นิพนธ์ต้นฉบับ

การศึกษาแบบสุ่มเปรียบเทียบประสิทธิภาพการใช้ยาแทมซูโลซินร่วมกับโซลิเฟนนาซินเปรียบเทียบกับแทมซูโลซินอย่างเดียวในการรักษาภาวะกระเพาะปัสสาวะไวเกินของผู้ป่วยต่อมลูกหมากโต

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลของการรักษาอาการทางระบบปัสสาวะในผู้ป่วยต่อมลูกหมากโตที่รับประทานแทมซูโลซินร่วมกับยาหลอก และแทมซูโลซินร่วมกับโซลิเฟนนาซิน

รูปแบบการศึกษา: การศึกษาเชิงทดลองทางคลินิกแบบปกปิดสองฝ่ายโดยการสุ่มร่วมกับการใช้ยาหลอก

สถานที่ทำวิจัย: โรงพยาบาลจุฬาลงกรณ์ ซึ่งเป็นโรงพยาบาลระดับตติยภูมิ

วิธีการศึกษา: ผู้ป่วย 55 ราย อายุเฉลี่ย 66.6 ปี มีอาการปัสสาวะผิดปกติซึ่งเกิดจากต่อมลูกหมากโตและมีอาการกระเพาะปัสสาวะบีบตัวไวเกิน โดยผู้ป่วยจะได้รับยาแทมซูโลซิน 2 สัปดาห์ก่อนมีการสุ่มเพื่อให้ยาแทมซูโลซินร่วมกับยาหลอก หรือยาแทมซูโลซินร่วมกับยาโซลิเฟนนาซิน เป็นเวลา 4 สัปดาห์ โดยประเมินความรุนแรงของการปัสสาวะด้วยแบบสอบถาม IPSS, OAB screener score ความแรงในการปัสสาวะและปริมาณปัสสาวะเหลือค้าง ตลอดจนอาการไม่พึงประสงค์ต่างๆ

ผลการศึกษา: ผู้ป่วยที่รับยาแทมซูโลซินร่วมกับยาโซลิเฟนนาซินมีคะแนน Irritative symptom score และ Bladder sensation scale ลดลงอย่างมีนัยสำคัญทางสถิติเทียบกับกลุ่มที่ได้แทมซูโลซินร่วมกับยาหลอก (P=0.005, P=0.049) สำหรับค่าความแรงในการปัสสาวะและปริมาณปัสสาวะที่เหลือค้างไม่พบว่าต่างกันอย่างมีนัยสำคัญทางสถิติในแต่ละกลุ่ม อาการข้างเคียงที่เกิดขึ้นพบว่า อาการปากแห้งและท้องผูกพบบ่อยกว่าในกลุ่มที่ได้รับยาแทมซูโลซินร่วมกับยาโซลิเฟนนาซินอย่างมีนัยสำคัญทางสถิติ (P=0.005, P<0.001) แต่อาการที่พบมักเป็นน้อยและไม่มีผู้ป่วยหยุดการรักษาเนื่องจากผลข้างเคียง

สรุป: ผู้ป่วยต่อมลูกหมากโตที่มีความผิดปกติของการขับถ่ายปัสสาวะร่วมกับมีอาการกระเพาะปัสสาวะไวเกิน ได้รับยาแทมซูโลซินร่วมกับยาโซลิเฟนนาซิน พบว่ามีอาการ irritative symptoms ลดลงอย่างมีนัยสำคัญทางสถิติ โดยไม่พบว่ามีการเปลี่ยนแปลงของความแรงในการปัสสาวะและปริมาณเหลือค้าง แต่พบว่ามีผลข้างเคียงเพิ่มขึ้นโดยเฉพาะอาการปากแห้งและท้องผูก แต่ผลข้างเคียงที่เกิดขึ้นไม่รุนแรงและไม่รบกวนต่อคุณภาพชีวิตของผู้ป่วย

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A Randomized Controlled Trial Comparing the Efficacy of the Combination Treatment with Tamsulosin Plus Solifenacin and Tamsulosin Alone for Overactive Bladder Related with Benign Prostatic Hyperplasia.

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Abstract

Objective: To compare the efficacy of lower urinary tract symptoms (LUTS) relief in patients who had benign prostatic hyperplasia (BPH) and symptoms of overactive bladder (OAB) taking tamsulosin with placebo and tamsulosin with solifenacin.

Design: Randomized double-blind placebo controlled trial

Setting: King Chulalongkorn Memorial hospital which is a 1,500-bed tertiary care center

Research Methodology: Fifty five patients, mean age 66.6 years with LUTS from BPH and OAB symptoms were randomly allocated into two groups after receiving tamsulosin for 2 weeks. Control group received tamsulosin with placebo (vitamin C). Treatment group received tamsulosin with solifenacin. Both groups had 4 week course of study. Efficacy outcomes were recorded including IPSS score, OAB screener score and Bladder Sensation Scale. Safety and tolerability outcomes were uroflowmetry monitoring and any adverse events.

Results: Patients who receive both tamsulosin and solifenacin (treatment group) were significantly decreased in irritative symptom score and bladder sensation scale (P=0.005, P=0.49 respecticely). No difference in maximum urinary flow rate and residual urine was observed. Adverse events were found in treatment group more common than in control group, especially dry mouth and constipation (P=0.005, P<0.001).

Conclusion: Combination of tamsulosin (adrenergic blockade) and solifenacin (antimuscarinic agent) demonstrated significant reduction of irritative symptoms in BPH patient from IPSS questionnaire and Bladder sensation scale. No difference in maximum flow rate and post-void residual urine in both groups were observed. Adverse events were found in treatment group more often than in control group especially dry mouth and constipation. Although most adverse reactions were mild and tolerable.

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Introduction

Benign prostatic hyperplasia (BPH) is a common problem in elderly men[1]. The World Health Organization sponsored consultations on BPH and has recommended changes to the terminology related to urinary symptoms and the prostate in elderly men. The term LUTS (Lower Urinary Tract Symptoms) was introduced and has been adopted as the proper terminology to apply to any patient, regardless of age or sex, with urinary symptoms but without implying the underlying problem. LUTS were divided into ''irritative'' or ''storage/filling'' symptoms, which consist of urinary urgency, urge incontinence, frequency and nocturia. Another entity was ''obstructive symptoms'' or ''emptying/voiding'' symptoms which are hesitancy, poor stream, intermittency or dribbling, etc.

BPH is mostly a quality of life issue. We uncommonly see complication related to BPH at the present time except acute urinary retention. Pharmaceutical treatment is the first choice in the significant, troublesome symptoms. The two commonly used classes of drugs are alpha-blocker and 5AR inhibitors. Both are aimed at relieving the condition of bladder outlet obstruction. However detrusor overactivity is quite common in the patients with BPH and related to the symptoms of overactive bladder (frequency, urgency and nocturia)

Anticholinergic drugs are widely used in treatment of overactive bladder, especially in women. In this study, we prospectively evaluated the effectiveness and safety of combined therapy with alpha 1-Antagonist (Tamsulosin) plus a new anticholinergic (Solifonacin) in a selected patients with symptoms of BPH

Patients and Methods

60 male patients who had lower urinary tract symptoms and were clinically diagnosed to be benign prostate hyperplasia from history and physical examination by urologists at King Chulalongkorn Memorial hospital were recruited with other inclusion criteria including age more than 50 years old, total IPSS score more than 7 and Irritative symptom scores more than 3 (sum of item 2,4 & 7 of IPSS). Exclusion criteria were consisted of Maximum flow rate (Qmax) less than 8 ml/sec, Post-void residue urine (PVR) >200 ml, clinically suggestive prostate cancer and any contraindication for alpha-adrenergic blocker and cholinergic antagonist.

All patients received tamsulosin for two weeks before randomized allocation into two groups. In the control group, the patients received tamsulosin and placebo. In the treatment group, they received tamsulosin and solifenacin for 4 week period. All patients were monitored with uroflowmetry, PVR measurement and adverse event monitoring. The primary efficacy variable was improvement in irritative symptom scores from IPSS and OAB screener scores after 4 weeks of treatment. The primary comparison was the mean change of irritative symptoms score between 2 groups. The more negative mean change was the more efficacious. The secondary variable was any change in maximum flow rate and PVR. The mean change of both variables showed safety of combination treatment group compare to tamsulosin and placebo group. The more negative mean change of urinary flow rate or the more positive mean change of PVR would be the adverse events from solifenacin.

Data analysis

All data was analyzed as intention-to-treat basis composed with all included patients who had at least one study drug intake after randomization. Missing data would be checked in the data management report. The decision to replace a missing item for the calculation would be taken prior to the end of

the study. The demographic and baseline quantitative data were presented as mean, standard deviation, min, max. For the descriptive statistics used for the qualitative data (adverse events) were n and percentages.

For the primary efficacy endpoint of mean change of irritative symptom scores and OAB screener scores, analyses of co-variance (ANCOVA) or Mann-Whitney U test of difference would be used, based on whether there were assumption about parameter or not, to compare with the two treatment groups. The endpoint of mean change of urinary flow rate and PVR, ANCOVA or t-test of mean difference would be used. Regarding adverse events, Chi-square test or Fisher's exact test was used to analysis.

All statistical analysis would be calculated using SPSS/PC version 11.5. A two sided significant level of 0.05 was used for all analysis.

Result

Sixty patients were included in the study between July 2007 and February 2008. Five patients were excluded from the study before randomization because high serum prostatic specific antigen was observed. Fifty five patients were received randomization allocation into placebo (tamsulosin and placebo) group (27 patients) and treatment (tamsulosin and solifenacin) group (28 patients). All patients completed study. Demographic and baseline clinical characteristics are summarized in Table 1 and Table 2.

Mean age were 68.7 yr-old and 64.6 yr-old in control and treatment group respectively. The most common presented symptom was urinary frequency and the second most common symptom was urgency. Most patients had duration of symptoms more than one year. Maximum flow rate at baseline was 17.32 (9.7) ml/s and postvoid residual volume

Table 1 *Demographic data and baseline characteristics*

	Mean (SD) or Number		
	Tamsulosin & Placebo (n = 27)	**Tamsulosin & Solifenacin (n = 28)**	**Both (n = 55)**
Age (Yr)	68.7 (8.1)	64.6 (7.9)	66.6 (8.2)
Systolic BP (mmHg)	139.8 (16.4)	136.5 (18.2)	138.1 (17.3)
Chief complaint			
Incomplete emptying	1	2	3
Urgency	7	9	16
Poor stream	0	1	1
Nocturia	7	5	12
Frequency	10	11	21
Straining	2	0	2
Duration of symptom			
1-3 mo	3	3	6
3-6 mo	3	2	5
6mo-1yr	4	6	10
>1 yr	17	17	34
Qmax (ml/s)	18.2 (8.2)	16.5 (11.1)	17.32 (9.7)
PVR (ml)	46.9 (49.6)	58.4 (51.4)	52.8 (50.4)

Qmax: maximum urinary flow rate PVR: post-void residual urine
IPSS: International Prostate Symptom Score OAB score: Overactive Bladder screener score

Table 2 *Baseline clinical characteristics*

	Median (range)		
	Tamsulosin & Placebo (n = 27)	**Tamsulosin & Solifenacin (n = 28)**	**Both (n = 55)**
IPSS	16 (7-33)	18.5 (8-33)	16 (7-33)
Irritative symptom score	7 (3-13)	8 (4-15)	8 (3-15)
OAB score	21 (2-35)	19 (2-32)	20 (2-35)
Bladder sensasion scale	3 (2-5)	2 (2-5)	3 (2-5)
IPSS QOL	5 (2-6)	5 (2-6)	5 (2-6)

IPSS: International Prostate Symptom Score
OAB score: Overactive Bladder screener score
IPSS QOL: Quality of life assessment from IPSS questionnaire

was 52.8 (50.4) ml.

Median (range) of irritative symptom score which was primary end point was 7 (3-13) and 8 (4-15) in control and treatment group respectively. Baseline OAB screener score and bladder sensation scale were showed in Table 2. Both groups had the same median and range of Quality of life score from IPSS questionnaire (median = 5, range = 2-6).

Treatment efficacy for overactive bladder symptoms was assessed using data from IPSS questionnaire and OAB screener score. Irritative symptom score was derived from IPSS questionnaire by score summing only question 2, 4 and 7 which were the symptoms of OAB. Bladder sensation scale was created to classify the severity of overactive bladder symptoms, especially urinary urgency.

In the primary efficacy analysis, sum IPSS score and irritative symptom score of both control and treatment group, including OAB screener score, were not distributed in normal distribution. So I chose nonparametric statistic (Mann-Whitney U test) to analyze the outcome by comparing the difference of each score from second visit to last visit between control and treatment group. Compared with placebo, significant reduction for irritative symptom score was demonstrated in tamsulosin and solifenacin group (P=0.005). Total IPSS score was also reduced in treatment group than control group but there was no statistical significant (P=0.076). At the end of the study, Bladder Sensation scale in treatment group was significantly less than in control group (P=0.049). There was no different in OAB screener score in both groups. (Table 3). Considering

All patients were well tolerated. After randomization allocation, there was no drop out of all patients. Both groups demonstrated slight changes in maximum urinary flow rate compared with baseline (second visit) (tamsulosin plus placebo, -1.49; tamsulosin plus solifenacin, -0.28). But there was no statistical significant between two groups (P=0.627). Patients treated with tamsulosin plus placebo and those treated with tamsulosin plus solifenacin demonstrated 5.2 and 21.61 ml reduction of post-void residual urine. These reduction were not statistically or clinically significant and there were no significant differences in the change in post-void residual volume between 2 groups. No patient in both groups reported urinary retention or increased voiding difficulty during the study.

All adverse events in this study were primarily related to cholinergic blockade (dry, mouth, constipation, blurred vision) and adrenergic blockade (Postu-

ral hypotension). In Tamsulosin and Solifenacin group showed significantly increased in adverse events especially dry mouth (P=0.005) and constipation (P<0.001) compared to Tamsulosin and placebo group as shown in Table 5. Similar trend was found with blurred vision in treatment group but no statistical difference was observed. Other adverse events were not found between two groups.

Most patients who had experience of adverse events were in mild degree and did not disturb their quality of life. Even though the patients who experience in moderate and severe degree of adverse events, they refused to discontinue the study. The data of all adverse events had classified into two groups (no or mild symptom, moderate or severe symptom), there was no significant difference in both placebo and treatment group (Table 6)

Table 3 *Efficacy outcomes*

	Median (range)		
	Placebo	**Solifenacin**	**P value**
IPSS reduction	2 (-10 to 21)	4 (-2 to17)	0.076
Irritative symptom score reduction	1 (-5 to 21)	3 (-1 to 13)	0.005
OAB screener score reduction	2 (-11 to 15)	3 (-8 to 25)	0.302
Bladder sensation scale	2 (2-5)	2 (2-4)	0.049
IPSS QOL	2 (0-5)	1.5 (0-5)	0.034
IPSS QOL diff	0 (-4-4)	-1 (-4-1)	0.031

* Score before treatment minus with score after treatment

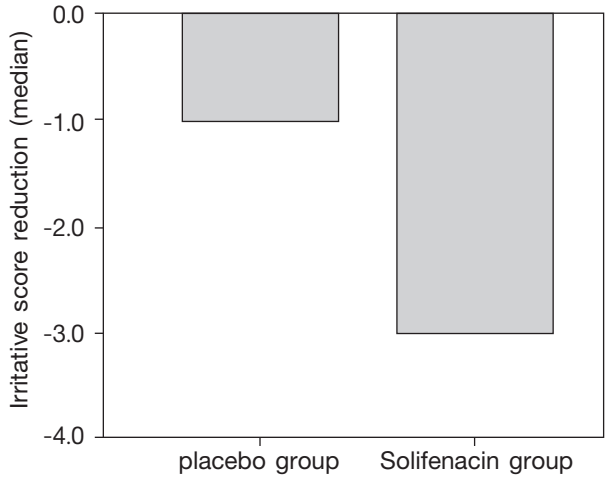

Figure 1 *Reduction of the irritative symptom scores after end of treatments*

Table 4 *Safety outcomes*

	Mean (SD)		
	Placebo	**Solifenacin**	**P value**
Qmax diff (ml/s)	-1.49 (6.95)	-0.28 (10.87)	0.627
PVR diff (ml)	-5.2 (48.43)	-21.61 (81.96)	0.37

Qmax diff: Difference of maximum flow rate (Qmax of last visit minus with Qmax of second visit)
PVR diff: Difference of post-void residual urine (PVR of last visit minus with PVR of second visit)

Table 5 *Adverse events*

All adverse events	Number (%)		P value
	Tamsulosin & Placebo (n = 27)	Tamsulosin & Solifenacin (n = 28)	
Dry mouth	7 (25.9)	18 (64.3)	0.005
Constipation	2 (7.4%)	20 (71.4)	<0.001
Dizziness	12 (44.4)	13 (46.4)	0.549
Indigestion	3 (11.1)	7 (25)	0.163
Difficult voiding	2 (7.4)	4 (14.3)	0.352
Blurred vision	5 (18.5)	9 (32.1)	0.198
Postural hypotension	10 (37)	13 (46.4)	0.333

Table 6 *Clinical significant adverse events*

Adverse events	Number of cases (%)		P value
	Tamsulosin & Placebo (n = 27)	Tamsulosin & Solifenacin (n = 28)	
Dry mouth			
no or mild symptom	26 (96.3%)	24 (85.7%)	0.352
moderate to severe	1 (3.7%)	4 (17.3%)	
Constipation			
no or mild symptom	25 (92.6%)	24 (85.7%)	0.669
moderate to severe	2 (7.4%)	4 (14.3%)	
Dizziness			
no or mild symptom	22 (81.5%)	26 (92.9%)	0.252
moderate to severe	5 (18.5%)	2 (7.1%)	
Indigestion			
no or mild symptom	25 (92.6%)	27 (96.4%)	0.611
moderate to severe	2 (7.4%)	1 (3.4%)	
Difficult voiding			
no or mild symptom	26 (96.3%)	28 (100%)	0.491
moderate to severe	1 (3.7%)	0 (0%)	
Blurred vision			
no or mild symptom	25 (92.6%)	24 (85.7%)	0.669
moderate to severe	2 (7.4%)	4 (14.3%)	
Postural hypotension			
no or mild symptom	23 (85.2%)	27 (96.4%)	0.193
moderate to severe	4 (14.8%)	1 (3.4%)	

Discussion

The mainstay of treatment for BPH patients is primarily to provide a rapid and sustained improvement in lower urinary tract symptoms (LUTS) and reduce the long term complications such as acute urinary retention or upper urinary tract deterioration[2]. LUTS can be divided into storage and obstructive symptoms. Storage symptoms consist of urgency, urge incontinence, frequent urination and nocturia. It is usually accepted that storage symptoms are more bothersome and significantly impact the quality of life to the BPH patients as measured by appropriate questionnaires. Detrusor overactivity is considered an obvious cause of storage symptoms. Obstructed-induced detrusor overactivity with irritative voiding symptoms (Storage symptoms) has been attributed to denervation supersensitivity because increased contractile responses of the bladder smooth muscle to cholinergic agonists and electrical stimulation have been observed[3].

At the beginning of this study (August 2006), there was no other randomized, double-blind, placebo-controlled study to evaluate the efficacy of an antimuscarinic agent and an alpha-adrenergic antagonist in BPH patients bothered by LUTS including overactive bladder symptoms. In this study, we evaluated the combination of tamsulosin (alpha-adrenergic antagonist) and solifenacin (antimuscarinic agent) in BPH patients with OAB symptoms. The primary end point in this study was irritative symptom scores which was derived from IPSS questionnaire by summing only symptoms of urgency, frequency and nocturia. Compared with placebo group, significant reduction of irritative symptom score and bladder sensation scale were observed in solifenacin plus tamsulosin group by week 4. No significant difference in total IPSS score and OAB screener score were demonstrated. These results suggest that combination treatment of alpha-adrenergic blocker and antimuscarinic agent may have some advantages in elderly men who have BPH and overactive bladder. In the present study, quality of life score from IPSS questionnaire also demonstrates significantly better in treatment group than in placebo group. The finding of reduction in irrtative symptom scores may indicate that the patients who received both active drugs may reduce the frequency of overactive bladder symptoms. Moreover, perception and quality of life of these patients may improve by the reduction of Bladder Sensation scale and quality of life score from IPSS in combined drug group. Similar trend was observed from total IPSS scores; the sum scores were reduced in combined group but could not demonstrate statistical significant difference. At the time of study, many patients were confused with some questions in OAB screener questionnaire; it was a possible cause that the result could not be evaluated properly.

Nevertheless, it is difficult to determine how much change in patient- reported outcome measure. The validated overactive bladder-specific health-related QOL questionnaire, the Overactive Bladder questionnaire[4] is not available in Thai language. The QOL score from IPSS questionnaire is too rough to precisely differentiate the change of quality of life of these patients. Moreover the minimally important difference for how patients perceive treatment benefit has not been determined. However, it is likely that patients reporting improvement from QOL score should experience advantage in their general quality of life perception.

Kaplan SA et al[5] reported the first large-scale, randomized, double-blind, placebo-controlled study to investigate the efficacy of an antimuscarinic agent (Tolterodine ER) and alpha-adrenergic blocker (tamsulosin) at November, 2006. They used patient perception of treatment benefit at week 12 as primary efficacy end point based on the assumption that the

patient provides a global response that weighs the risks and benefits of treatment. Eighty percent of 215 patients receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 60% of 214 receiving placebo (P<0.001), 65% of 209 receiving tolterodine ER (P=0.48 vs placebo), or 71% of 207 receiving tamsulosin (P=0.03 vs placebo). They found that the tolterodine ER group (single agent) could reduce urgency, urinary incontinence episodes per 24 hours significantly, but no difference in treatment benefit and IPSS scores were demonstrated. Whereas in tamsulosin monotherapy group, urge incontinence and micturition per 24 hours were significantly reduced but overall perception of treatment benefit was significantly less than combination group. These findings confirm that antimuscaric agent can use as an additional agent for BPH patients who experience overactive bladder symptoms. However we need further studies to classify who are really benefited from the incremental advantages of an antimuscarinic agent.

The benefits and the risks of any treatment should be weighed before applying to the clinical practices. Adverse events of any antimuscarinic agent were primarily related to cholinergic blockade (dry mouth, constipation, blurred vision), but the most serious side effect from previous belief was aggravation of acute urinary retention. However this event may occur only in case of impending bladder decompensation from prolonged bladder outlet obstruction, not in the usual circumstances of BPH patients. The low incidence of acute urinary retention was found from previous reports of men enrolled in 3- to 6-month studies of tolterodine ER monotherapy[1,6,7] or in addition to alpha-adrenergic blockers. In this study, the patients with significant post-void residual volume (more than 200ml) and Maximum urinary flow rate less than 8 ml/s were excluded from the study and no any event of acute retention or impending retention was observed at the end of study. Moreover, No difference in post-void residual urine and maximum flow was demonstrated in both placebo and treatment groups.

Regarding other adverse events, dry month and constipation were observed in treatment group more often than in control group with statistical significant difference. In addition to indigestion and blurred vision, similar trends of increasing in treatment group were observed. Even in the control group, the patient did not receive any antimuscarinic agent but the incidence of antimuscarinic-related adverse events was higher than expectation. This finding may explain by all patients were received the information of all possible adverse events at the beginning of study and asked for each adverse event in every visit. Considering the severity, no difference in clinically significant adverse events (from moderate to severe) were observed with statistical significant.

In some previous studies[8,9], invasive urodynamic studies such as cystometry or pressure-flow study were used to demonstrate detrusor overactivity or degree of bladder outlet obstruction. These guidelines were useful in research practices but irrelevant to most clinical practices. In this study, only uroflowmetry and residual urine measurement with ultrasonogram were used to monitor only the safety outcomes.

In the present study, alpha-adrenergic blocker was started for 2 week before random allocation into two groups was initiated. This strategy was carried on because of safety consideration by opening the bladder outlet before starting the agent to suppress bladder contraction. However, the appropriate guideline to administer the combined treatment is not determined because adequate information is still lacking. There were several studies demonstrated some insight into which men will respond to alpha-adrenergic blocker monotherapy

and which men may require antimuscarinic combination. For example, the higher baseline IPSS scores appear to be mostly driven by storage subscale or irritative symptom scores[10]. In addition, patients who did not respond to alpha-adrenergic blockers had a trend of more severe symptoms at baseline, including the symptoms that characterize overactive bladder. These patients may benefit in the combination of alpha-adrenergic blocker and antimuscarinic agent. However, future studies are necessary to determine the best methods to identify this group of candidates.

Conclusion

The results of this study demonstrate that some men who had problems of LUTS from BPH especially including overactive bladder symptoms might respond with combined treatment of alpha-adrenergic blockers and antimuscarinic agents as demonstrated by statistically and clinically significant treatment benefit. However adverse events should be weighed in on the decision because the goal of the treatment is to improve the quality of life of these patients

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