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Meta-Analysis of the Efficacy and Safety of Imidafenacin for Overactive Bladder Induced by Benign Prostatic Hyperplasia in Men Receiving Alpha-Blocker Therapy

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Purpose: The aim of this meta-analysis was to evaluate the efficacy and safety of imidafenacin for overactive bladder (OAB) induced by benign prostatic hyperplasia (BPH) in men receiving alpha-blocker monotherapy.
Methods: We performed a systematic research of the PubMed, Embase, and Cochrane Library databases, and searched for studies about alpha-blocker with or without imidafenacin treatment for OAB in patients with BPH. We also investigated the original references of the included texts.
Results: Four randomized controlled trials including 779 participants with BPH (389 in the alpha-blocker+imidafenacin group and 390 in the alpha-blocker only group) were studied. The main efficacy endpoint was the Overactive Bladder Symptom Score, which showed a mean difference of -1.88 (95% confidence interval, -2.32 to -1.44; $P<0.00001$), suggesting that alpha-blocker and imidafenacin treatment was effective in treating men with OAB. As other primary efficacy end points, the International Prostate Symptom Score (IPSS) total score ($P=0.47$), the IPSS storage symptom score ($P=0.07$), the IPSS voiding symptom score ($P=0.60$), and the IPSS quality of life score ($P=0.18$) indicated that 2 methods had no significant differences in treating men with OAB. In terms of safety, which was assessed using postvoid residual volume ($P=0.05$) and maximum flow rate ($P=0.53$), the analysis suggested that combination treatment was very well tolerated.
Conclusions: This study suggested that imidafenacin plus alpha-blocker was an efficacious and safe treatment for OAB symptoms in BPH patients.

Keywords: Imidafenacin; Alpha-blocker; Urinary bladder, Overactive; Prostatic hyperplasia; Lower urinary tract symptoms; Randomized controlled trial

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INTRODUCTION

As one of the most common conditions that cause lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH) often causes urinary tract dysfunction in men aged 50 years and older, with a prevalence of 19%–30% [1,2]. The Inter-

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national Continence Society defined overactive bladder (OAB) as urinary urgency with urinary frequency, nocturia, and sometimes urgency incontinence. In the course of everyday life, OAB is the most inconvenient symptom for men with BPH [3]. At present, in order to relieve the symptoms of BPH, the main treatment pattern is drug therapy, especially alpha-blockers. Currently, alpha-blockers are widely used as the first-line therapy for BPH, but it is difficult to improve the storage symptoms of OAB with alpha-blockers alone. However, anticholinergic agents have been recommended to treat the symptoms of OAB, as they have been found to be efficient in alleviating storage symptoms for men with BPH [4-7].

Imidafenacin, a selective antimuscarinic drug, was proposed to treat the symptoms of OAB. Recent studies have shown that imidafenacin can decreased urine volume via suppression of C-fibers and reduced nocturnal urine volume for OAB patients [8]. In some studies, anticholinergics combined with alpha-blockers have shown demonstrable effects in treating OAB in men with BPH, but their clinical effect is limited [9]. In clinical practice, there have been concerns that anticholinergic agents are infrequently used to treat BPH in patients because the inhibitory effect of anticholinergics, which produce detrusor muscle contractions that aggravate urinary symptoms, may increase the risk of the numbers of adverse events or acute urinary retention. Urinary retention can reduce patients' quality of life (QoL). Research has shown an incidence of 68 per 10,000 person-years among men [10]. Dry mouth, as one of the most common and problematic side effects, can often lead to discontinuation of anticholinergic therapy [11]. On the basis of the 2019 European Association of Urology Guideline, patients with BPH who have OAB symptoms may use anticholinergic agents simultaneously with an alpha-blocker. Meanwhile, some randomized controlled trials (RCTs) and other studies have sought to demonstrate the effects of anticholinergic agents [12-14].

In order to evaluate the curative effect and safety of combined alpha-blocker and imidafenacin treatment for persistent OAB associated with BPH, we performed a systematic review and meta-analysis of RCTs.

MATERIALS AND METHODS

Information Sources and Literature Search

We systematically retrieved articles from the PubMed, Embase, and the Cochrane Library databases published before January 2020, and searched for studies about alpha-blocker with or without imidafenacin treatment for OAB in patients with BPH. We searched using the following keywords: "alpha-blocker," "imidafenacin," "RCT," "BPH," "male-LUTS" and "OAB." We also examined original references of the texts that were included.

Inclusion Criteria

RCTs were included if they met the following criteria: (1) the RCT was topically relevant to this meta-analysis (i.e., it analyzed alpha-blocker with or without imidafenacin treatment for OAB symptoms resulting from BPH); (2) the full text was available and the study was an RCT; and (3) similar observation indicators were used to compare the alpha-blocker+imidafenacin group and the alpha-blocker only group in every RCT.

The following studies were excluded: (1) those that were not RCTs, such as abstracts, reviews, or comments; and (2) those that involved catheterization or patients with a prior diagnosis of neurogenic bladder.

If a duplicate study had been published in different journals or at different time points, we included only the most recently published study. However, every study was included if different measures were evaluated. Fig. 1 presents a flow chart of the selection process for the study.

Quality Assessment

The Jadad scale was used to determine the quality of the re-

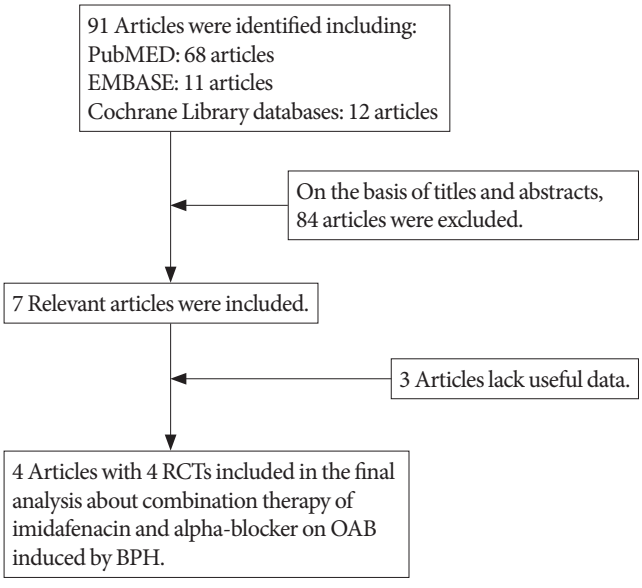

Fig. 1. Flowchart of the study selection process. RCT, randomized controlled trial; OAB, overactive bladder; BPH, benign prostatic hyperplasia.

trieved RCTs [15]. In the meta-analysis, several metrics were used to assess the quality of the individual studies, including the assignment method of patients, the concealment of allocation, the blinding method, the results of loss to follow-up, and whether there was a calculation of sample size or intention-to-treat analysis. The studies were then classified qualitatively using the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions v.5.1.0 [16]. The quality of every RCT was evaluated as follows: (1) if the study satisfied almost all of the quality criteria, it was considered to have a low risk of bias; (2) if the article partially satisfied the quality criteria or was ambiguous, it would be considered to have a moderate risk of bias; (3) if the quality criteria were rarely met or not described, an article was considered to have a high risk of bias. All authors took part in the quality assessment of each text, and every author agreed with all outcomes. Any differences in opinion regarding the RCTs were resolved through discussion among the authors. All studies were evaluated by all reviewers independently to determine whether they satisfied the inclusion criteria.

Data Extraction

One author read the articles and collected the following data from studies: (1) the common data in the study(e.g., the baseline demographic and clinical characteristics of study participants); (2) the name of the RCT and authors; (3) the research design and sample size in the study (e.g., the interventions in the different groups; the prostate volume was greater than 16 mL in the 4 RCTs that were included, and there were no significant differences between the alpha-blocker+imidafenacin group and the alpha-blocker only group in any of the RCTs); (4) data on efficacy in terms of changes in the following parameters, such as total Overactive Bladder Symptom Score (OABSS), the International Prostate Symptom Score (IPSS) total score, the IPSS storage symptoms score, the IPSS voiding symptoms score, the IPSS QoL score, postvoid residual volume (PVR), and maximum flow rate (Qmax). Finally, another author checked the data that we retrieved from the texts. Meanwhile, our team cross-checked the reference documents and data for each study, in order to maintain the integrity of the meta-analysis and the absence of overlapping data in the meta-analysis.

Statistical Analysis and Meta-Analysis

This meta-analysis of the data was carried out using the RevMan ver. 5.3.0 (Cochrane Collaboration, Oxford, UK) [16]. In order to evaluate the difference between the start and the endpoint in each RCT, our team analyzed changes in the total OABSS, the IPSS total score, the IPSS storage symptoms score, the IPSS voiding symptoms score, the IPSS QoL score, PVR, and Qmax. The mean difference (MD) was used to evaluate continuous data, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate dichotomous data. A fixed-effects model was used a P-value >0.05 was considered to indicate homogeneity. We utilized the I2 statistic to analyze inconsistent results, as this statistic can reflect the proportion of heterogeneity across trials. For this meta-analysis, it was not necessary to obtain ethical approval and patient consent because all the data were acquired from articles that had already been published. A random-effects model was used when the results showed $P<0.05$ and $I2>50\%$. Moreover, if the results of the study showed a P-value <0.05, the result was deemed to be statistically significant.

RESULTS

Characteristics of the Individual Studies

We searched for 91 original studies in commonly used databases. On the basis of the aforementioned inclusion and exclusion criteria, 84 studies were excluded. Three other studies were excluded because they lacked informative data. Thus, our final analysis included 4 RCTs [17-20]. The 4 studies included 779 patients (389 in the alpha-blocker+imidafenacin group and 390 in the alpha-blocker only group). A detailed flowchart showing the selection process is shown in Fig. 1. Table 1 displays the baseline characteristics of the studies.

Quality of the Individual Studies

All 4 RCTs had double-blind processes. All of the RCTs that we found explained their randomization process. Each of the 4 RCTs carried out a calculation to determine the optimal sample size (Table 2). Table 2 demonstrates the quality of each included study. In Fig. 2, a funnel plot displays a qualitative estimation of publication bias for each RCT.

Efficacy

OABSS

Three RCTs containing 558 participants (279 in the alpha-blocker+imidafenacin group and 279 in the alpha-blocker only group) measured changes in the OABSS. A fixed-effects model was used to evaluate changes between the alpha-blocker+imidafenacin

Table 1. The details of individual study

Study	Country	Study design	Therapy in experimental group	Therapy in control group	Sample size		Method	Time of therapy (wk)	Main inclusion criteria
					Experimental	Control			
Cho et al. 2017 [17]	Korea	RCT	Imidafenacin+alpha-blocker (alfuzosin)	alpha-blocker (alfuzosin)	110	111	Oral	12	IPSS≥12, an IPSS question 4 score ≥2, ≥8 micturition in 24 hours, and PV>20 mL
Takeda et al. 2013 [13]	Japan	RCT	imidafenacin+alpha-blocker (tamsulosin)	alpha-blocker (tamsulosin)	154	154	Oral	12	Patients with BPH ≥50 years old, with urinary urgency at least once per week and total OABSS ≥3 points after ≥8-week treatment with tamsulosin, PVR urine <50 mL, and PV≥20 mL
Yamanishi et al. 2017 [20]	Japan	RCT	Imidafenacin+alpha-blocker (tamsulosin) and dutasteride	alpha-blocker (Tamsulosin)+ dutasteride	82	79	Oral	24	the BPH patients aged 50–89 years, OABSS urinary urgency score ≥2 and OABSS total score ≥3 despite at least 8 weeks, PV ≥30 mL
Yokoyama et al. 2015 [18]	Japan	RCT	Imidafenacin+alpha-blocker (tamsulosin, naftopidil, and silodosin)	alpha-blocker (tamsulosin, naftopidil, and silodosin)	43	46	IM	24	OAB symptom, mean urinary frequency ≥8 times/24 hr and ≥1 micturition-related urgency episode/week, PV≥16 mL

RCT, randomized controlled trial; OAB, overactive bladder; OABSS, overactive bladder symptom score; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PV, prostate volume; PVR, postvoid residual.

Fig. 2. Funnel plot of the studies included in our meta-analysis. MD, mean difference; SE, standard error.

group and the alpha-blocker only group, showing an MD of -1.88 (95% CI, -2.32 to -1.44; P<0.00001). This finding demonstrates that, compared with the imidafenacin group (Fig. 3), the alpha-blocker+imidafenacin group showed a statistically significant greater reduction in the OABSS.

IPSS total score

Four RCTs containing 779 participants (389 in the alpha-blocker+imidafenacin group and 390 in the alpha-blocker only group) were included. A random-effects model was chosen to evaluate changes between the alpha-blocker+imidafenacin group and the alpha-blocker only group, showing an MD of -0.77 (95% CI, -2.85 to -1.31; P=0.47). Thus, the alpha-blocker+imidafenacin group showed an equivalent effect in terms of the IPSS total score to that of the alpha-blocker only group (Fig. 4).

IPSS storage symptoms score

Three RCTs containing 690 participants (346 in the alpha-blocker+imidafenacin group and 344 in the alpha-blocker only group) were included. A random-effects model was used to evaluate changes between the alpha-blocker+imidafenacin group and the alpha-blocker only group, showing an MD of -0.99 (95% CI, -2.07 to 0.10; P=0.07). This result shows that the 2 groups had no significant differences in the IPSS storage symptoms score (Fig. 4).

IPSS voiding symptoms score

Three RCTs including 690 participants (346 in the alpha-blocker+imidafenacin group and 344 in the alpha-blocker only group) were included. A random-effects model was chosen to

Table 2. Quality assessment of individual study

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	ITT analysis	Level of quality
Cho et al. 2017 [17]	A	A	A	0	YES	ANCOVA	NO	A
Takeda et al. 2013 [13]	A	A	A	0	YES	ANCOVA	NO	A
Yamanishi et al. 2017 [20]	A	A	A	6	YES	ANCOVA	NO	A
Yokoyama et al. 2015 [18]	A	A	B	2	YES	ANCOVA	NO	B

A, all quality criteria met (adequate): low risk of bias; B, one or more of the quality criteria only partly met (unclear): moderate risk of bias; C, one or more criteria not met (inadequate or not used): high risk of bias; ITT, intention-to-treat analysis; ANCOVA, analysis of covariance.

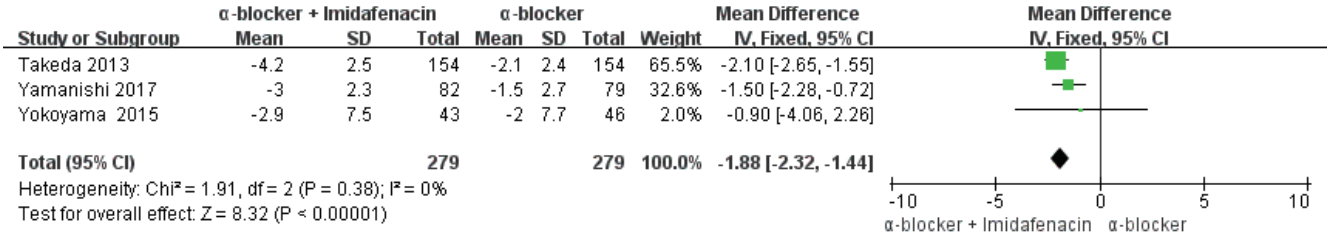

Fig. 3. Forest plots showing changes between the 2 groups in the Overactive Bladder Symptom Score. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

evaluate changes between the alpha-blocker and imidafenacin group and the alpha-blocker only group, showing an MD of -0.34 (95% CI, -0.94 to 1.61, P=0.60). Thus, the alpha-blocker+imidafenacin group showed an equivalent effect in terms of the IPSS voiding symptom score to that of the imidafenacin group (Fig. 4).

IPSS QoL

Four RCTs containing 779 participants (389 in the alpha-blocker+imidafenacin group and 390 in the alpha-blocker only group) were included. A random-effects model was used to evaluate changes between the alpha-blocker+imidafenacin group and the alpha-blocker only group, showing an MD of -1.49 (95% CI, -3.65 to 0.67; P=0.18). This finding demonstrates that the 2 groups were similar in terms of the IPSS QoL (Fig. 4).

Safety

PVR

Four RCTs containing 779 participants (389 in the alpha-blocker+imidafenacin group and 390 in the alpha-blocker only group) analyzed PVR. A random-effects model was adopted to evaluate changes between the alpha-blocker+imidafenacin group and the alpha-blocker only group, showing an MD of 6.88 (95% CI, 0.07 to 13.68; P=0.05). This result shows that the alpha-blocker+imidafenacin group had equivalent outcomes to the alpha-blocker only group in terms of PVR (Fig. 5).

Qmax

Three RCTs containing 690 participants (346 in the alpha-blocker+imidafenacin group and 344 in the alpha-blocker group) were included. A random-effects model was used to evaluate changes between the two groups, showing an MD of 0.55 (95% CI, -1.16 to 2.26, P=0.53). Thus, there was no significant difference in terms of Qmax between the 2 groups (Fig. 5).

DISCUSSION

In recent years, increasingly many BPH patients have shown symptoms of OAB, and alpha-blockers used alone cannot relieve the symptoms of OAB in these patients. Therefore, there is increasing interest in combining drugs to treat OAB symptoms in patients with BPH.

The meta-analysis integrated evidence from 4 studies to evaluate the efficacy and safety of combination therapy that comprised an alpha-blocker (tamsulosin, alfuzosin, naftopidil, or silodosin), and imidafenacin (0.1 mg or 0.2 mg twice a day), an anticholinergic agent, in BPH patients with OAB. In this meta-analysis, compared with the alpha-blocker only group, the alpha-

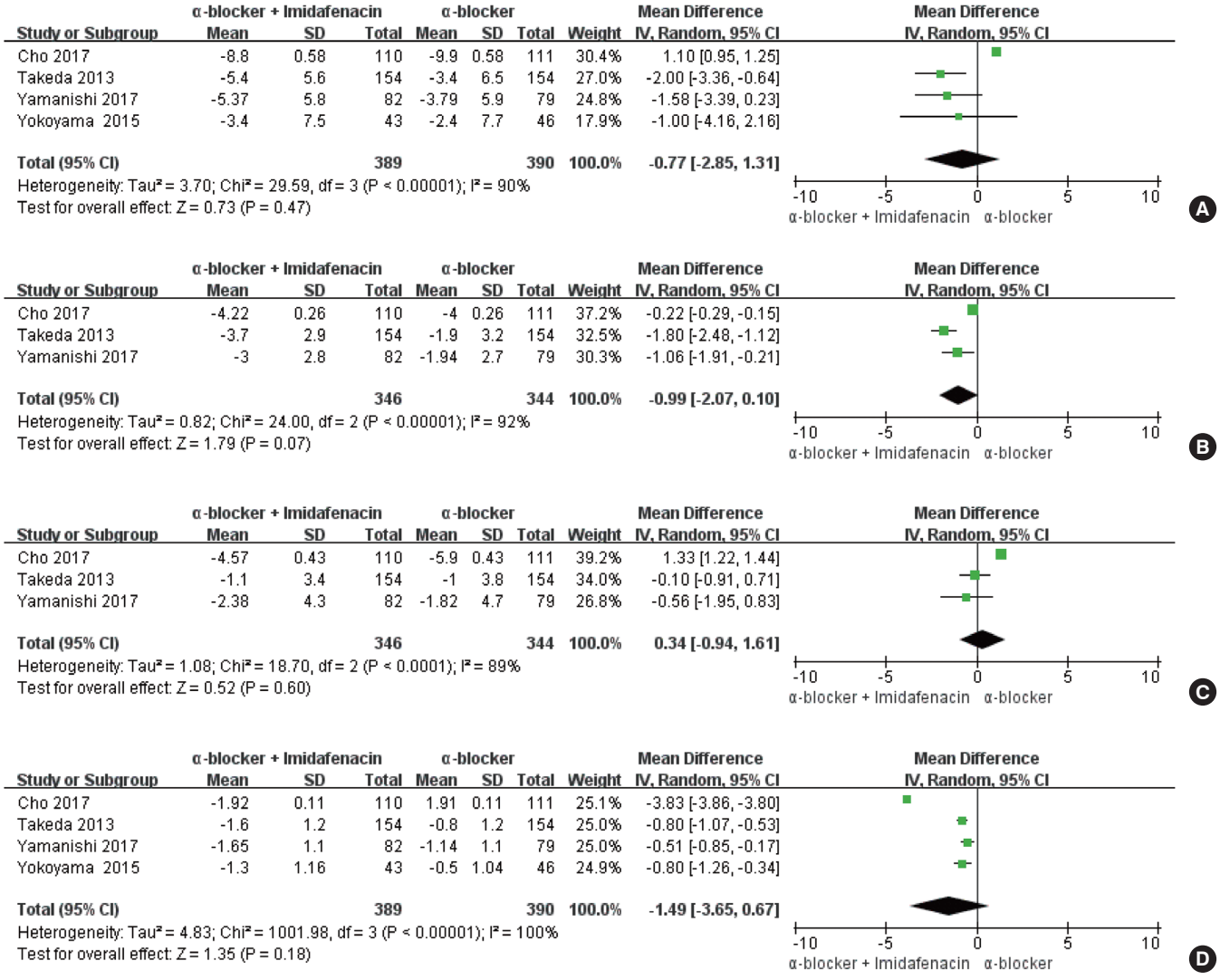

Fig. 4. Forest plots showing changes between the 2 groups in the International Prostate Symptom Score (IPSS) total score (A), the IPSS storage symptoms score (B), the IPSS voiding symptoms score (C), and the IPSS quality of life (D). SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

blocker+imidafenacin group showed a statistically significant greater reduction in OABSS compared with the alpha-blocker only group ($P<0.00001$). The alpha-blocker+imidafenacin group showed better results in terms of improvements in OAB symptoms than the alpha-blocker only group up to 12 weeks in BPH patients. At the same time, compared with the alpha-blocker only group, the alpha-blocker+imidafenacin group showed equivalent results in treating OAB with BPH in terms of the IPSS total score ($P=0.47$), the IPSS storage symptoms score ($P=0.07$), the IPSS voiding symptoms score ($P=0.60$), and the IPSS QoL ($P=0.18$). In the present study, the alpha-blocker+imidafenacin group demonstrated significant improvements from baseline in the OABSS, and the 2 group also had equivalent effects in the IPSS and other indexes related to BPH. As a result, combination therapy with an imidafenacin add-on to alpha-blocker can significantly improve the symptoms of OAB compared with alpha-blocker monotherapy without deteriorating urination symptoms.

The efficacy of imidafenacin was similar to those of conventional anticholinergic agents, with a favorable tolerance profile. In a rat experiment, it was potently inhibited the rhythmic contractions of the bladder and significantly increased bladder capacity [21]. It has high affinities for the M3 and M1 muscarinic receptor subtypes and a low affinity for M2 receptors [21,22].

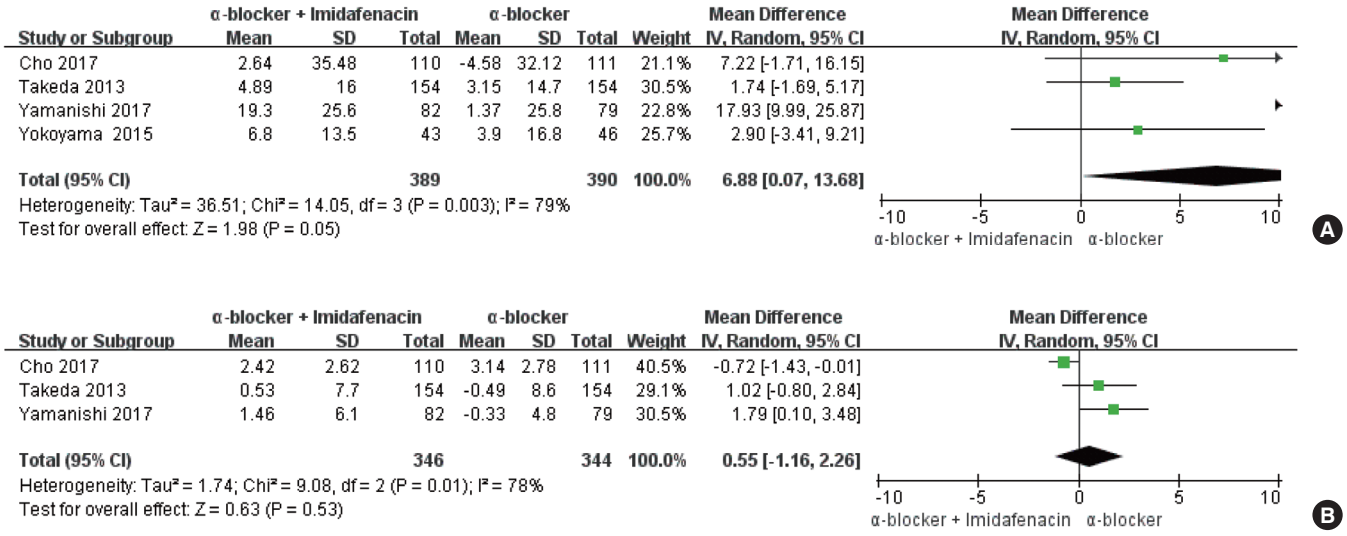

Fig. 5. Forest plots showing changes between the 2 groups in postvoid residual volume (A), maximum flow rate (B). SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

Meanwhile, in clinical experiments, imidafenacin blocked postjunctional M3 receptors and prejunctional M1 receptors to inhibit the contractions of the detrusor to smooth muscles in humans. In addition, imidafenacin displayed a high organ selectivity for the bladder and a low selectivity for salivary gland tissues [23]. Thus, compared with other antimuscarinics, imidafenacin may produce fewer side effects. As we all know, alpha-blockers reduce voiding and storage symptoms for BPH, but sometimes it is difficult to improve storage symptoms by using alpha-blockers alone [24-27]. Several studies have shown that the application of an anticholinergic agent with an alpha-blocker was effective for patients with BPH who had storage symptoms [28-32]. Meanwhile, according to the literature, adding an anticholinergic is recommended in cases of recalcitrant OAB [33].

We have noted that many clinicians are hesitant to use anticholinergics in clinical practice because they may exacerbate the symptoms of OAB, particularly in patients with possible BPH. In this meta-analysis, the alpha-blocker+imidafenacin group and alpha-blocker only group showed similar results in terms of the Qmax (P=0.53). It is remarkable that compared with the alpha-blocker group, the alpha-blocker+imidafenacin group had a similar effect regarding PVR in treating OAB with BPH (P=0.05). These results demonstrate that for men with OAB, imidafenacin add-on treatment with an alpha-blocker was safe. Although the 4 RCTs reported adverse events, no notable events were reported including urinary retention or diminished cognitive function. The results of safety and tolerability in this meta-analysis demonstrated that alpha-blocker+imidafenacin combination treatment was well-tolerated. It is worth mentioning that the combination of alpha-blocker and imidafenacin did not lead to significant improvements in IPSS storage symptoms. Two possible reasons for this are: (1) the RCTs that we reviewed had short intervention periods, and it may take a longer time to achieve significant improvement, and (2) we primarily evaluated the additional benefits of the addition of imidafenacin; if a different dose of imidafenacin had been used, different results would be expected.

Compared with salivary gland tissue, imidafenacin, as a short circulating half-life anticholinergic, has higher selectivity for bladder tissue. Wada et al. [34] showed that imidafenacin reduced the frequency of nocturia and improved quality of sleep. Two reasons may explain how imidafenacin decreases nocturnal urine volume: (1) it could inhibit the bladder afferent nerves directly to affect nocturnal urine volume, or (2) it may improve sleep quality indirectly. Research has shown that the use of sleeping pills by patients with BPH could decrease the frequency of nocturia. In this study, the results regarding PVR were analogous between the 2 groups [35], which may be related to the dose of the drug. In the alpha-blocker+imidafenacin group, the risk of urinary retention may be reduced with a lower dose than usual. Simultaneously, compared with other anticholinergic drugs, imidafenacin has a shorter half-life (2.9 hours) and lower accumulation, and it did not cause urinary retention at a

dose of 0.2 mg/day [23,36]. However, the results for Qmax showed that the combination of alpha-blocker+imidafenacin did not reduce voiding pressure and flow rates. A massive release of acetylcholine could reduce the effect of imidafenacin [37]. Therefore, high anticholinergic doses damage bladder contractility. Furthermore, compared with alpha-blocker monotherapy, add-on imidafenacin treatment showed better results in terms of improvements in OAB symptoms for BPH patients in a long-term evaluation [38]. Of course, much more research is needed to demonstrate the above points conclusively.

This meta-analysis included 4 RCTs and focused on the efficacy and safety of alpha-blocker+imidafenacin combination treatment on OAB associated with BPH in men compared with alpha-blocker monotherapy. Compared with previous studies, our study had some advantages; principally, the data were derived from randomized, double-blind, controlled trials. Furthermore, we draw conclusions with meaningful clinical significance based on the most up-to-date, accurate data. However, this study also has some limitations, which reflect common limitations of systematic reviews and meta-analyses. First of all, this article did not include numerous RCTs or unpublished studies, and the availability of limited evidence may have affected the study quality. Second, different types of alpha-blockers were used, which may have affected the results, and people in different regions have different reactions to imidafenacin, which also affects the test results to some extent. Furthermore, urodynamic examinations are an important assessment method, the RCTs included in the current study did not analyze a full range of urodynamic parameters. Furthermore, these 4 RCTs mainly investigated populations in Asia. The result of PVR is precisely on the threshold of statistical significance, and we need more appropriate high-quality trials to improve the accuracy of the results.

In conclusion, in BPH patients with persistent OAB symptoms, combination therapy with imidafenacin add-on to an alpha-blocker showed improved efficacy and safety compared with an alpha-blocker alone.

AUTHOR CONTRIBUTION STATEMENT

Conceptualization: *YC*
Data curation: *NW*, *LL*
Formal analysis: *TC*
Funding acquisition: *YZ*
Methodology: *TC*
Project administration: *YC*
Visualization: *LL*, *ZZ*
Writing-original draft: *TC*, *NW*
Writing-review & editing: *ZZ*, *YZ*, *YC*

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