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Combination of α -blocker and 5 α -reductase inhibitor for treatment of benign prostatic hyperplasia

Abstract

Purpose: This study compared the efficacy of an α -blocker monotherapy alone with a combination of α -blocker plus 5 α -reductase in treatment of benign prostatic hyperplasia (BPH).

Methods: Medline (PubMed), EMBASE, CENTRAL (Cochrane databases) and Google Scholar were searched until May 2015 using the following search terms: ($[\alpha$ -blocker] AND 5 α -reductase inhibitor) AND benign prostatic hyperplasia; and benign prostatic hyperplasia AND (adrenergic alpha blockers OR 5 alpha reductase inhibitor). Randomized controlled trials (RCTs) that included men with a clinical diagnosis of BPH were included. Eligible studies had to have an intervention group that received combination therapy (5 α reductase inhibitor plus α -blocker) and a control group that received only α -blocker. Quality assessment and sensitivity analysis were performed.

Results: Six studies were included. Combination therapy was found to significantly reduce urinary retention incidence rate (OR=0.286, 95%CI: 0.199 - 0.412, $P<0.001$) and lower the risk of surgical treatment (OR=0.277, 95%CI: 0.20- 0.384, $P<0.001$), and to result in a greater reduction in prostate volume (mean difference = -7.387, 95%CI: -12.982 to -1.791, $P=0.010$) and larger increase in maximal urinary flow rate (mean difference = 0.527, 95%CI: 0.052 - 1.003, $P=0.030$) compared with monotherapy. The two treatments were similar with respect to improvement in the International Prostate Symptom Score (IPSS) (mean difference = -0.087, 95%CI: = -0.231 to 0.058, $P=0.239$). Sensitivity analysis indicated that no one study overly influenced the findings and that the findings are robust. Quality analysis indicated the included studies were of good quality.

Conclusion: These findings indicate that combined α -blocker plus 5 α -reductase therapy is more beneficial in treating benign prostatic hyperplasia in contrast to α -blocker monotherapy.

Manuscript submitted 19th March, 2017
Manuscript accepted 18th August, 2017

Clin Invest Med 2017; 40 (5): E200-E210.

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Benign prostatic hyperplasia (BPH) is prevalent in older men: approximately 50% of men over the age of 50 years have BPH [1,2]. The risk of developing BPH increases with age and approximately 90% of men over the age of 90 years have BPH [3]. BPH compresses the urethra, which can result in lower urinary tract symptoms (LUTS) due to bladder outlet resistance [4]. LUTS can impact a patient's quality of life by disturbing sleep and daily activities [5].

The treatments for BPH/LUTS aim to relieve symptoms and to reduce the clinical progression of the disease. Guidelines recommend oral treatments that include α -adrenoceptor agonists (α -blockers), 5 α -reductase inhibitors and antimuscarinic agents [6,7]. The α -adrenoceptor agonists and 5 α -reductase inhibitors differ in their mechanisms of action and clinical profiles [8]. The α -adrenoceptor agonists cause smooth muscle relaxation in the prostate/bladder neck, resulting in increased urinary flow and a reduction of LUTS [6,9,10]. The 5 α -reductase inhibitors reduce prostate hyperplasia by blocking the conversion of testosterone to the active form [8]. As there is incomplete correlation between prostate enlargement and LUTS, treatments targeting prostate hypertrophy may not adequately control LUTS [11].

Several prior studies have evaluated the efficacy and tolerability of monotherapy with α -adrenoceptor agonists or with 5 α -reductase inhibitors. It was found α -adrenoceptor agonists were effective in managing BPH-related LUTS and improving urinary flow rate, whereas, 5 α -reductase inhibitors were effective in improving International Prostate Symptom Score (IPSS) score, reducing prostate size and preventing disease progression [8].

On the other hand, combination therapy of both α -adrenoceptor agonists and 5 α -reductase inhibitors has the potential to overcome some of the limitations with the respective monotherapies. Studies that compared the efficacy of monotherapy with combination therapy showed that, in general, combination therapy improved symptoms, reduced frequency of acute urinary retention, slowed clinical progression and reduced the need for surgery better than monotherapy [8,12-16]. Consistent with current lines of evidence, the guideline from American Urology Association recommends treating patients with moderate to severe symptoms and with enlarged prostates with both α -adrenoceptor agonists and 5 α -reductase inhibitors [7].

Although several studies have shown that combination therapy is beneficial in treating BPH and associated symptoms, clinical studies comparing monotherapy versus combination therapy for the management of LUTS/BPH are limited [8,16]. Specifically, the importance

and value of adding a 5 α -reductase inhibitor to α -blocker-based monotherapy is not fully understood. The objective of the present study was to compare previously published studies on α -blocker monotherapy versus α -blocker plus 5 α -reductase inhibitor combination therapy for treatment of benign prostatic hyperplasia.

Materials and Methods

Search strategy

The study was performed in accordance with the PRISMA guidelines. The following electronic databases were searched: MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials, CENTRAL) (The Cochrane Library) and Google Scholar. All searches were updated on May 2015 using the following search terms: (α -blocker AND 5 α -reductase inhibitor) AND benign prostatic hyperplasia; and benign prostatic hyperplasia AND (adrenergic α -blockers OR 5 α -reductase inhibitor). Randomized controlled trials (RCTs) that included men with a clinical diagnosis of BPH were included. Eligible studies had to have an intervention group that received combination therapy (5 α -reductase inhibitor plus α -blocker) and a control group that received only α -blocker therapy.

In addition, reference lists of reviews and retrieved articles were checked for additional studies. Trial registers were searched for ongoing clinical trials. Studies were excluded if they evaluated patients with diagnosed bladder or prostate cancer or were not published in either English or Chinese. Letters, comments, editorials, case report, proceedings and personal communication were also excluded.

Two of the review's authors independently checked all electronic search results for eligibility. When search results could not be assessed with certainty based on title, abstract or both, full-text material was obtained and reviewed. Two of the review's authors independently applied the inclusion and exclusion criteria. Disagreements were resolved by discussion and with the involvement of a third of the review's authors.

Data extraction

Piloted extraction forms were used for epidemiological studies and RCTs to document data from the original material and to assess the quality of studies. Two of the authors extracted data independently and a third author was consulted for resolution of any disagreement.

The following data were extracted: first author's name, study design, number of patients, treatment group,

interventions, description of the interventions, mean age, length of follow-up and summary of outcomes of interest.

Assessment of risk of bias in included studies

Generation of allocation sequence, allocation concealment, blinding and completeness of outcome data were categorized as adequate (low risk of bias), inadequate (high risk of bias) or unclear, according to the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions [17]. These four categories were considered to be key domains for risk of bias assessment. Studies that were categorized as “adequate” in all four domains were considered to have a low risk of bias; studies with inadequate procedures in one or more key domains were considered to have a high risk of bias. Studies with unclear procedures in one or more key domains were considered to have an unclear risk of bias.

Data analysis

The outcomes of interest included rate of acute urinary retention, change of IPSS, rate of patients received operation and change from before and after intervention in prostate volume and maximum flow rate.

For dichotomous outcomes (e.g., rate of acute urinary retention and rate of patients received operation), the number of patients in each treatment arm who experienced the outcome of interest was abstracted. In order to estimate the effect size, an odds ratio (OR) of combination therapy as comparing with monotherapy. An effect size greater than 1 ($OR > 1$) indicated the combination therapy had a higher rate compared with the monotherapy, if $OR < 1$, then the combination therapy had lower rate compared with the monotherapy and if the $OR = 1$, then the outcome rate was similar between treatment groups. For continuous outcomes (e.g., IPSS, prostate volume and maximum flow rate), the final value and standard deviation of the outcome of interest in each treatment arm at the end of follow-up was abstracted for each study. An effect size of 0 indicated that the change in an outcome was similar between groups. The treatment effect for maximum flow rate was inversely related to difference in means.

For continuous outcomes, we pooled the mean differences between the treatment arms at the end of follow-up using the mean difference (MD) method if all trials have measured the outcome on the same scale, or using the standardized mean difference (SMD) method otherwise. For dichotomous outcomes, we calculated the OR for each study and then all studies were pooled.

Heterogeneity among the studies was assessed by calculating Cochran Q and the I^2 statistic simultaneously. A Q statistic with $P < 0.1$ [18] or an I^2 statistic $> 50\%$ [19] was indicative of obvious heterogeneity among the studies. When obvious heterogeneity was observed, a random-effect model (DerSimonian-Laird method) [20] was used; otherwise a fixed-effect model was employed (Mantel-Haenszel method). Sensitivity analysis for each outcome was carried out based on the leave-one-out approach. Publication bias was not assessed because of the limitation in the number of studies included in the meta-analyses [21]. All data were arranged using Microsoft Office Excel 2007 and all analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Search results

Of the 147 studies initially identified, 116 were removed for not being relevant or not meeting the inclusion/exclusion criteria. Thirty-one articles were fully assessed and 23 were excluded for being retrospective studies, review articles or not reporting findings on 5α -reductase inhibitor plus α -blocker compared with α -blocker alone (Figure 1).

Six RCTs, reported in eight articles, with a total of 6,838 participants were included in this review [13,14,22-28]. Kaplan *et al.* (2008) and Fwu *et al.* (2013) were additional analyses of the study of McConnel *et al.* (2003) (Table 1). The total patient population included was 3,438 for the combination therapy and 3,400 for the monotherapy group. The number of patients in each study ranged from 98 to 1,610 in the combination therapy group and from 95 to 1,611 in the monotherapy group. The mean age ranged from 63 to 66 years. The mean follow-up time ranged from 6 to 54 months. The treatments used varied across studies and are summarized in Table 1. The results of outcomes are summarized in Table 2.

Quality assessment

Overall the six studies were of adequate quality (data not shown but are available upon request). Joo *et al.* (2012) had high risk of bias in allocation concealment and blinding of participants and personnel. Joo *et al.* (2012) and Debruyne *et al.* (1998) had high risk of bias in intention-to-treat analysis (data not shown but are available upon request).

Meta-analysis

Four studies reported full data for evaluation of acute urinary retention and only three [13,22,27] were used for the meta-analysis because of statistical limitation in one of the studies [14] (Figure 2). A fixed-effect model was used as there was no sign of heterogeneity (Q statistic =0.780; $I^2 = 0\%$; $P=0.677$). The analysis for three RCT studies [13,22,27] indicated patients who received combination therapy had lower rates of urinary retention than those who received α -blocker monotherapy (OR=0.286, 95%CI: 0.199 – 0.412, $P<0.001$) (Figure 2).

Three studies [13,14,27] reported data regarding the incidence of surgical treatment (Figure 3). A fixed-effect model was used as heterogeneity in the data was not observed (Q statistic =2.146; $I^2 = 6.80\%$; $P=0.342$). The analysis for three RCT studies [13,14,27] indicated that patients who received combination therapy had lower rates of surgery than those who received α -blocker monotherapy (OR: 0.277, 95%CI: 0.200 – 0.384, $P<0.001$) (Figure 3).

We also performed a subgroup analysis of the combination therapy of doxazosin plus finasteride versus doxazosin alone. Two studies were included in this subgroup analysis [13,14]. The findings suggest that patients who received combination therapy had lower rates of surgery than those who received doxazosin monotherapy (OR: 0.429, 95%CI: 0.218 – 0.843, $P=0.014$).

Two studies [22,25] were included for the analysis of treatment effect on prostate volume (Figure 4). A random-effect model was used as significant heterogeneity in the data was seen (Q statistic =7.545; $I^2 = 86.75\%$; $P=0.006$). The analysis for RCT studies [22,25] indicated that patients treated with combination therapy had significantly greater reductions in prostate volume than patients treated with α -blocker monotherapy (RCT studies: mean difference = -7.387, 95%CI: -12.982 – -1.791, $P=0.010$) (Figure 4).

Three studies [14,22,25] were included in the analysis to evaluate the effect of combined and monotherapy on urinary flow rate (Figure 5). A fixed-effect model was used since there was no heterogeneity in the data (Q statistic =0.035; $I^2 = 0\%$; $P=0.982$). The overall analysis revealed that patients treated with combination therapy had higher maximum urinary flow rates than those who received α -blocker monotherapy (mean difference =0.527, 95%CI: 0.052 - 1.003, $P=0.030$).

A total of four studies [14,22,23,25] were included in the analysis of therapeutic impact on IPSS score (Figure 6). A fixed-effect model was used (Q statistic =0.769; $I^2 = 0\%$; $P=0.857$). The overall analysis found no difference in the change in IPSS score from baseline between treatment groups

(mean difference = -0.087, 95%CI: -0.231 – 0.058, $P=0.239$) (Figure 6).

We also did a subgroup analysis of combination therapy of doxazosin plus finasteride versus doxazosin alone [14, 23] and similar changes from baseline in IPSS score after 1-year follow-up were seen (mean difference = -0.083, 95%CI= -0.230 – 0.064, $P=0.268$).

Sensitivity analysis was performed using the leave-one-out approach for each of the evaluated outcomes (data not shown but are available upon request). The pooled effect for each outcome between the combination therapy and the monotherapy did not change when each study was removed in turn. These findings indicate that no one study overly influenced the pooled estimates and the findings are robust.

Supplementary data

Supplementary data are available, from the corresponding author, upon request.

Discussion

This study compared the efficacy of α -blocker monotherapy with that of α -blocker therapy plus 5 α -reductase in the treatment of patients with BPH. We found that combination therapy significantly reduced urinary retention and the risk of need for surgery and resulted in a greater reduction in prostate volume and a larger increase in maximal urinary flow rate compared with α -blocker monotherapy. The two treatments were similar with regard to improvement in IPSS scored. Our findings indicate that 5 α -reductase combined with α -blocker is more efficacious in treating benign prostatic hyperplasia compared with α -blocker monotherapy, particularly in reducing risk of acute urinary retention (AUR) and the need for surgery.

The mechanism of action and clinical profiles of α -adrenoceptor agonists and 5 α -reductase inhibitors are different [8]. The α -adrenoceptor agonists act by reducing sympathetic tone through blocking α adrenergic receptors causing smooth muscle relaxation in the prostate/bladder neck and, consequently, increasing urinary flow and reducing LUTS [6,9,10]. The 5 α -reductase inhibitors block the conversion of testosterone to its active form, dihydroxytestosterone, and inhibit prostate growth [8]. The α -adrenoceptor agonists are beneficial in providing symptom relief and improving urinary flow; however, they cannot reduce either prostate volume or the risk of disease progression [8]. By combining α -adrenoceptor agonists with 5 α -reductase inhibitors, it is

possible to overcome these limitations and thereby to better control BPH and associated symptoms.

Several clinical studies have evaluated the efficacy of the combination therapy in treating BPH [8,12-15]. The Symptom Management After Reducing Therapy (SMART) study was a randomized, double-blind, placebo-controlled study that investigated how withdrawal of an α -adrenoceptor agonist, tamsulosin, from an initial combination therapy with a 5α -reductase inhibitor, dutasteride, would affect patients with symptomatic BPH [12]. Patients (N=327) received either monotherapy for 36 weeks or combination therapy for 24 weeks, followed by 12 weeks of dutasteride monotherapy plus placebo. The SMART study found combination therapy resulted in rapid onset of symptom relief in patients at risk for disease progression. They also found that in the patients who discontinued tamsulosin but remained on dutasteride, 77% felt the same or better compared with the combination therapy; however, patients with severe symptoms experienced greater relief with the combination therapy (i.e., 42.5% felt their symptoms worsened when tamsulosin was removed) than with the dutasteride monotherapy. The authors concluded that it is possible to discontinue the α -adrenoceptor agonist from therapy in the majority of patients but that patients with severe symptoms should remain on the combination treatment.

The Prospective European Doxazosin and Combination Therapy (PREDICT) study was a one-year, randomized, controlled trial that evaluated doxazosin and finasteride and their combination in men (N=1,097) with BPH [14]. PREDICT found that there were significant improvements in IPSS and peak urinary flow rate in patients receiving combination therapy or doxazosin alone compared with finasteride or placebo ($P<0.01$); however, there was no significant difference between doxazosin and combination therapy.

Both the SMART and PREDICT trials were limited by the short duration of therapy and were not designed to assess the long-term efficacy of combination therapy. In addition, the PREDICT trial was limited in scope, as 5α -reductase inhibitors may take more than one-year to reach maximum efficacy [8]. This is of particular importance as BPH is a progressive disease with frequent LUTS complicated by acute urinary retention, the latter of which is a clinical indication for surgery [15]. The risk of AUR in patients whose PSA is ≥ 3.4 ng/mL is about four times that of patients with PSA ≤ 1.2 ng/mL [28].

The Medical Therapy of Prostatic Symptoms (MTOPS) study was a long-term (mean follow-up 4.5 years),

double-blinded study of men (N=3,047) with BPH [13]. The study assessed whether doxazosin or finasteride, or the two agents combined, could prevent the progression of symptomatic BPH. It was found that the risk for clinical progression was reduced to greater extent with both drugs in comparison with either drug alone ($P<0.001$). Finasteride or both drugs combined, but not doxazosin, also significantly reduced the risk of acute urinary retention and the need for invasive surgery ($P<0.001$). Therapy with both drugs combined was superior to that with either one alone for improvement of symptom scores. The MTOPS study demonstrated that, unlike α -blocker monotherapy, long-term combination therapy with α -blocker and a 5α -reductase inhibitor can inhibit the progression of BPH. Overall, these studies support the use of combination therapy in treating BPH.

The benefit of long-term combination therapy in suppressing BPH progression is also supported by the findings of Shin *et al.* (2012) [15]. Shin *et al.* performed a retrospective chart review of men (N=620) with BPH who received an α -blocker or an α -blocker plus a 5α -reductase inhibitor over a 12-year period. They found that the incidence of AUR was lower in the combination group (2.8%) than the monotherapy group (13.6%) ($P<0.001$). In addition, the incidence of AUR decreased in the combination group during the follow-up period and the frequency of BPH-related surgery was also significantly reduced after seven years of combination therapy. The findings of the SMART study and that of Shin *et al.* suggest that monotherapy may not be appropriate for long-term use in patients with a large prostate and residual urinary volume.

A meta-analysis by Wang *et al.* (2014) compared the effectiveness of different classes of oral drugs on LUTS and BPH [29]. They analyzed α -blockers, 5α -reductase inhibitors, muscarinic receptor antagonists and phosphodiesterase-5 inhibitors, alone or combination, for treatment of LUTS/BPH using consistency models and network meta-analysis. A total 66 randomized controlled trials with 29,384 patients were included in the meta-analysis. They found that α -blockers plus phosphodiesterase-5 inhibitors ranked highest in reduction of IPSS total score, storage subscore and voiding subscore. In contrast, the combination of α -blockers and 5α -reductase inhibitors was the best therapy for increasing maximum urinary flow rate.

It had been assumed that $\alpha 1$ -antagonists improve LUTS through relaxation of smooth muscle. A review of the literature (Kortmann, *et al.*, 2003) concluded that $\alpha 1$ -antagonists led to only a small reduction in bladder outlet

TABLE 1. Summary of basic characteristics of selected studies for meta-analysis

1 st AU (year)	Trial name	Study design	# of Patients	Group	Intervention	Description of Intervention	Mean age (years)	Length of follow-ups (month)
Fwu (2013) [23] Kaplan (2008) [25] McConnell (2003) [13]	MTOPS	RCT	786	Combined	Doxazosin + finasteride	Combination of doxazosin and finasteride taken once daily	63	54
			756	Control	Doxazosin	Dose of doxazosin was doubled at 1-week intervals, beginning with 1 mg daily for the 1st week, until the final daily dose of 8 mg was reached, once daily	63	
Joo (2012) [24]		RCT	98	Combined	Tamsulosin + dutasteride	Dutasteride 0.5 mg and tamsulosin 0.2 mg once daily	66	12
			95	Control	Tamsulosin	Tamsulosin 0.2 mg once daily	66	
Rochrborn (2010) [27]	CombAT	RCT	1610	Combined	Tamsulosin + dutasteride	Dutasteride 0.5 mg and tamsulosin 0.4 mg once daily	66	48
			1611	Control	Tamsulosin	Dutasteride-matched placebo and tamsulosin 0.4 mg once daily	66	
Kirby (2003) [14]	PREDICT	RCT	286	Combined	Doxazosin + finasteride	Combination of doxazosin and finasteride once daily	64	12
			275	Control	Doxazosin	Doxazosin was initiated at 1 mg/day, and titrated to 2 mg/day at the end of week 2 and to 4 mg/day at the end of week 6. At the end of week 10, the 4-mg dose was maintained	63	
Debruyne (1998) [22]	ALFIN	RCT	349	Combined	Alfuzosin + finasteride	Combination of SR alfuzosin 5 mg and finasteride 5 mg once daily	64	6
			358	Control	Alfuzosin	SR alfuzosin 5mg twice daily	63	
Lepor (1996) [26]		RCT	309	Combined	Terazosin + finasteride	Combination of terazosin and finasteride once daily	65	12
			305	Control	Terazosin	Terazosin 1 mg on days 1-3, 2 mg on days 4-7, 5 mg on days 8-14, and 10 mg on day 15 through the completion of study, once daily	65	

Abbreviations: RCT, Randomized-controlled trial; SR, sustained-release;

obstruction and a decrease in urodynamic parameters of less than 50% [30]. In addition, Barendrecht *et al.* (2008) performed a retrospective analysis of a prior reported RCT that compared urodynamic outcomes between a placebo and modified-release tamsulosin [31]. They found that LUTS, bladder outlet obstruction and maximum urinary flow rate were loosely related at baseline and, importantly, treatment-related improvements in these parameters were also loosely related. The study raised questions about whether α 1-antagonists improved LUTS merely by reducing outlet

obstruction and suggested that they could also act independent of smooth muscle relaxation. The study by Kortmann *et al.* did not analyze the data quantitatively and the study by Barendrecht *et al.* extracted data only from patients receiving α 1-antagonists and was a *post hoc* retrospective analysis. A meta-analysis of 17 studies by Fusco *et al.* (2015) investigated the effectiveness of several α 1-antagonists on benign prostatic obstruction in patients with LUTS/BPE [32]. They found a clinically significant reduction in bladder outlet obstruction index (mean change -14.19, $P < 0.001$). Subgroup analysis for

TABLE 2. Summary of the outcomes for the selected studies.

1st AU (year)	Trial name	Group	# of Patients	AUR (%)	Received Operation (%)	IPSS		Prostate volume (ml)		Maximum Flow rate (Qmax) (ml/s)	
						Baseline	1-year after intervention	Before intervention	1-year after intervention	Baseline	1-year after intervention
Fwu (2013) [23]	MTOPS	Combined	571	na	na	3.0±1.3	-1.26±1.34	36.3±18.	na	10.6±2.5	na
		Control	565	na	na	3.0±1.3	-1.18±1.21	36.9±21.6	na	10.3±2.6	na
Combined		786	na	na	na	na	<25	21.6±10.3	10.6±2.5	na	
							25-30	26.2±8.5			
							30-40	33.9±11.9			
							≥40	51.7±21.7			
Control		756	na	na	na	na	<25	25.8±11.0	10.3±2.5	na	
							25-30	33.4±8.7			
							30-40	42.3±13.2			
							≥40	71.3±33.0			
McConnell (2003) [13]		Combined	786	<1%	1%	AUA SS: 16.8±5.8	-6.0*	36.4±19.2	-12%*	10.6±2.5	3.6*
		Control	756	1%	3%	AUA SS: 17.0±5.8	- 6.0*	36.9±21.6	29%*	10.3±2.5	3.0*
Joo (2012) [24]	Combined	98	na	na	19.94±6.14	12.52±4.58	37.26±13.22	27.22±8.37	11.13±5.08	14.59±5.11	
	Control	95	na	na	19.95±5.54	13.25±4.80	36.63±13.16	37.01±13.01	11.32±5.77	14.01±5.11	
Roehrborn (2010) [27]	CombAT	Combined	1113	2.2%	2.40%	16.6±6.35	- 5.6†	54.7±23.51	na	10.9±3.61	2.0†
	Control	989	6.8%	7.80%	16.4±6.10	- 4.5†	55.8±24.18	na	10.7±3.66	0.9†	
Kirby (2003) [14]	PREDICT	Combined	265	0	0	17.3±4.7	17.3±4.7	37±14 g	na	10.4±2.7	14.5±5.1
	Control	250	0	0.40%	17.1±4.2	17.1±4.2	36±14 g	na	10.4±2.5	14.0±4.9	
Debruyne (1998) [22]		Combined	295	0	0	17.3±4.7	8.7±6.2	37±14 g	na	10.1±3.5	2.3*
	Control	318	0	0.40%	17.1±4.2	8.7±5.8	36±14 g	na	9.7±2.8	1.8*	
Lepor (1996) [26]		Combined	254	na	na	AUA SS: 15.9±5.7	- 6.2*	37.2±1.1	7.0*	10.4±2.7	3.2*
	Control	256	na	na	AUA SS: 16.2±5.5	- 6.1*	37.5±1.1	0.5*	10.5±2.6	2.7*	

IPSS, prostate volume, and maximum flow rate were summarized as mean±SD.

Abbreviations: AUA, American Urological Association; IPSS, International Prostate Symptom Score; na, not available; TPV, total prostate volume.

*: mean change; †: mean adjusted change

individual α 1-antagonists showed a reduction in bladder obstruction index for all drugs evaluated. Fusco *et al.* also found a significant reduction in maximum urinary flow and detrusor pressure at maximum urinary flow ($P<0.0001$) with α 1-antagonist treatment, and the effects were stronger in

patients with urodynamic obstruction at baseline. The findings of Fusco *et al.* support the idea that α 1-antagonists improve benign prostatic obstruction.

In our study, we saw no difference between combination therapy and monotherapy with respect to improvement in

FIGURE 1. Schematic of search

Heterogeneity test : Q-value=0.780, df=2, p-value=0.677, I-squared=0%

FIGURE 2. Forest plot showing acute urinary retention rate after intervention compared between patients underwent combination therapy and monotherapy treatments. Abbreviations: 1st AU, first author; 95%CI, lower limit and upper limit.

Heterogeneity test : Q-value=2.146, df=2, p-value=0.342, I-squared=6.80%

FIGURE 3. Forest plot showing received operation rate after intervention compared between patients underwent combination therapy and monotherapy treatments. Abbreviations: 1st AU, first author; 95%CI, lower limit and upper limit.

Heterogeneity test : Q-value=7.545, df=1, p-value=0.006, I-squared=86.75%

FIGURE 4. Forest plot showing change in prostate volume at 1-year after intervention compared between patients underwent combination therapy and monotherapy treatments. Abbreviations: 1st AU, first author; 95%CI, lower limit and upper limit.

Heterogeneity test : Q-value=0.035, df=2, p-value=0.982, I-squared=0%

FIGURE 5. Forest plot showing change in prostate volume at 1-year after intervention compared between patients underwent combination therapy and monotherapy treatments. Abbreviations: 1st AU, first author; 95%CI, lower limit and upper limit.

Heterogeneity test : Q-value=0.035, df=2, p-value=0.982, I-squared=0%

FIGURE 6. Forest plot showing change in IPSS score at 1-year after intervention compared between patients underwent combination therapy and monotherapy treatments. Abbreviations: 1st AU, first author; 95%CI, lower limit and upper limit.

IPSS score. Several prior randomized controlled studies of long-term therapy (≥ 4 years) found that combined therapy of finasteride plus doxazosin [13] or dutasteride plus tamsulosin [27] lead to greater improvement in IPSS than either drug alone. It is possibly that if follow-up periods in the studies included in our analysis were longer, we may also have seen a greater improvement in IPSS with combination therapy compared with monotherapy.

Our analysis is limited by the fact that protocols used differed markedly between the studies and that retrospective studies were included. In addition, the drugs used and the doses used were heterogeneous. The analysis is also limited by the small number of studies included for a relatively large number of study outcomes. The small sample size also precluded our ability to perform subgroup analysis to assess

potential differences in specific drugs used to treat BPH. We assess neither quality of life nor safety. Both safety and the influence of treatment of a patient's quality of life can impact the choice of drug used and patient counselling [33].

Conclusions

This study showed that combination therapy of α -blocker and 5 α -reductase inhibitor would be beneficial in treating men with BPH/LUTS to help manage clinical symptoms and reduce the need for an operation. Additional randomized controlled trials are necessary with similar study designs, patient populations and drug dosing to further investigate which (if any) specific combination therapies are more beneficial than others in treating LUTS/BPH.

Acknowledgements

The medical writing and editorial assistance provided by Dr. Elizabeth Goodwin, MedCom Asia, was funded by MSD China.

Conflict of interest

Dr. Yan-yan Fu is an employee of MSD China Holding Company (Shanghai China).

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