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Efficacy of Naftopidil versus Tamsulosin for Lower Urinary Tract Symptoms in Benign Prostatic Enlargement Patients

A Systematic Review and Meta-Analysis

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Objective: To analyze the effectiveness of naftopidil versus tamsulosin as a therapy for patients with LUTS.

Methods: The study was conducted by searching for published studies using the Cochrane Central Register of Controlled Trial search engine, PUBMED, Google Scholar, and Science-Direct. Randomized Controlled Trials (RCTs) that compare naftopidil with tamsulosin as therapy for Lower Urinary Tract Symptoms in BPE patients were identified. A systematic review carried out using protocols The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Results: Five RCTs were included in the IPSS Storage outcome. Naftopidil was not significant (mean difference (MD) -0.56, 95% Confidence Interval (CI) -1.16-0.04, P = 0.07). Three RCTs studies matched the IPSS Voiding outcome (MD -0.28, 95% CI -1.45-0.89, P = 0.63). Seven RCTs studies according to Qmax outcome (MD -0.66.95% CI -1.54-0.22, P = 0.13), Seven RCTs studies according to PVR outcome (MD 1.75, 95% CI -0.49-3.9, P = 0.14). Four RCTs had a low risk of bias, four RCTs unclear of bias, one RCTs had a high risk of bias.

Conclusion: Naftopidil did not have a significant difference compared to tamsulosin in reducing IPPS storage, IPSS voiding, decreasing PVR, increasing Qmax.

Keywords: Naftopidil, tamsulosin, BPE, BPH, LUTS, Qmax, PVR

I. INTRODUCTION

Benign prostate enlargement (BPE) is a disease found in many elder men, caused by the non-malignant proliferation of smooth muscle, connective tissue, and glandular epithelium in the prostate, which obstructs urine flow in the prostatic urethra. Adenoma formation in the transitional and periurethral zones causes pressure on the bladder neck and pars prostatic urethra, and causes lower urinary tract symptoms (LUTS), divided into voiding symptoms (hesitancy, weak stream, urine retention, terminal dribble, straining, and incomplete emptying) and storage symptoms (frequency, urgency, and nocturia) (1).

The incidence of BPE, LUTS, and abnormal urodynamic outcomes will increase with age. The prevalence of moderate/ severe LUTS (IPSS> 7) is about 20% in the 5th decade of life, 30% in the 6th decade, and 40% in the 8th decade of life. In a prevalence study of 2,096 men in Austria, it was found that about 350,000 men aged over 40 years living in Austria (total population of 8.7 million) had moderate to severe symptoms of LUTS. Due to demographic changes, this figure will increase substantially to around 500,000 in the next 2 decades (2).

Increased symptoms of LUTS are associated with decreased quality of life (Qol) and require therapy (1). Various types of alpha-blockers have been used in the past 30 years in BPE patients. Alpha blockers are drugs commonly used to treat BPE. Apha-blocker type drugs continue to change from non-selective short-acting to long-acting selective α1 antagonists. Alpha-blockers consist of three subtypes α 1 A, α 1 B, α 1 D adrenoreceptors (AR). Drug preparations that are often used by alpha blockers are tamsulosin (alpha 1a receptor blocker) and alfuzosin (non-selective alpha 1 blocker) (3).

The safety and efficacy of tamsulosin for LUTS therapy in BPE have been proven based on several randomized clinical trials (RCTs). An alpha blocker with selective pharmacokinetics against the urinary tract (uroselective) was found that inhibits α1D-adrenoreceptor (AR) (naftopidil), which some studies in Japan claim to have lower side effects than α1A-AR (4). Other literature reports that naftopidil is more effective in improving symptom storage than tamsulosin (3,5,6).

A meta-analysis study published in Cochrane, the use of naftopidil in BPE patients with LUTS (data sourced from RCTs) showed an increase in IPSS and Qol similar to that of tamsulosin (1,7). Both meta-analyzes did not explain the outcome storage symptoms, voiding symptoms, maximum flow rate (Qmax), and post-void residual urine (PVR). This meta-analysis aimed to conduct a more detailed analysis and statistical analysis of the storage symptoms, voiding symptoms of Qmax, and PVR; based on various publications that examine the comparison of the efficacy between naftopidil and tamsulosin in BPE patients.

II. RESEARCH METHODS

The systematic review method begins with using the protocol The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The research has been registered in the international database of prospective register of systematic reviews (PROSPERO) with the article code CRD42020202519.

Systematic search

A systematic search for literature published in journal form was carried out from February to March 2021, using the PUBMED and SCIENCE-DIRECT search engines. There is no limit to the year the journal was published. The initial selection was carried out by sorting out titles, abstracts, and keywords according to this study's inclusion criteria. Searches in this study followed the appropriate keywords in each database (Table 1). Further investigation by reading the entire contents of the studies that have been used.

Table 1. Search keywords in each database

Database	Search Terms
PubMed/MEDLINE	("naftopidil"[All Fields] OR "Alpha1-adrenoreceptor antagonist "[All Fields] OR "Alpha Blocker"[All Fields]) AND ("tamsulosin"[All Fields] OR "Alpha1-adrenoreceptor antagonist "[All Fields] OR "Alpha Blocker"[All Fields]) AND ("Benign prostatic hyperplasia"[All Fields] OR "Benign prostatic enlargement"[All Fields] OR "BPH"[All Fields] OR "BPE"[All Fields]) AND ("LUTS"[All Fields] OR "Lower Urinary Tract Symptoms"[All Fields] OR "IPSS"[All Fields] OR "International Prostate Symptoms Score"[All Fields] AND ("QoL"[All Fields] OR "Quality of life"[All Fields]) AND ("Qmax"[All Fields] OR "Uroflowmetri"[All Fields])
Science Direct	(Naftopidil AND Tamsulosin) AND (Lower urinary tract symprom OR BPH) Article types: Research articles

Inclusion and exclusion criteria

This study involved randomized controlled trials (RCTs) in English only. Studies comparing naftopidil and tamsulosin directly in BPE / BPH patients with LUTS, and studies with two or more arms were included in the inclusion criteria. Research with observational design (cohort, case control, and cross sectional), comments, editorial, review, case report / case series, studies on neurogenic bladder patients, articles that is only in the form of abstract, animal studies and in-vitro studies are excluded.

Study Selection and Data Extraction

The selection process in this study used the PRISMA flowchart guideline (Figure 1). The first, second, and third authors all contributed to the study selection and data extraction. If there are problems and disagreements, it will be resolved by discussion. Data extraction performed in each study were: Name and year of study author, study design, number of samples, type of intervention, prostate size, mean difference and confidence interval (95% CI) of each outcome.

Data Analysis Techniques and Statistical Testing

Data extraction from each study will be entered into tabulations. Continuous data were analyzed using mean difference with confidence interval (CI) at 95%, and p value below 0.05 was considered statistically significant. Heterogeneity between studies is calculated using I^2, if I^2> 50% is considered statistically high heterogeneity and a random effect model is applied. If I^2 <50%, then the fixed effect model is applied to this meta-analysis. Statistical analysis using RevMan 5.4 software for Windows is presented in the form of a forest plot and descriptive narrative.

Risk of Bias

The risk of bias in each study that met the inclusion criteria using the method from the Cochrane Risk of Bias Tools In For Randomized Trial 2 which divides the risk of research bias based on the randomization process, deviation from intervention, missing outcome data, measurement of study results, and selection of research results. that was reported.

III. RESULTS

There are 528 journal articles obtained using the initial selection keywords, and there are four additional studies obtained from the bibliography of several studies. We eliminated 56 studies because they were duplicate studies. In the further selection stage, by reading the title, abstract, keywords and full text, nine randomized controlled trials (RCTs) studies were obtained which matched with the study inclusion criteria. Name and year of study author, study design, number of samples, type of intervention, and prostate size were included in the tabulation of this study's baseline characteristics (Table 1).

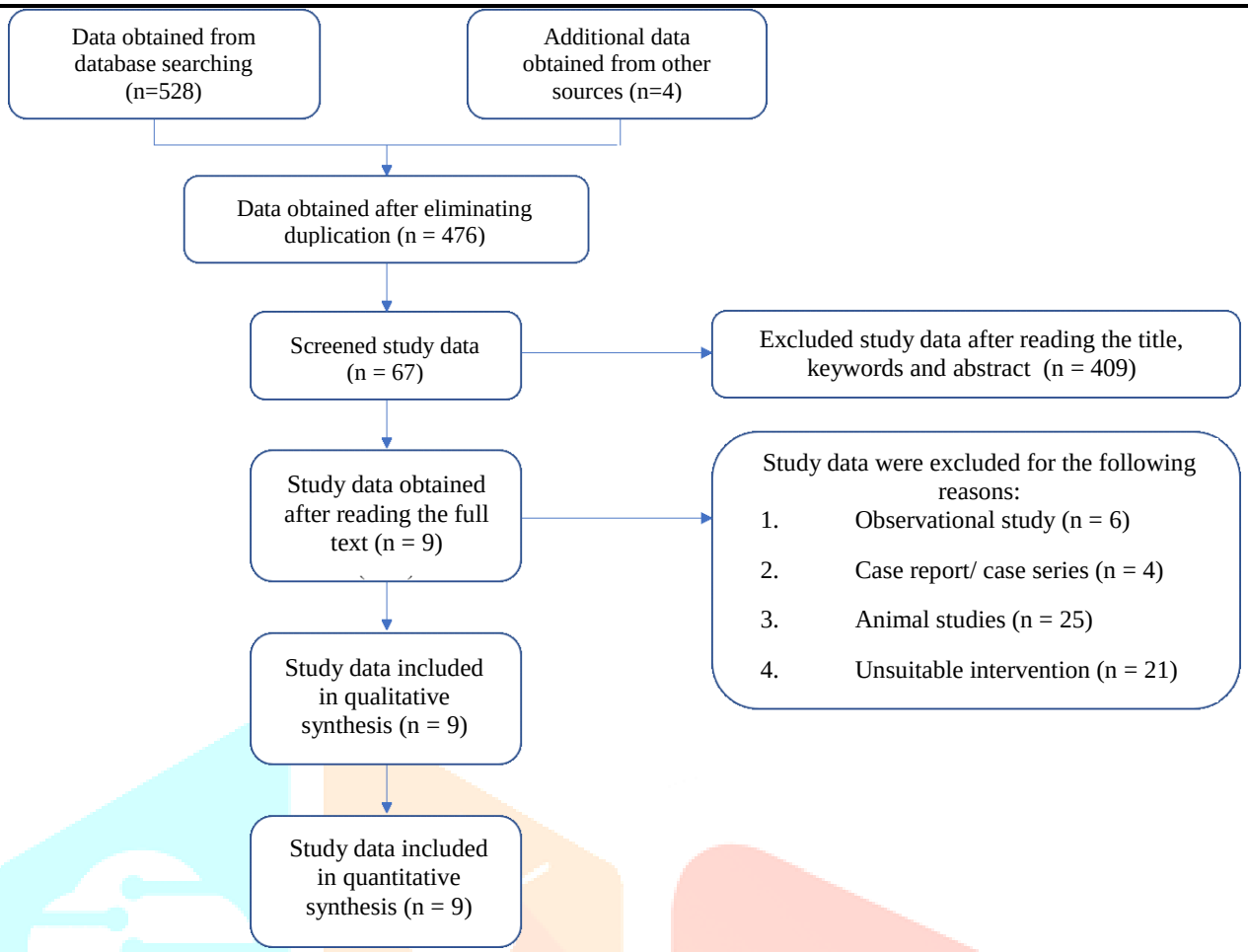

Figure 1. Flow diagram of meta-analysis

Baseline characteristics of research data

There are five studies originating from Japan (5,6,8–10), three studies from India (3,4,11), and one from South Korea (12). The total sample of all studies that met the inclusion criteria of this study was 876 patients. The number of each sample from each intervention group was divided equally. There is a difference in the mean of prostate size between each study, but the study conducted by Perumal et.al 2015 did not include the mean prostate size in the study subjects (3,12).

Table 1. Baseline characteristics of research articles

Author	Country	Design	Sample	Intervention	Prostate size	
					Naftopidil	Tamsulosin
Yokoyama (13)	Japan	RCT	96	Naftopidil vs Tamsulosin	38.9	32.7
Gotoh (9)	Japan	RCT	185	Naftopidil vs Tamsulosin	33.6	29
Nishino (5)	Japan	RCT	45	Naftopidil vs Tamsulosin	20.6	18.9
Ukimura (6)	Japan	RCT	77	Naftopidil vs Tamsulosin	24.4	26.7
Shigemura (10)	Japan	RCT	81	Naftopidil vs Tamsulosin	30	28.5
Singh (14)	India	RCT	110	Naftopidil vs Tamsulosin	31.38	30.01
Griwan (11)	India	RCT	120	Naftopidil vs Tamsulosin	57.73	56.81
Perumal (3)	India	RCT	60	Naftopidil vs Tamsulosin	No data available	
Kwon (15)	Korea	RCT	102	Naftopidil vs Tamsulosin	37.5	36.8

Risk of bias

Risk of bias analysis used the Cochrane Risk of Bias Tools In For Randomized Trials 2 (Figure 2). There were three studies included in the research inclusion criteria that did not adequately describe the samples' randomization process into each intervention group (3,11,13). Five studies did not explain whether the treatments were blinded or not (3,9,10,13,15). One study has a high risk of bias because it does not explain the randomization process. The reporting of research results is incomplete and does not include standard deviation in outcomes with continuous data (3).

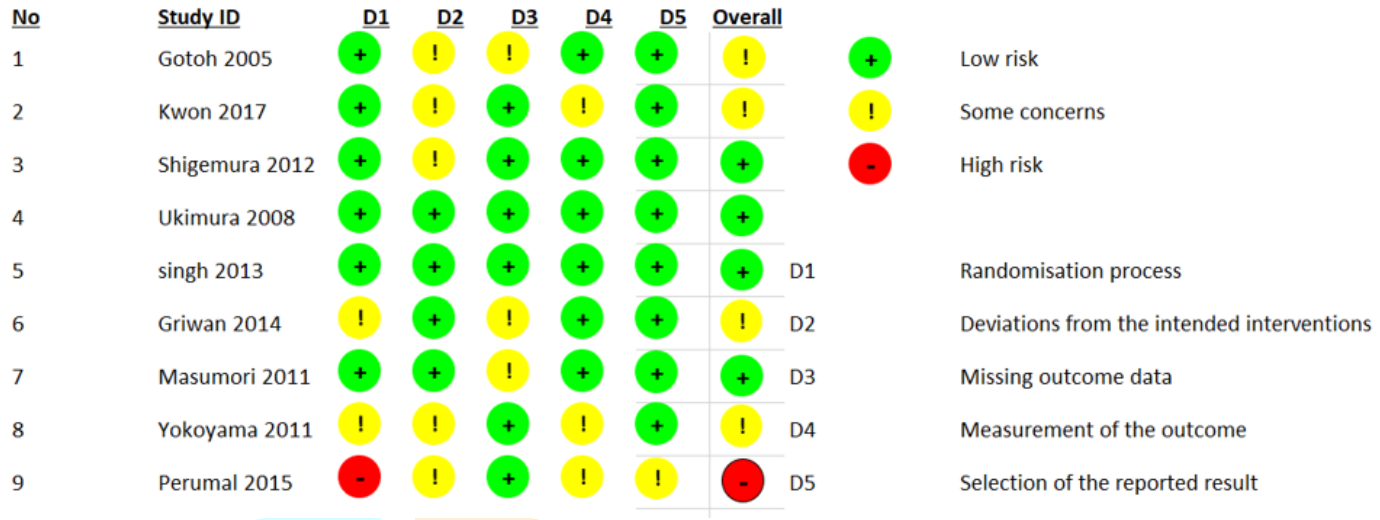

Figure 2. Summary of the risk of bias

IPSS Storage Score Between Naftopidil Compared with Tamsulosin

One of the aims of this study was to evaluate the differences in IPSS storage scores in BPE patients given naftopidil and tamsulosin. The IPSS Storage score is the total score on the storage symptom questions on the IPSS questionnaire, which includes frequency, urgency and nocturia. Five studies from nine studies that have the same showed a higher mean difference (SD) -2.4 (5.796) from the naftopidil group, but the tamsulosin group had a higher mean difference, -3.4 (8,592). In contrast to the three other studies that examined differences in IPSS storage, the naftopidil group had a greater mean difference in IPSS storage scores than the tamsulosin group, especially a study conducted by Singh et.al for the naftopidil group, the mean difference (MD) was -4.14. (3.102) and -2.54 (3.102) for the tamsulosin group (Table 2).

Table 2. IPSS - storage score for each group

Author	Sample	Mean difference in IPSS storage (SD)	
		Naftopidil	Tamsulosin
Gotoh 2005	Naftopidil (69) vs Tamsulosin (75)	-2,4 (5,796)	-3.4 (8,592)
Kwon 2017	Naftopidil (49) vs Tamsulosin (45)	-1,5 (2,995)	-1.4 (2,858)
Shigemura 2012	Naftopidil (41) vs Tamsulosin (36)	-1,9 (2,131)	-1.44 (2,021)
Singh 2013	Naftopidil (50) vs Tamsulosin (51)	-4,14 (3,102)	-2.54 (3,102)
Ukimura 2008	Naftopidil (22) vs Tamsulosin (25)	-3.5 (4,934)	-2.8 (7,658)

In the forest plot analysis, the four studies' combination has heterogeneity, which is still classified as low statistically with I^2 = 22% (P = 0.27). Therefore, a fixed effect statistical model is used to determine the results of the study. Furthermore, in this study, there was an insignificant difference (P = 0.07) between the IPSS storage score of the naftopidil group compared to the tamsulosin group with an accumulated mean difference of -0.56 (95% CI = -1.16-0.04) (Figure 3).

IPSS Voiding Score Between Naftopidil Compared with Tamsulosin

The IPSS Voiding score is the total score on the questions of voiding symptoms on the IPSS questionnaire which includes weak stream, intermittency, straining and incomplete emptying. Three out of nine studies compared differences in mean IPSS scores for voiding in patients with BPE who were given naftopidil or tamsulosin. The study results showed that there were two studies that stated that the tamsulosin group had a greater mean difference in IPSS voiding score compared to the naftopidil group. However, in the study conducted by Shigemura et.al, the naftopidil group had a greater mean difference (SD), namely -2.22 (3.040) when compared to the tamsulosin group, namely -1.55 (2.843) (Table 3).

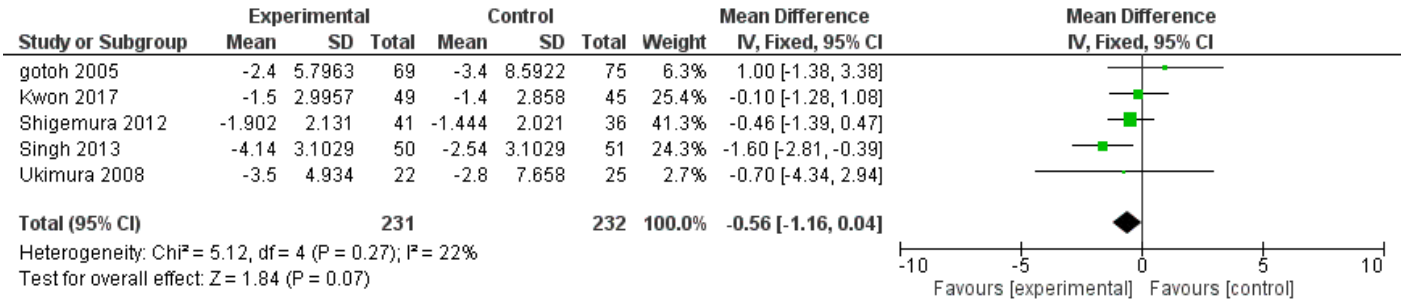

Figure 3. Forest plots of differences in IPSS storage scores between naftopidil and tamsulosin

Table 3. IPSS Voiding score of each group

Author	Sample	Mean difference in IPSS voiding (SD)	
		Naftopidil	Tamsulosin
Gotoh 2005	Naftopidil (69) vs Tamsulosin (75)	-3,7 (7,434)	-5,3 (11,158)
Shigemura 2012	Naftopidil (41) vs Tamsulosin (36)	-2,22 (3,040)	-1.55 (2,843)
Shigemura 2012	Naftopidil (50) vs Tamsulosin (51)	-3,6 (6,256)	-3,8 (11,053)

In the Forest plot analysis, the four studies' combination has heterogeneity, which is still classified as low statistically with I^2 = 22% (P = 0.27). Therefore, a fixed effect statistical model is used to determine the results of the study. Furthermore, in this study, there was an insignificant difference (P = 0.07) between the IPSS storage score of the naftopidil group compared to the tamsulosin group with an accumulated mean difference of -0.56 (95% CI = -1.16-0.04) (Figure 4).

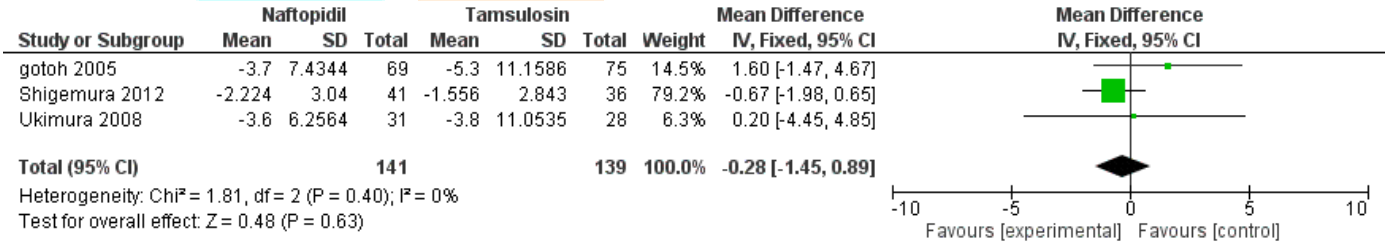

Figure 4. Forest plots of differences in the IPSS voiding score between naftopidil and tamsulosin

PVR Value Between Naftopidil Compared with Tamsulosin

The mean difference in PVR value is also an outcome to be investigated. PVR is the residual or residual urine that remains in the bladder after urinating completely. Seven of the nine studies had the same outcome measures the mean value of PVR, but not all studies include a standard deviation. Therefore, a function in the RevMan 5.4 software is used to measure the estimated standard deviation. Four studies stated that the naftopidil group had a higher mean difference in PVR values than the tamsulosin group (Table 4).

Table 4. The mean difference in PVR of each group

Author	Sample	Mean difference in PVR (SD)	
		Naftopidil	Tamsulosin
Gotoh 2005	Naftopidil (69) vs Tamsulosin (75)	-13,6 (36,697)	-9,6 (29,506)
Griwan 2014	Naftopidil (60) vs Tamsulosin (60)	-50,37 (146,58)	-60,58 (176,29)
Kwon 2017	Naftopidil (49) vs Tamsulosin (45)	-6,4 (5,734)	-8,3 (5,734)
Masumori 2011	Naftopidil (38) vs Tamsulosin (35)	4,3 (72,570)	1.1 (16.9)
Perumal 2015	Naftopidil (30) vs Tamsulosin (30)	-76,43 (114,39)	-75,77 (113,41)
Ukimura 2008	Naftopidil (23) vs Tamsulosin (14)	-15,9 (22,123)	-3.5 (92,851)
Yokoyama 2011	Naftopidil (50) vs Tamsulosin (51)	-10,8 (30,873)	-22,8 (68,196)

In the Forest plot analysis, the combined seven studies had statistically low heterogeneity with I^2 = 0% (P = 0.89). Therefore, a fixed effect statistical model is used to determine the results of the study. Furthermore, although the analysis showed that tamsulosin was better at reducing the amount of PVR, statistically insignificant differences (P = 0.13) were found between the mean difference

in the PVR value of the naftopidil group compared to the tamsulosin group; with an accumulated mean difference of -1.75 (95 % CI = - 0.49-3.99) (Figure 5).

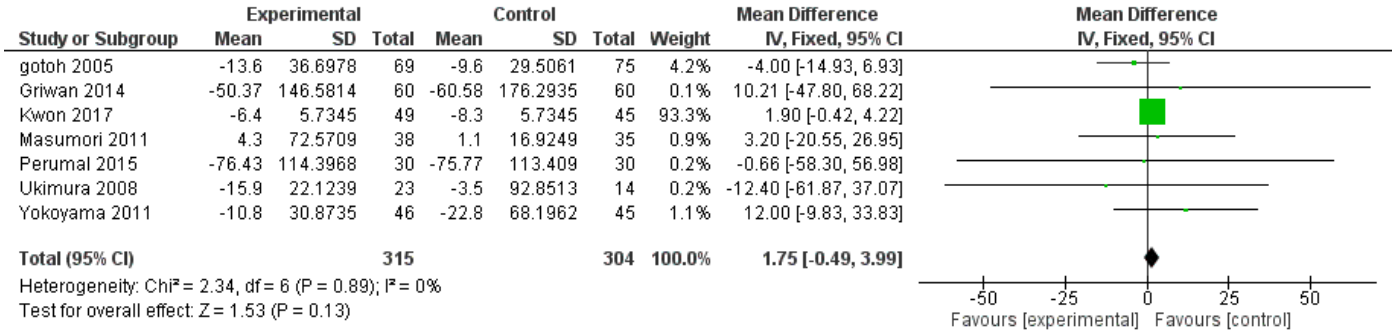

Figure 5. Forest plot of the PVR mean difference value between naftopidil and tamsulosin

Qmax Value Between Naftopidil Compared with Tamsulosin

The difference in the mean value of Qmax is also the outcome to be studied. Qmax is the maximum rate of urinary flow that can be achieved by the patient through a uroflowmetry device. Seven of the nine studies had the same outcome. However, not all studies include standard deviation, therefore a function in RevMan 5.4 software is used to measure the estimated standard deviation. Only Perumal et.al who stated that naftopidil could increase Qmax greater than tamsulosin with a mean difference of 9.2 (13,770) in the naftopidil group and 7.2 (10,776) in the tamsulosin group (Table 6).

Table 5. The mean difference of Qmax from each group

Author	Sample	Mean difference in Qmax (SD)	
		Naftopidil	Tamsulosin
Gotoh 2005	Naftopidil (69) vs Tamsulosin (75)	2,1 (5,071)	2,1 (3,834)
Griwan 2014	Naftopidil (60) vs Tamsulosin (60)	1,12 (3,259)	1,87 (5,441)
Kwon 2017	Naftopidil (49) vs Tamsulosin (45)	-0,9 (3,991)	1 (6,030)
Masumori 2011	Naftopidil (38) vs Tamsulosin (35)	1,2 (5,889)	2 (6,932)
Perumal 2015	Naftopidil (30) vs Tamsulosin (30)	9,2 (13,770)	7,2 (10,776)
Ukimura 2008	Naftopidil (18) vs Tamsulosin (13)	1,3 (3,466)	2,8 (9,731)
Yokoyama 2011	Naftopidil (46) vs Tamsulosin (45)	2,7 (11,361)	3,5 (13,729)

In the Forest plot analysis, the combined 7 studies had statistically low heterogeneity with I^2 = 0% (P = 0.82). Therefore, a fixed effect statistical model is used to determine the results of the study. Furthermore, although the analysis showed that tamsulosin was better at increasing the Qmax value, statistically there was no significant difference (P = 0.14) between the mean difference in Qmax value of the naftopidil group compared to the tamsulosin group with an accumulated mean difference of -0.66 (95 % CI = -1.54-0.22) (Figure 6).

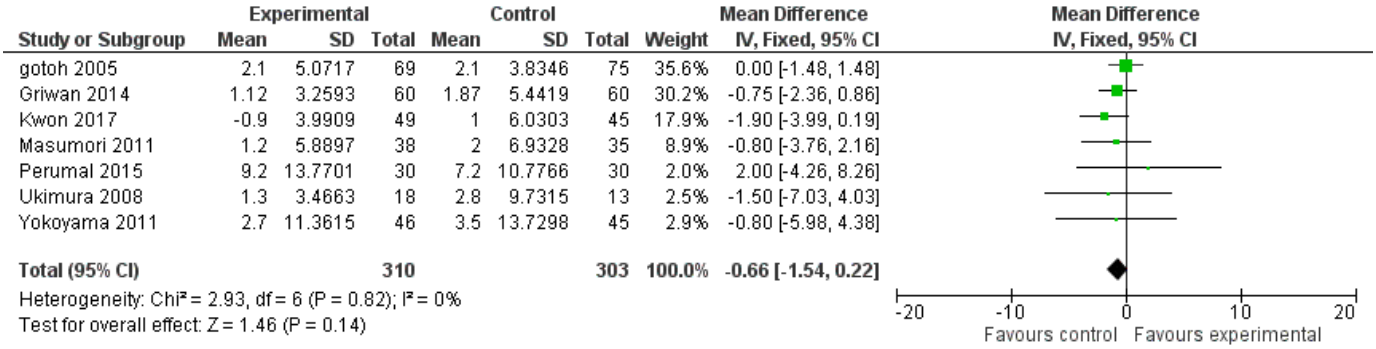

Figure 6. Forest plot of Qmax mean difference value between naftopidil and tamsulosin

IV. Discussion

Alpha blockers are a therapy option that is often used for BPE patients with complaints of LUTS due to fast and safe drug reactions. Various types of alpha-blockers have been used in the past 30 years in BPE patients. Alpha blockers are drugs commonly used to treat BPE. Apha-blocker type drugs continue to change from non-selective short-acting to long-acting selective α1 antagonists. Alpha blockers consist of three subtypes α 1 A, α 1 B, α 1 D adrenoreceptors (AR). Drug preparations that are often used by alpha blockers are tamsulosin (alpha 1a receptor blocker) and alfuzosin (non-selective alpha 1 blocker) (3).

The safety and efficacy of tamsulosin for LUTS therapy in BPE have been proven based on several randomized clinical trials (RCTs). It has been found that alpha blockers with selective pharmacokinetics of the urinary tract (uroselective) block other α1D-adrenoreceptors (AR) (naftopidil). Other literature reports that naftopidil is more effective in improving symptomatic storage than tamsulosin (3,5,6).

Naftopidil, has three times greater affinity for α1D than subtype α1A-AR, which is an α1-blocker that has been approved for clinical use for LUTS / BPE in Japan, since 1999. It differs from tamsulosin and silodosin, which have a higher affinity. and very high for the α1A-AR subtype than for the α1D-AR subtype, respectively. Since BPH tissue exhibits nine and threefold increased mRNA expression in the α1A and α1D-AR subtypes, compared to normal prostate tissue, there is a theory that not only α1A, but also α1D-AR contributes to prostate smooth muscle contraction (11). Besides, α1D-adrenoreceptors are involved in increased stimulation of the bladder at the spinal level (3). Naftopidil, which blocks the α1D adrenoceptor is expected to improve urinary symptoms and may be effective in treating men with BPH-related storage symptoms, namely nocturia. Of the overall studies, some studies have used a dose of 50 mg of naftopidil and some have used a dose of 75 mg. The dose of tamsulosin used for comparison also ranged from 0.2 mg to 0.4 mg.

The mean difference in IPSS storage scores did not have a statistically significant value (P = 0.07) with the accumulated mean difference of -0.56 (95% CI = -1.16-0.05). Of the five studies that met the inclusion criteria, the 2013 Singh study showed a significant difference between the mean differences in IPSS storage scores. Previous studies have shown that there is a significant decrease in the value of IPSS storage in patients with LUTS who are given naftopidil therapy. The difference is not significant when compared to tamsulosin although there are several studies that show that naftopidil is slightly superior in reducing storage symptoms (9,10,12,16). In contrast to the research conducted by Iqbal et al. that at 15 and 30 days of treatment, naftopidil can relieve symptoms of storage better than tamsulosin. The initial improvement in storage symptoms induced by naftopidil may be related to its strong effect on nerves that have alpha-1D receptors, and to inhibition of stimulation of detrusor muscle afferents (4).

Three out of nine studies met the inclusion criteria measuring the outcome differences in the mean of IPSS voiding. After analyzing visualized with a forest plot, there was no significant difference (P = 0.63) between the naftopidil and tamsulosin groups with a mean difference of -0.28 (95% CI = -1.45-0.89). Previous studies that examined the comparison of the effectiveness of naftopidil and tamsulosin on voiding symptoms also stated that there was no difference in reducing voiding symptoms between naftopidil and tamsulosin (6,9). The study by Shigemura et al., 2012 showed that the difference in the naftopidil group was better than the tamsulosin group due to the 75 mg dose used which had a better effect on storage and voiding symptoms than other studies using 50 mg doses more dominant improvement in complaints of storage, such as nocturia (10).

The mean difference in PVR value is also an outcome to be investigated. PVR is the residual urine that is still in the bladder after urinating completely. Four studies stated that the naftopidil group had a higher mean difference in PVR values than the tamsulosin group (3,6,9,13). After analyzing using a forest plot, the mean difference in PVR values was not statistically significant (P = 0.13) between the naftopidil and tamsulosin groups. The decrease in PVR value with naftopidil administration is associated with alpha-1D which can increase bladder compliance (3).

The difference in Qmax value did not have a statistically significant value (P = 0.14) with the accumulated mean difference of -0.66 (95% CI = -1.54-0.22). There were 2 studies that did not report the standard deviation of research data, therefore the calculation of the estimated standard deviation was used (6,13). Previous RCT studies also support the results of this study that although naftopidil can increase Qmax in patients with LUTS due to BPH, the difference is not significant when compared with tamsulosin (3,10–12).

This study has several limitations, including 1 study that met the inclusion criteria in this study had a high risk of bias and there were 4 studies that were feared to have a high bias. Existing studies are limited to the population of Japan, India and South Korea. There are several studies that do not include a standard deviation or standard error in the results of the study with continuous data. Therefore, a supporting tool is used to measure the estimated standard deviation provided by the Revman 5.4 software. Further studies are needed to be carried out, especially focus on the use of naftopidil in multicentre and multinational research design. The existence of differences in the genotype of one population with another population may affect studies' results. Besides, standard deviations and data completeness in assessing each score system in the group under study needs special attention. It is intended to facilitate analysis using secondary data in the future study.

V. Conclusion

Our meta-analysis study showed that naftopidil did not significantly decrease storage symtoms, voiding symptoms, increasing maximum flow rate (Qmax), decreasing post-void residual urine (PVR); compared to tamsulosin. It can be concluded that naftopidil has similar effectiveness to tamsulosin. Therefore, naftopidil can be used as a therapeutic option to treat LUTS symptoms in patients with BPE. Further RCT studies are needed to compare the efficacy between naftopidil and tamsulosin and other alpha-blockers with samples from several countries. The existing RCTs are only limited to populations in Japan, Korea and India.

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