin is effective and tolerable at doses of 0.2–0.8 mg once daily in patients with symptomatic BPH.^{3–7} In Asian countries, tamsulosin 0.2 mg has been widely used because of their relative low body mass index (BMI).^{3,5,7}

Although tamsulosin is one of worldwide favored alpha blockers due to good efficacy and relatively fewer adverse events,

tamsulosin has some adverse events including retrograde ejaculation and anejaculation. Considering that most of the adverse events are tolerable, abnormal ejaculation is significant because it increases the drug withdrawal rate. Abnormal ejaculation is a dose-related phenomenon.⁸ It is due to anemission, which is attributed to the alpha 1A receptor selectivity of seminal vesicle and vas deferens.⁹

Several studies reported the efficacy and safety of tamsulosin 0.2 mg,^{5,10-12} but the results were varied, thus hampering any decision of whether to apply tamsulosin 0.2 mg as an initial treatment in real practice. Several studies reviewed the efficacy and safety of tamsulosin with or without meta-analysis,^{13,14} however, there have been no comparative studies on the tamsulosin 0.2 mg with other alpha blockers, especially including outcome measurement such as International Prostate Symptom Score (IPSS). Our previous study has focused on the improvement of LUTS by treatment with low-dose tamsulosin, however, it did not show the differences from other alpha blockers;¹⁵ the study merely described the overall improvement by tamsulosin 0.2 mg, and there were no controls for comparison.¹⁵

The present study attempted to overcome the limitation of previous study¹⁵ and demonstrate the treatment efficacy and safety of tamsulosin 0.2 mg compared with other alpha-blockers. In addition, this is the first meta-analysis of tamsulosin 0.2 mg to evaluate the moderate effects comparing with other alpha blockers.

MATERIALS AND METHODS

This systematic review and meta-analysis were guided by the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and also guided by the Cochrane Collaboration.^{16,17}

Searching strategy

A MEDLINE and Cochrane Collaboration search for studies from 1980 to 2013 were selected using electronic database search formula: Search (((((((“Lower Urinary Tract Symptoms” [Mesh]) OR “lower urinary tract symptom” [tiabkw]) OR “LUTS” [tiabkw]) OR “Prostatic hyperplasia” [Mesh]) OR “benign prostatic hyperplasia” [tiabkw]) OR “BPH” [tiabkw])) AND (((“tamsulosin” [Supplementary Concept]) OR “tamsulosin” [tiabkw]) OR “YM178” [all]). Same electronic database search formula using Emtree was adopted for EMBASE search. Screening criteria were comparison (adrenergic alpha-1 receptor antagonists), outcome (IPSS), and article type (randomized controlled trial) without language restrictions.

Study selection

The studies were included if they met the following criteria: 1) reported outcome measurements included IPSS, 2) interventions included administration of tamsulosin and other alpha-

blockers, 3) participants included BPH, and 4) reasonable intention-to-treat (ITT) analysis was performed in randomized controlled trials (RCTs). Two authors (SR Shim and JH Kim) reviewed all filtered articles with title and abstract using pre-defined inclusion and exclusion criteria. Final inclusion was determined by the GRADE Working Group. References and data for each included study were carefully cross checked to ensure no overlapping data was presented and to maintain the meta-analysis integrity.

Types of interventions and outcomes

The experimental group received tamsulosin 0.2 mg and the control group orally received other standard dose of alpha-blockers (terazosin, doxazosin, naftopidil, silodosin). Outcomes measured mean changes of IPSS, quality of life (QoL), maximal urinary flow rate (Qmax), and post-voided residual volume (PVR) from baseline in patients receiving tamsulosin versus patients receiving other alpha-blockers. Adverse events measured the proportional differences between the tamsulosin group and the other alpha-blockers group.

Types of moderators

Earlier studies have differed in a number of parameters such as countries, control agents, the number of patients, and study duration. We now elaborated on how differences in some of these moderators affect outcomes.

Quality assessment

The risk of bias and methodological quality were assessed in duplicate using the Cochrane Collaboration tool.¹⁶ We evaluated the following six parameters: 1) random sequence generation, 2) allocation concealment, 3) blinding of caregivers, personnel, and outcome assessors, 4) incomplete outcome data, 5) selective outcome reporting, and 6) other bias. We graded each parameter of trial quality as low risk of bias, unclear risk of bias, and high risk of bias, and conducted an overall assessment for each controlled trial using the same three criteria. The quality of the evidence related to the estimation of benefits and disadvantages in the population followed the suggestions of the GRADE Working Group by adopting the use of Grade Pro software 3.6.

Meta-analysis assessment of outcome findings and statistical analysis

All variables used the same measurement units and outcomes were recorded as continuous data. The primary outcome was change in LUTS measured by IPSS. Secondary measures included QoL, Qmax, PVR, and adverse events. In the study without standard deviation, the estimate of the pooled standard deviation of the two groups (before/after) was applied. Standardized mean differences (SMD, Hedges' g, the difference between experimental and control group pooled mean change) along with their 95% confidence intervals (CIs) were calculated.

ed for continuous variables. Random-effects model of DerSimonian and Laird¹⁸ were conducted to obtain pooled overall SMD and 95% CIs for outcomes.

Meta-ANOVA or meta-regression analysis was conducted for each moderator. To examine potential moderators, we used the meta-analytic mixed effects model (MEM).¹⁹ We analyzed the variability in the effect sizes due to differences between the categorical moderators (e.g., countries and control agents) with a weighted meta-analytic analogue to the analysis of variance. For continuous moderators (e.g., number of patients and study duration), we used a restricted maximum likelihood (REML) estimator of the variance of the true effects. However, we didn't analyze moderator effects of post-voided residual urine due to insufficient observations and also we excluded the moderator if there was one observation in each category. The above mentioned analyses were conducted with Comprehensive Meta-Analysis version 2.2 software (Biostat, Englewood, NJ, USA) and STATA version 11.2 software (Stata Corp LP, College Station, TX, USA). SPSS version 21.0 software (IBM, New York, NY, USA) was used to perform the chi-squared-test.

Assessment of heterogeneity

Statistical heterogeneity was assessed by the Cochran's Q test and the I^2 statistic. For Cochran's Q, a value of $p < 0.1$ was considered to indicate statistically significant heterogeneity. If either the Cochran's Q statistics ($p < 0.1$) or I^2 statistic ($> 50\%$) indicated the existence of significant heterogeneity between studies, a random-effects model of analysis (DerSimonian and Laird method) was used.

Assessment of potential publication bias

Publication bias was explained by Funnel plot of this meta-analysis using standard error as the measure of study size and ratio measures of treatment effect. Asymmetry findings in funnel plots indicate publication bias, but the shape of the plot in the absence of bias depends on the choice of axes.

RESULTS

Inclusion of studies

The initial search identified a total of 2862 articles from the electronic database (PubMed: n=722, Cochrane: n=129, Embase: n=2011). After exclusion of 690 studies containing overlapping data or appearing in more than one database and after screening the titles and abstracts, 2026 studies that did not meet the inclusion criteria were further excluded. After intensive screening by detailed evaluation of 146 studies, a total of 21 studies were found to be eligible. Of these, 11 were excluded due to not using low-dose (0.2 mg) tamsulosin in the experimental group (n=5), not using alpha blocker in control group (n=4), and outcome value discordance (n=4). Finally, 10 studies that met all inclusion criteria were included.^{4,6,12,20-26} The 10 studies consisted of 1418 subjects (722 experimental group and 696 control group). A detailed flow chart showing the selection process is shown in Fig. 1. A systematic review of 10 studies was conducted on the detailed experimental differences and subject descriptions (doxazosin 4 mg, one study; terazosin 5 mg, one study; terazosin 2 mg, two studies; silodosin 8 mg, two studies; naftopidil 25 mg, one study; naftopidil 50 mg, three studies) (Table 1). The duration of treatment ranged

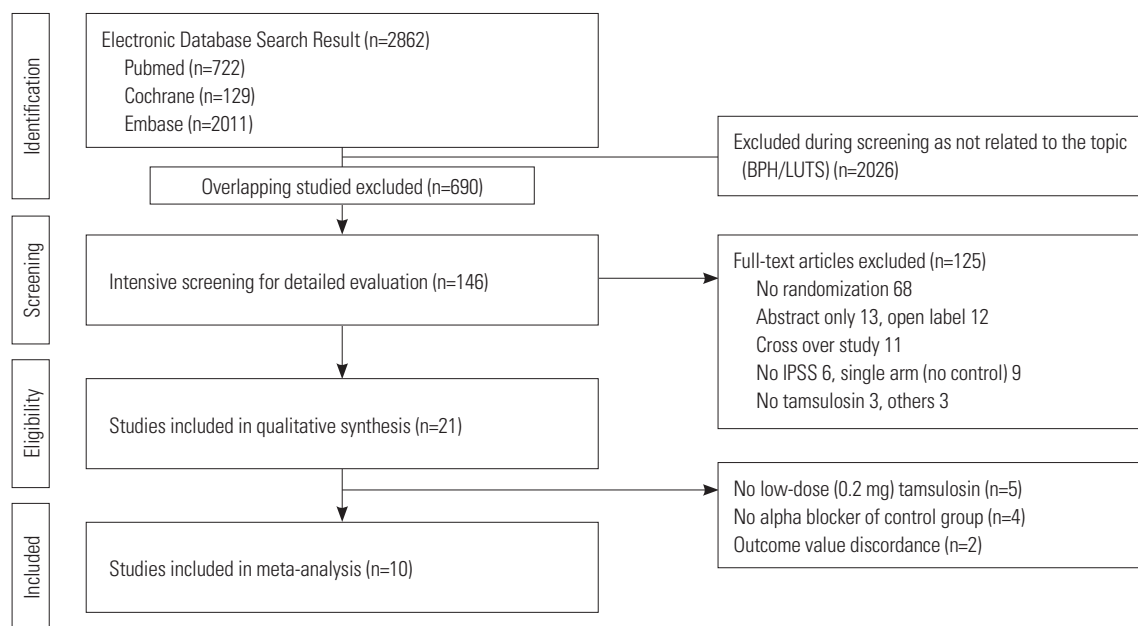


Fig. 1. Flowchart of the study selection process. BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; IPSS, International Prostate Symptom Score.

Table 1. Randomized Trials of Tamsulosin 0.2 mg for BPH

Study	Subjects for analysis Tamsulosin/control	Drug or procedure Tamsulosin/control	Study duration	Assessment	Inclusion criteria	Quality of the evidence (grade)
Na, et al. ⁶	Chinese men (mean age 68.5 yrs) with symptomatic BPH 104/97	Tamsulosin (0.2 mg qd)/ terazosin (2 mg qd)	6 wks (2 wks for wash out and 4 wks for treatment)	IPSS, Qmax	IPSS >13, Qmax 5–15 mL/s, AFR ≥7.5 mL/s Multicenter study (15 sites)	Moderate
Zhang, et al. ¹²	Chinese men (mean age 68.6 yrs) with symptomatic BPH 95/94	Tamsulosin (0.2 mg qd)/ doxazosin (4 mg qd)	10 wks (2 wks for screening and 8 wks for treatment)	IPSS, QoL, Qmax, PVR	IPSS ≥8, Qmax 5–15 mL/s on 150 mL void, nocturia once or more per night Multicenter study (4 sites)	Low
Ju, et al. ²²	Chinese men (mean age 65.9 yrs) with symptomatic BPH 38/39	Tamsulosin (0.2 mg qd)/ naftopidil (25 mg qd)	6 wks	IPSS, Qmax	IPSS ≥13, Qmax 5–15 mL/s, voided volume >150 mL, PSA ≤4 Single center study	Moderate
Yu, et al. ²⁶	Taiwanese men (mean age 66.3 yrs) with symptomatic BPH 83/87	Tamsulosin (0.2 mg qd) plus placebo qd/silodosin (4 mg bid)	14 wks (2 wks for screening and 12 wks for treatment)	IPSS, QoL, Qmax	IPSS ≥13, Qmax ≤15 mL/s, QoL score of ≥3, PVR ≤250 mL, total voided volume ≥100 mL, prostate volume ≥20 mL Multicenter study (9 sites)	Moderate
Kawabe, et al. ²³	Japanese men (mean age 65.6 yrs) with symptomatic BPH 192/175/89	Tamsulosin (0.2 mg qd)/ silodosin (4 mg bid)/placebo	14 wks (2 wks for screening and 12 wks for treatment)	IPSS, QoL, Qmax	IPSS ≥8, QoL ≥3, Qmax ≤15 mL/s, voided volume ≥100 mL, prostate volume ≥20 mL Multicenter study (88 sites)	Moderate
Okada, et al. ²⁵	Japanese men (mean age 65.7 yrs) with symptomatic BPH 29/28	Tamsulosin (0.2 mg qd)/ terazosin (1 mg qd) for 2 wks and then 1 mg bid for 2 wks	4 wks	IPSS, QoL, Qmax	IPSS ≥13, Qmax ≤12 mL/s Multicenter study (21 sites)	Moderate
Gotoh, et al. ²⁰	Japanese men (mean age 68.3 yrs) with symptomatic BPH 75/69	Tamsulosin (0.2 mg qd)/ naftopidil (25 mg for 2 wks followed by 50 mg for 10 wks)	12 wks	IPSS, QoL, Qmax, PVR	IPSS ≥8, Qmax <15 mL/s, voided volume of ≥150 mL, prostate volume ≥20 mL Multicenter study (16 sites)	Moderate
Masumori, et al. ²⁴	Japanese men (mean age 64.9 yrs) with symptomatic BPH 35/38	Tamsulosin (0.2 mg qd)/ naftopidil (50 mg qd)	12 wks	IPSS, QoL, Qmax, PVR	IPSS ≥8, PVR ≤200 mL Multicenter study (17 sites)	Low
Hanyu, et al. ²¹	Japanese men (mean age 70.7 yrs) with symptomatic BPH 32/36	Tamsulosin (0.2 mg qd)/ naftopidil (50 mg qd)	12 wks	IPSS, QoL, Qmax, PVR	IPSS ≥8, QoL ≥2, PVR ≤100 mL, prostate volume ≥20 mL Multicenter study (2 sites)	Low
Lee and Lee ⁴	Korean men (mean age 67.1 yrs) with symptomatic BPH 39/33	Tamsulosin (0.2 mg qd)/ terazosin 1 mg qd for 1 day, 2 mg for 6 days, and then 5 mg for last period	9 wks (1 wk for screening and 8 wks for treatment)	IPSS, Qmax	IPSS ≥8, Qmax 5–15 mL/s, PVR ≤150 mL Single center study	Moderate

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; Qmax, maximal urinary flow rate; AFR, average urinary flow rate; QoL, quality of life; PSA, prostatic specific antigen; PVR, post-voided residual volume.
 Grade: Group Working grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

Table 2. Quality Assessment of Included Studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Na, et al. ⁶	Described "randomized"	Unclear	Described "patients were single-blind"	High risk	Overly assumed ITT analysis using whole sample set, and low dropout rate (5.2%)	Low risk (almost patients of analysis set were completed)	Unclear
Zhang, et al. ¹²	Described "randomized"	Unclear	Unclear	Unclear	Overly assumed ITT analysis using whole sample set, and low dropout rate (1.5%)	Low risk (almost patients of analysis set were completed)	Unclear
Ju, et al. ²²	Described "randomized"	Unclear	Described "double-blinding"	Described "double-blinding"	Overly assumed ITT analysis using whole sample set, and low dropout rate (3.8%)	Low risk (almost patients of analysis set were completed)	Unclear
Yu, et al. ²⁶	Described "randomized"	Unclear	Described "double-blinding"	Described "double-blinding"	Overly assumed ITT analysis using whole sample set, and low dropout rate (2.9%)	Low risk (almost patients of analysis set were completed)	Unclear
Kawabe, et al. ²³	Described "randomized"	Unclear	Described "double-blinding"	Described "double-blinding"	Overly assumed ITT analysis using whole sample set, and low dropout rate (0.2%)	Low risk (almost patients of analysis set were completed)	Unclear
Okada, et al. ²⁵	Described "randomized"	Overly assumed allocation concealment procedure. The rigid regulations was applied to 16 sites and 17 urologists	Described "single-blind"	High risk	Overly assumed ITT analysis using whole sample set, and low dropout rate (1.6%)	Low risk (almost patients of analysis set were completed)	Unclear
Gotoh, et al. ²⁰	Described "randomized"	Unclear	Unclear	Unclear	Overly assumed ITT analysis using whole sample set, and low dropout rate (3.2%)	Low risk (almost patients of analysis set were completed)	Unclear
Masumori, et al. ²⁴	Described "randomized"	Unclear	Unclear	Unclear	Overly assumed ITT analysis using whole sample set, and low dropout rate (5.3%)	Low risk (almost patients of analysis set were completed)	Unclear
Hanyu, et al. ²¹	Described "randomized"	Unclear	Unclear	Unclear	Overly assumed ITT analysis using whole sample set, and low dropout rate (2.0%)	Low risk (almost patients of analysis set were completed)	Unclear
Lee and Lee ⁴	Described "randomized"	Unclear	Described "single-blind"	High risk	Overly assumed ITT analysis using whole sample set, and low dropout rate (2.0%)	Low risk (almost patients of analysis set were completed)	Unclear

ITT, intention-to-treat.

Dropout rate due to adverse events of treatment.

from 4–12 weeks. The language of included studies were English,^{4,6,12,20,23-26} Chinese,²² and Japanese.²¹

Quality assessment

Two authors (SR Shim and JH Kim) critically appraised the selected studies using critical criteria of Cochrane Collaboration. Table 2 shows the quality assessment and characteristics of the included studies. All of the studies described randomized methods and reasonable ITT analysis. One study²⁰ included allocation concealment. Blinding methods were conducted as single-blind in three studies^{4,6,25} and double-blind in three studies.^{22,23,26} After rating of each item of the critical appraisal, allocation concealment, blinding method, and detection bias resulted in a moderate grade.

Outcome findings

IPSS

Ten studies (n=1418; 722 experimental group and 696 control group)^{4,6,12,20-26} reported detailed data on IPSS. The pooled overall SMD in the mean change of IPSS from baseline for the tamsulosin group versus the control group was 0.02 (95% CI; -0.20, 0.25). There was no statistical difference between groups. Heterogeneity test produced $p < 0.01$ and the Higgins' I^2 was 75.9%. For evaluation of control agents that have an impact on the improvement of BPH, we also conducted subgroup analysis. The SMD changes of IPSS for the tamsulosin group versus the control group were -0.15 (95% CI; -0.43, 0.13) in terazosin 2 mg, 0.21 (95% CI; 0.04, 0.38) in silodosin 8 mg, and -0.30 (95% CI; -0.68, 0.09) in naftopidil 50 mg (Fig. 2).

QoL

Seven studies (n=1068; 541 experimental group and 527 control group)^{12,20,21,23-26} reported detailed data on QoL. The pooled overall SMD in the mean change of QoL from baseline for the tamsulosin group versus the control group was 0.16 (95% CI; -0.16, 0.48). There was no statistical difference between groups. Heterogeneity test produced $p < 0.01$ and the Higgins' I^2 was 83.8%. For evaluation of control agents that have an impact on the improvement of BPH, we also conducted subgroup analysis. The SMD changes of QoL for the tamsulosin group versus the control group were 0.21 (95% CI; 0.04, 0.38) in silodosin 8 mg, and -0.11 (95% CI; -0.57, 0.35) in naftopidil 50 mg (Fig. 3).

Qmax

Ten studies (n=1418; 722 experimental group and 696 control group)^{4,6,12,20-26} reported detailed data on Qmax. The pooled overall SMD in the mean change of Qmax from baseline for the tamsulosin group versus the control group was 0.00 (95% CI; -0.16, 0.16). There was no statistical difference between groups. Heterogeneity test produced $p = 0.03$ and the Higgins' I^2 was 51.2%. For evaluation of control agents that have an impact on the improvement of BPH, we also conducted subgroup analysis. The SMD changes of Qmax for the tamsulosin group versus the control group were 0.02 (95% CI; -0.28, 0.32) in terazosin 2 mg, 0.22 (95% CI; 0.05, 0.39) in silodosin 8 mg, and 0.02 (95% CI; -0.21, 0.26) in naftopidil 50 mg (Fig. 4).

PVR

Four studies (n=474; 237 experimental group and 237 control group)^{12,20,21,24} reported detailed data on PVR. The pooled overall SMD in the mean change of PVR from baseline for the

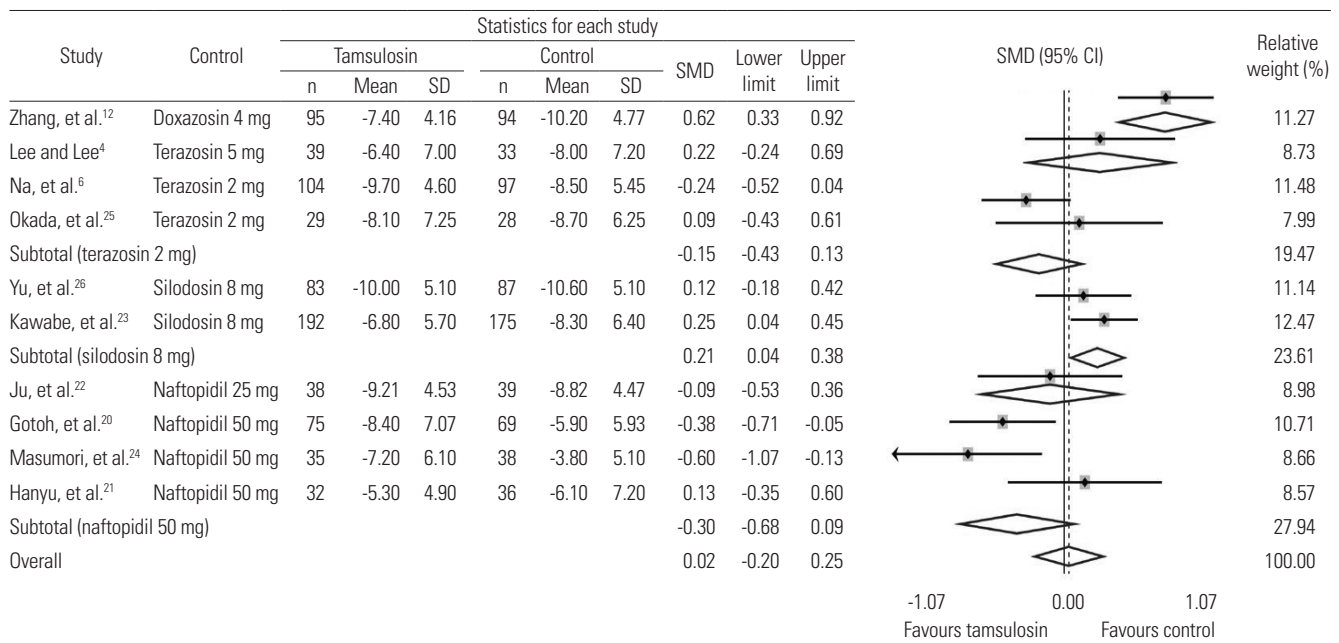


Fig. 2. Forest plot diagram showing the effect of tamsulosin 0.2 mg on International Prostate Symptom Score. SDM, standardized mean difference; CI, confidence interval.

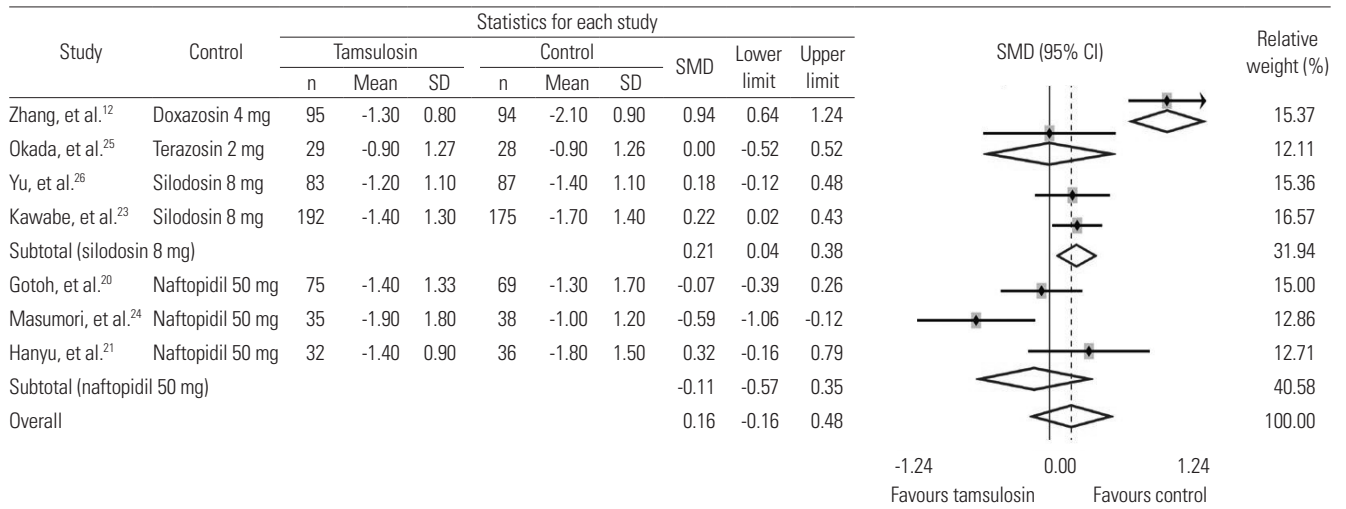


Fig. 3. Forest plot diagram showing the effect of tamsulosin 0.2 mg on quality of life. SDM, standardized mean difference; CI, confidence interval.

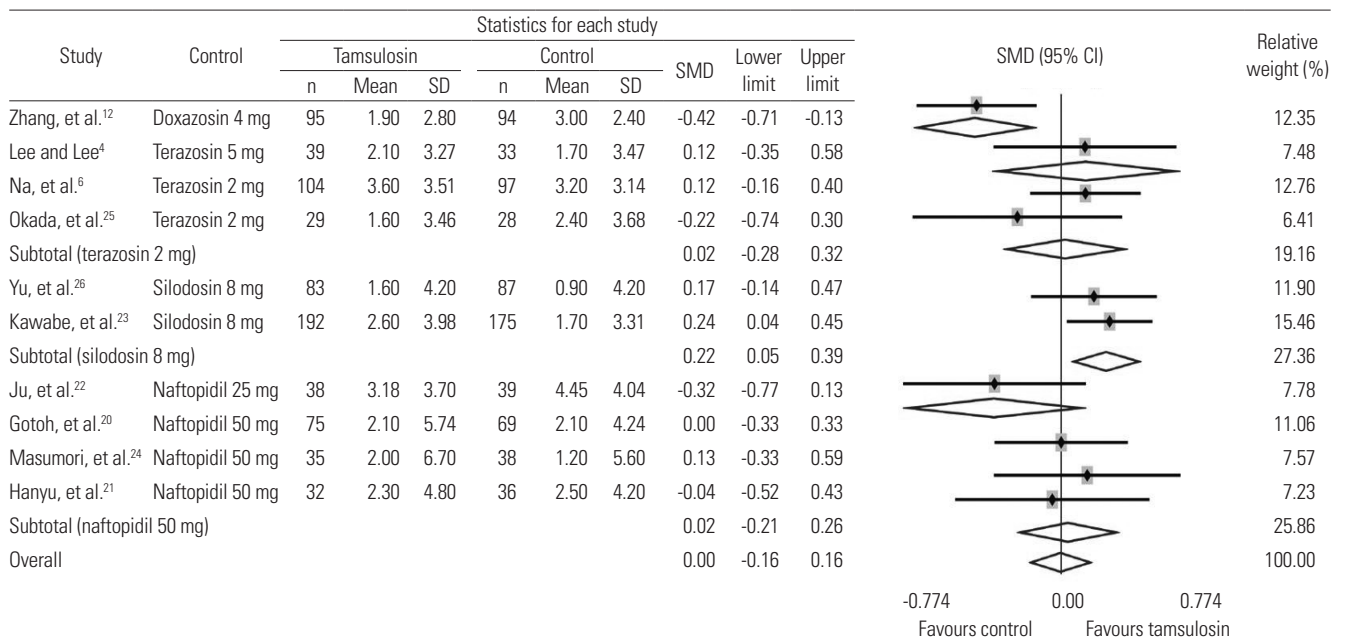


Fig. 4. Forest plot diagram showing the effect of tamsulosin 0.2 mg on maximal urinary flow rate. SDM, standardized mean difference; CI, confidence interval.

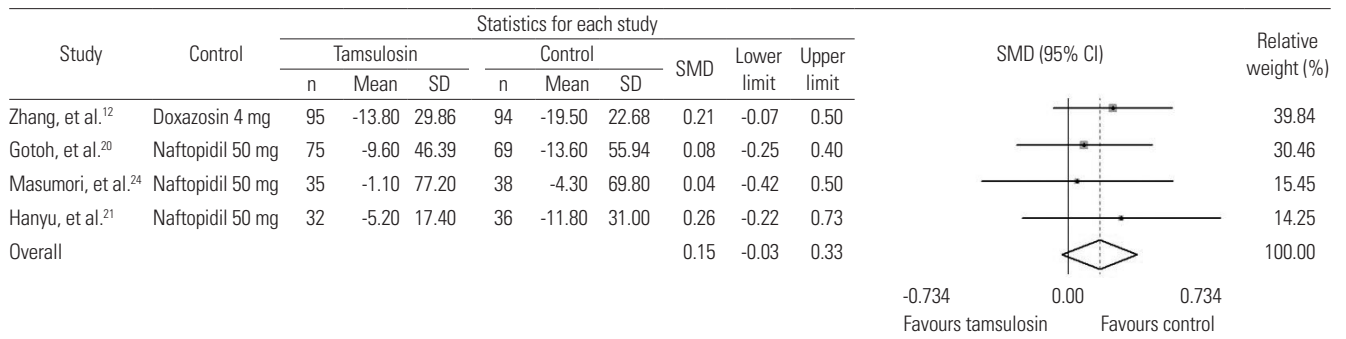


Fig. 5. Forest plot diagram showing the effect of tamsulosin 0.2 mg on post-voided residual volume. SDM, standardized mean difference; CI, confidence interval.

tamsulosin group versus the control group was 0.15 (95% CI; -0.03, 0.33). There was no statistical difference between groups (Fig. 5).

Moderator analyses

Table 3 provides an overview of the moderator analyses. The regression analysis with the continuous variables (number of patients, study duration) revealed no significance in all outcomes as IPSS, QoL, and Qmax. With respect to study duration, there were slightly higher effect sizes in tamsulosin with IPSS and Qmax than control groups (Fig. 6). However, the differences were not significant in IPSS and Qmax ($p=0.832$ and 0.265 , respectively). Subgroup analysis for the pooled IPSS, QoL, and Qmax was performed according to country and control agent. In particular, it was performed for the control group which included more than two studies in each category. The results of meta-ANOVA were not statistically significant in all outcomes. With respect to country, the SMD in China of QoL was 0.559 (95% CI; 0.040, 1.077) and it was in favor of control than tamsulosin. However, it didn't show the difference in the category ($p=0.074$). With respect to control agent, the SMD in silodosin of Qmax was 0.219 (95% CI; 0.050, 0.389) and it was in favor of tamsulosin than control. However, it didn't show the difference in the category ($p=0.127$).

Safety

Three of the 10 studies did not describe adverse events.^{12,21,22} The remaining seven studies^{4,6,20,23-26} described the adverse events including urogenital system, circulatory system, digestive system, nervous system, respiratory system, dermatic system, and others. Although not all studies mentioned specific adverse events, tamsulosin was generally well tolerated and had a lower rate of adverse events, especially compared with terazosin (Table 4). Tamsulosin versus silodosin was described in two studies.^{23,26} Adverse events were reported in 52.4% (144/275) of the tamsulosin group and 70.2% (184/262) of the silodosin group. The differences were statistically significant ($p<0.001$). In more detailed analysis, the tamsulosin group showed high rhinitis value and the silodosin group showed high values of abnormal ejaculation, dry mouth, and loose stool. All were statistically significant. Tamsulosin versus nafopidil was described in two studies.^{20,24} The incidence of adverse events was not significantly different ($p=0.935$). Tamsulosin versus terazosin was described in three studies.^{4,6,25} Adverse events were reported in 8.7% (15/172) of the tamsulosin group and 50.0% (79/158) of the terazosin group. The differences were statistically significant ($p<0.001$). In more detailed analysis, the terazosin group showed higher values of orthostatic hypotension, headache, dizziness, dyspepsia, and dry mouth than the tamsulosin group. All were statistically significant.

Table 3. Effects of Moderators on Each Outcome

Variables	IPSS						QoL value						Qmax							
	k	Coef.*	SMD	SE	95% CI	P value†	k	Coef.*	SMD	SE	95% CI	P value†	k	Coef.*	SMD	SE	95% CI	P value†		
Number of patients	10	0.001	-	0.001	-0.002	0.004	-	0.002	-0.003	0.006	-	0.459	10	0.001	-	0.001	-0.001	0.003	-	0.247
Study duration (wks)	10	-0.008	-	0.037	-0.094	0.078	-	0.065	-0.208	0.128	-	0.568	10	0.029	-	0.025	-0.027	0.086	-	0.265
Country						0.444	-				0.074	-								0.369
Japan	5	-	-0.094	0.183	-0.453	0.264	5	-	-0.010	0.178	-0.358	0.338	5	-	0.060	0.120	-0.175	0.295		
China	4	-	0.111	0.196	-0.274	0.496	2	-	0.559	0.265	0.040	1.077	4	-	-0.095	0.124	-0.339	0.148		
Control agent						0.061	-				0.193	-								0.127
Nafopidil	4	-	-0.252	0.129	-0.505	0.001	3	-	-0.110	0.170	-0.443	0.223	4	-	-0.051	0.104	-0.256	0.154		
Terazosin	3	-	-0.039	0.143	-0.320	0.242							3	-	0.059	0.110	-0.155	0.274		
Silodosin	2	-	0.193	0.137	-0.075	0.461	2	-	0.204	0.171	-0.131	0.538	2	-	0.219	0.086	0.050	0.389		

SMD, standardized mean difference (Hedges's g); k, number of effect sizes; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximal urinary flow rate; SE, standard error; CI, confidence interval. *Regression coefficient, †p values from meta-ANOVA for categorical moderators, ‡p values from random effect meta-regression using restricted maximum likelihood for continuous moderators.

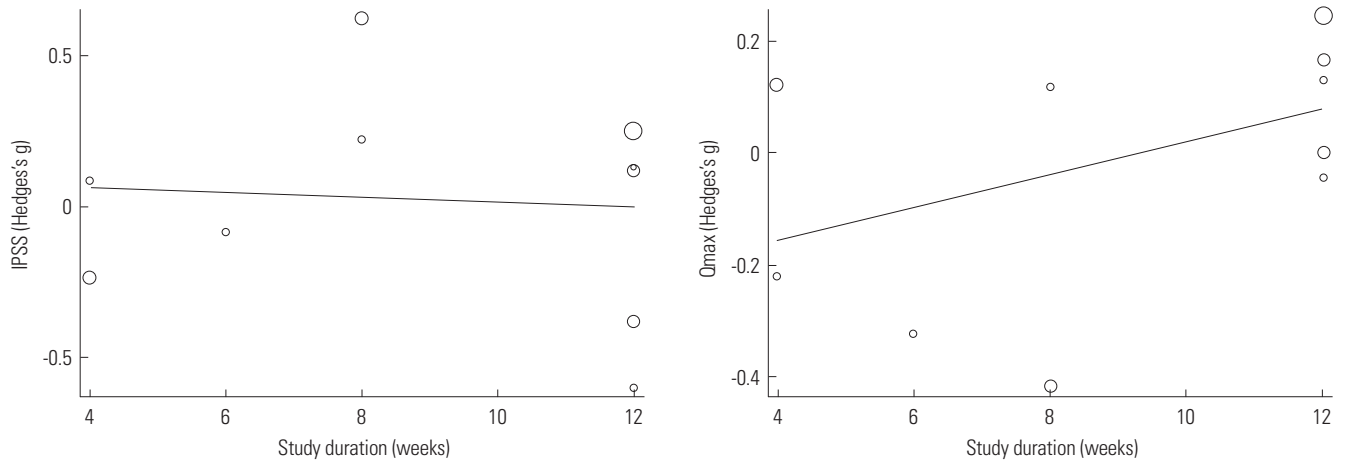


Fig. 6. Meta-regression analysis of IPSS & Qmax vs. study duration. IPSS, International Prostate Symptom Score; Qmax, maximal urinary flow rate.

Publication bias

The Funnel plot to detect the publication bias or small-study effect in the included studies is summarized in Fig. 7. In the IPSS analysis, three studies lay to the left and one study lay to the right of the funnel. Individual studies are distributed symmetrically about the combined effect size and toward the top of the graph. Thus, there was no evidence of publication bias in this meta-analysis.

DISCUSSION

Transurethral prostatectomy has traditionally been regarded as the most effective method, but most patients prefer medical treatment.²⁷ Currently, the efficacy and tolerability of alpha-1-adrenergic blocker are of great interest and regarded as the first-line treatment for treating BPH/LUTS.²⁸ Among the currently available alpha 1 adrenergic blockers (terazosin, doxazosin, alfuzosin, and tamsulosin), tamsulosin is one of the most commonly used alpha blocker due to its well-known efficacy and safety.²⁹ Tamsulosin is known to have less descending effect of blood pressure compared with other non-selective alpha blockers.^{30,31}

An initial study by Abrams, et al.³² showed the efficacy and safety of tamsulosin and suggested the optimum dosage of tamsulosin as 0.4 mg. The standard treatment dosage of tamsulosin in clinical practice in Western countries starts from 0.4 mg/day. However, tamsulosin 0.2 mg as an initial treatment has also been found to be effective in several studies in Asian countries.^{3,5,7} The main reason is the relatively lower BMI of Asian men than Western men. East Asian males, especially Korean, Japanese, and Chinese, have smaller BMIs than Western men, and initial tamsulosin 0.2 mg was set because of expected adverse effects if the same dose used in Western men was adopted. Previous studies with standard dose of tamsulosin showed that the total IPSS score was improved by 36.2% and the Qmax by 13.7% compared with baseline.³²⁻³⁶ Long-term safety and efficacy of tamsulosin 0.4 mg/day were also

demonstrated.³⁶

In our meta-analysis, the improvements of IPSS, QoL, Qmax, and PVR were similar to other alpha-blockers; thus, tamsulosin 0.4 mg and also tamsulosin 0.2 mg are suitable for initial treatment strategy, especially in Asians.

Another merit of tamsulosin 0.2 mg is the lower rate of adverse events. Although most adverse events associated with alpha 1 blockers, especially compared with terazosin, are generally mild and well-tolerated, retrograde ejaculation is an important reason for patient withdrawal. The prevalence of retrograde ejaculation by tamsulosin is known to be about 7%.³⁷ Several reports showed favorable outcome of retrograde ejaculation during intermittent tamsulosin treatment.^{38,39} Giuliano⁸ reported that tamsulosin 0.8 mg decreased mean ejaculatory volume in almost 90% of men while no ejaculation was noted in 35% of men. This ejaculatory side effect is related with the dose of tamsulosin. This is also a reasonable ground for recommending tamsulosin 0.2 mg as a first-line treatment unless the efficacy of tamsulosin 0.2 mg is not inferior to other standard dose of alpha blockers.

Although retrograde ejaculation is a weak point of tamsulosin, a recent large retrospective study described the benefit of taking tamsulosin to improve sexual function in which erectile function was best preserved in men treated with tamsulosin, compared with not taking tamsulosin.⁴⁰ This abnormal ejaculation is related with the dose of tamsulosin. This is also a reasonable ground for recommending tamsulosin 0.2 mg as a first-line treatment.

To the best of our knowledge, this study is the first scientific reviews about tamsulosin 0.2 mg for BPH/LUTS as an initial treatment strategy to investigate, comparing the efficacy and safety with other alpha blockers. Our prior study has investigated the general effect of tamsulosin 0.2 mg using single arm analysis.¹⁵ Using analysis with moderation including meta-regression and meta-ANOVA, we could overcome the heterogeneity of control including different types of alpha blockers. Moreover, the objective analysis of IPSS is the most prominent feature of our study.

Table 4. Adverse Events in Low-Dose Tamsulosin (0.2 mg) Randomized Trials for Benign Prostatic Hyperplasia

Adverse events	No. patients/No. reporting				No. studies	p value
	Tamsulosin	%	Control	%		
Vs. silodosin:					2	
Any adverse event	144/275	52.4	184/262	70.2		<0.001*
Rhinitis	53/275	19.3	33/262	12.6		0.035*
Diarrhea	13/275	4.7	12/262	4.6		0.936
Dizziness	16/275	5.8	16/262	6.1		0.888
Abnormal ejaculation	11/275	4.0	48/262	18.3		<0.001*
Dry mouth	7/275	2.5	18/262	6.9		0.017*
Urinary incontinence	11/275	4.0	11/262	4.2		0.908
Loose stool	7/275	2.5	16/262	6.1		0.042*
Vs. naftopidil:					2	
Any adverse event	15/110	13.6	15/107	14.0		0.935
Headache	2/110	1.8	1/107	0.9		1.000
Diarrhea	1/110	0.9	1/107	0.9		1.000
Abdominal distention	0/110	0.0	1/107	0.9		0.493
Dizziness	5/110	4.5	1/107	0.9		0.212
Orthostatic hypotension	1/110	0.9	2/107	1.9		0.618
Abnormal ejaculation	4/110	3.6	2/107	1.9		0.683
Rash	0/110	0.0	1/107	0.9		0.493
Urinary incontinence	1/110	0.9	0/107	0.0		1.000
Vertigo	1/110	0.9	0/107	0.0		1.000
Sleepiness	0/110	0.0	1/107	0.9		0.493
Numbness tongue	0/110	0.0	4/107	3.7		0.057
Unsteady gait	0/110	0.0	1/107	0.9		0.493
Vs. terazosin:					3	
Any adverse event	15/172	8.7	79/158	50.0		<0.001*
Headache	1/172	0.6	7/158	4.4		0.030†
Constipation	0/172	0.0	4/158	2.5		0.052
Abdominal distention	1/172	0.6	0/158	0.0		1.000
Dyspepsia	0/172	0.0	5/158	3.2		0.024†
Dizziness	10/172	5.8	41/158	25.9		<0.001*
Orthostatic hypotension	1/172	0.6	10/158	6.3		0.004*
Rash	1/172	0.6	1/158	0.6		1.000
Pruritus	1/172	0.6	1/158	0.6		1.000
Dry mouth	0/172	0.0	8/158	5.1		0.003†
Palpitation	0/172	0.0	2/158	1.3		0.228

*Statistically significant differences between categories with same footnote symbol using χ^2 -test, †Statistically significant differences between categories with same footnote symbol using Fisher's exact test.

Limitations of this meta-analysis reflect common limitations of other systematic reviews and meta-analyses. Indirect evidence should be cautiously applied in practice as it is usually considered less reliable than direct evidence.^{41,42} In the present study, however, two sets of controlled trials were sufficiently similar in terms of moderators of relative treatment effect, which enabled scientific indirect analysis with moderation. These systematic reviews and meta-analyses could not overcome the bias of the original studies. Moreover, they were themselves influenced by selection bias and publication bias. For instance, four trials in the present study were laid out of the funnel plot, indicating publication bias. However, Sutton,

et al.⁴³ reviewed 48 articles from Cochrane Database of Systematic Reviews and showed publication or related biases were common in the investigation of meta-analyses. Moreover, they found that these biases did not affect the conclusions in most cases.

Our meta-analysis focused on the comparison between tamsulosin 0.2 mg and other alpha blockers as an initial treatment option. Although we performed a subgroup analysis with limited circumstance due to small number of studies for each subgroup, all other alpha-blockers were compared as controls. This was reasonable for the initial hypothesis of our study. To control the heterogeneity of control groups, we implemented

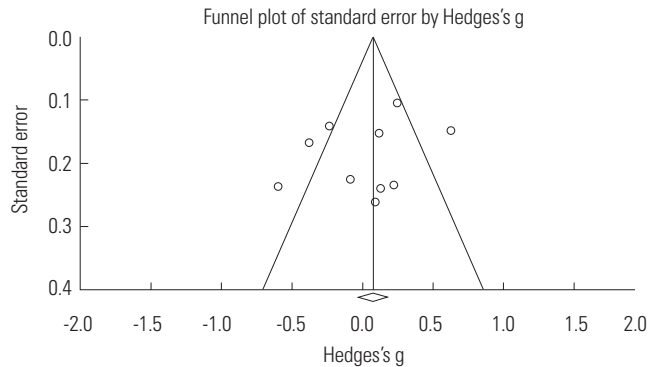


Fig. 7. Funnel plot with pseudo 95% confidence limits of International Prostate Symptom Score.

the meta-regression method to identify the moderator's effect. By this meta-analysis and meta-regressions, we could clarify the efficacy of tamsulosin 0.2 mg compared with other alpha blockers with standard doses.

Although social-demographic factors such as income and extent of education could affect the treatment pattern and outcome in BPH,⁴⁴ we did not include those factors because of the widened heterogeneity and missing data. However, this overview of tamsulosin 0.2 mg provides more scientific evidence of efficacy and safety of tamsulosin 0.2 mg, and also advocates the use of tamsulosin 0.2 mg for first-line treatment.

In conclusion, tamsulosin 0.2 mg is efficacious, with improvements of IPSS, QoL, Qmax, and PVR. Tamsulosin 0.2 mg is suitable as an initial treatment for symptomatic BPH. Considering dose-related adverse events, the indication for tamsulosin 0.2 mg could be widened.

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