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THE IMPACT OF ADDING SOLIFENACIN TO TAMSULOSIN THERAPY FOR TREATMENT OF STORAGE LOWER URINARY TRACT SYMPTOMS IN BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT **Background:** Benign prostatic hyperplasia (BPH) is a common condition among aging males that significantly affects their health-related quality of life. OAB symptoms frequently accompany BPH, further degrading patients' quality of life (QoL). In comparison to tamsulosin monotherapy, this study aims to assess the safety and effectiveness of adding solifenacin to tamsulosin therapy in improving OAB symptoms, IPSS, QoL, Qmax, and PVR in patients with BPH. **Methods:** Ninety male patients with OAB symptoms and BPH were divided into two groups at random. Patients in Group 1 (control) received tamsulosin(0.4 mg) alone., whereas patients in Group 2 (observation) received combination of tamsulosin (0.4 mg) and solifenacin (5 mg). A 12-week therapy regimen was administered to both groups. The Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS), and Quality of Life (QoL) questionnaires were used to measure clinical outcomes both before and after treatment, also post-void residual (PVR) and Qmax were assessed. **Result:** There were no notable distinctions between the two groups before therapy. Following treatment, the IPSS, OABSS, and QoL scores of the combination therapy group were significantly improved than those of the monotherapy group ($P<0.01$). Additionally, there was a decrease in nocturia, urge incontinence, frequency, and urgency of urination during the day in the combination therapy group. The combination group saw a slightly decreased rate of side events, although this difference was not statistically significant ($P>0.05$). **Conclusion:** The addition of solifenacin(5mg) to tamsulosin(0.4mg) therapy in patients with BPH and OAB symptoms resulted in superior symptom relief and improvement in QoL, IPSS, Qmax, PVR compared to tamsulosin alone, without a significant increase in adverse reactions. These findings support the clinical use of combination therapy for enhanced management of BPH with associated OAB symptoms.

KEYWORDS : Benign Prostatic Hyperplasia, Overactive Bladder, Solifenacin, Tamsulosin, Combination Therapy

INTRODUCTION

In older men, benign prostatic hyperplasia (BPH) is a common disorder that frequently results in lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO). Patients' quality of life in relation to their health is greatly impacted by these symptoms, which can be either obstructive or irritating. Urinary frequency, urgency, nocturia, and urge incontinence are examples of irritative symptoms that can cause difficulties sleeping, anxiety, depression, a higher risk of falls, and sexual dysfunction. Obstructive symptoms include straining, intermittency, weak stream, and incomplete emptying of the bladder.

Studies show that up to 50% of individuals with BOO have overactive bladder (OAB), which is a common finding of BOO brought on by BPH. Frequency, urgency, nocturia, and urge incontinence are of the symptoms of OAB that significantly lower quality of life. The disorder is brought on by aberrant afferent signaling and detrusor hyperactivity, which frequently follow secondary alterations in bladder sensitivity, elasticity, and stability brought on by BOO.

Alpha-1 adrenergic blockers (α1-blockers), 5-alpha reductase inhibitors (5ARIs), anticholinergic drugs, β3-adrenoceptor agonists, and phosphodiesterase type-5 inhibitors (PDE5i) are among the therapy options available for treating BPH. According to recent research, anticholinergic drugs and α1-blockers together may be more effective and improve quality of life than monotherapy, especially for men who have both LUTS and OAB.

Combination medications are gaining popularity because α1-blocker monotherapy can't always effectively manage storage symptoms, especially when detrusor overactivity is the cause of the symptoms. Combining M receptor antagonists(anticholinergic) with α1-blockers has showed potential in improving symptom control. In order to treat patients with BPH and related OAB symptoms, this study intends to further examine and assess the therapeutic efficacy of combining the M receptor antagonist solifenacin with the α1-blocker tamsulosin.

MATERIALS AND METHODS

In this prospective study, 90 male patients who were 50 years of age or older and receiving treatment for benign prostatic hyperplasia (BPH) with related symptoms of an overactive bladder (OAB) were included. This study was done between August to October 2023 and patients were chosen from our hospital's urology outpatient clinics. Ultrasonography, computed tomography (CT), prostate-specific antigen (PSA) testing, and digital rectal examination, uroflometry were among the diagnostic methods performed on patients to confirm BPH. Patients had to meet the following requirements in order to be eligible: an International Prostate Symptom Score (IPSS) of 12 or higher; an Overactive Bladder Symptom Score (OABSS) of at least 3; an average frequency of at least 8 urination per day; nocturia occurring at least twice per night; and a Post Void Residual urine volume(PVR) < 100 ml.

Patients with neurogenic conditions affecting bladder function, such as spinal cord injury, prostatic cancer, urethral stricture, phimosis, PVR(residual urine volume< 100 ml), acute infections, prior TURP surgery, higher grades of prostatomegaly and BPH with vesical calculus were excluded from the study. Two groups were randomly selected from among the patients. 0.4 mg of tamsulosin was given once daily to Group 1 (n=45), and a combination of 0.4 mg tamsulosin and 5 mg solifenacin was given once daily to Group 2 (n=45). The duration of both treatment plans was twelve weeks in both groups.

The OABSS, IPSS, and Quality of Life (QoL) questionnaires were

used to evaluate clinical results, which were documented at the beginning and at conclusion of the therapy period. Other characteristics were examined as well, including post-void residual volume (PVR), maximal urine flow rate (Qmax). Both groups' pre and post-treatment follow-up assessments score were collected and compared and carried out to evaluate symptom improvement and the occurrence of adverse events.

All procedures were performed in accordance with ethical standards of the Institutional Ethical Committee, Ethical Committee Approval No: IEC-CMC/Approval/19/2022, Dated: 06-07-2023. Informed consent was obtained from each participant included in the study.

Overactive Bladder Symptom Score (OABSS)

Sco	Frequency	Questions
0	<=7	How many times do you typically urinate from waking in the morning until sleeping at night?
1	8-14	
2	>=15	
0	0	How many times do you typically wake up to urinate from sleeping at night until waking in the morning?
1	1	
2	2	
3	>=3	
0	Not at all	How often do you have a sudden desire to urinate, which is difficult to defer?
1	Less than once a week	
2	Once a week or more	
3	About once a day	
4	2-4 times a day	
5	5 times a day or more	
0	Not at all	How often do you leak urine because you cannot defer the sudden desire to urinate?
1	Less than once a week	
2	Once a week or more	
3	About once a day	
4	2-4 times a day	
5	5 times a day or more	

International Prostate Symptom Score (IPSS)

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying: How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency: How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency: How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency: How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream: How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining: How often have you had to strain to start urination?	0	1	2	3	4	5	
7. Nocturia: How many times did you typically get up at night to urinate?	None	1 Time	2 Times	3 Times	4 Times	5 Times	

Quality of Life Due to Urinary Symptoms

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying: How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency: How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency: How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency: How often have you found it difficult to postpone urination?	0	1	2	3	4	5	

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6. Straining: How often have you had to strain to start urination?	0	1	2	3	4	5	
7. Nocturia: How many times did you typically get up at night to urinate?	None	1 Time	2 Times	3 Times	4 Times	5 Times	

SAMPLE SIZE CALCULATION

The sample size was determined using G*Power software version 3.1.9.4, with an effect size of 0.64, α error of 0.05, and power (1−β) of 0.8. Assuming an equal allocation ratio between groups, the required sample size was calculated to be 45 patients per group, ensuring sufficient power to detect statistically significant differences.

Statistical Analysis

IBM SPSS software, version 23.0, was used to analyze the data. Numbers and percentages were used to represent categorical data, and descriptive statistics were displayed as mean ± standard deviation (SD). Results was analyzed using student t-test for continuous variable and chi-square test(x2-test) for discrete variables.

OBSERVATIONS

Table -1: Basic Characteristics

Score	Description
0	Delighted
1	Pleased
2	Mostly Satisfied
3	Mixed
4	Mostly Dissatisfied
5	Unhappy
6	Terrible

Table -2: Effect Of Tamsulosin Only On Group 1

Parameters	Group-1	Group-2	P-value
Age (mean ± SD)	59.4 ± 4.8	59.1 ± 4.6	0.76
Weight of prostate	43.5 ± 8.4	42.6 ± 7.1	0.58

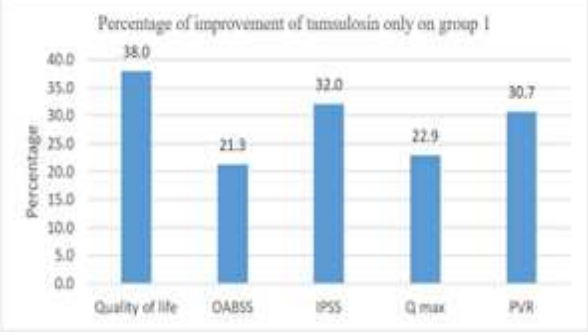
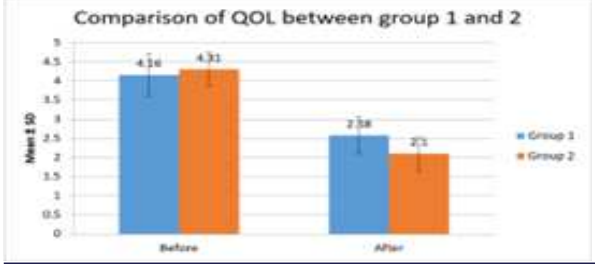


Table -3: Effect Of Tamsulosin Plus Solifenacin On Group 2

	Group 1	Group 2	p-value
Before	8.3 ± 1.8	8.3 ± 2.0	0.99
After	10.2 ± 2.1	11.3 ± 2.8	0.04

Table -4: Comparison Of QOL Between Group 1 And 2



Parameters	Before (Mean ± SD)	After (Mean ± SD)	p-value
Quality of life	4.16 ± 0.55	2.58 ± 0.48	<0.001
OABSS	9.8 ± 1.41	7.71 ± 1.49	<0.001
IPSS	18.1 ± 2.0	12.3 ± 2.4	<0.01
Q max	8.3 ± 1.8	10.2 ± 2.1	<0.01
PVR	34.8 ± 13.2	24.1 ± 9.1	<0.01

Table -5: Comparison Of OABSS Between Group 1 And 2

	Group 1	Group 2	p-value
Before	4.16 ± 0.55	4.31 ± 0.44	0.16
After	2.58 ± 0.48	2.10 ± 0.45	<0.001

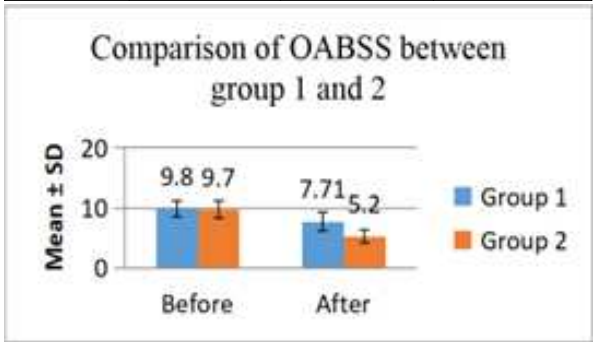


Table -6 : Comparison Of IPSS Between Group 1 And 2

Parameters	Before (Mean ± SD)	After (Mean ± SD)	p-value
Quality of life	4.31 ± 0.44	2.1 ± 0.45	<0.001
OABSS	9.7 ± 1.40	5.2 ± 1.04	<0.001
IPSS	18.1 ± 2.1	9.4 ± 2.5	<0.001
Q max	8.3 ± 2.0	11.3 ± 2.8	<0.001
PVR	35.5 ± 14.1	22.4 ± 9.2	<0.001

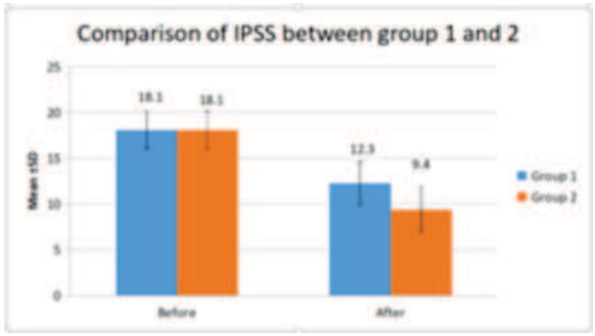


Table -7 : Comparison Of QMAX Between Group 1 And 2

	Group 1	Group 2	p-value
Before	8.3 ± 1.8	8.3 ± 2.0	0.99
After	10.2 ± 2.1	11.3 ± 2.8	0.04

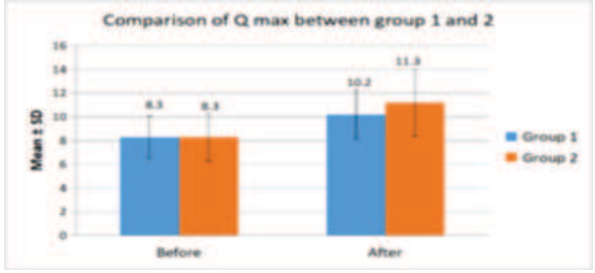
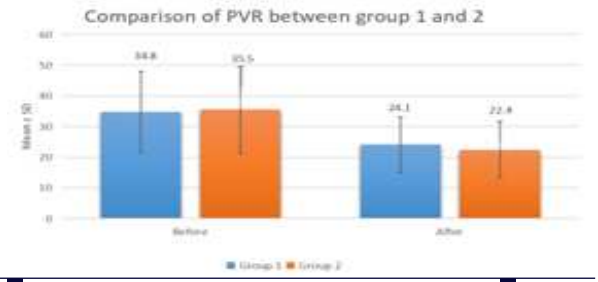
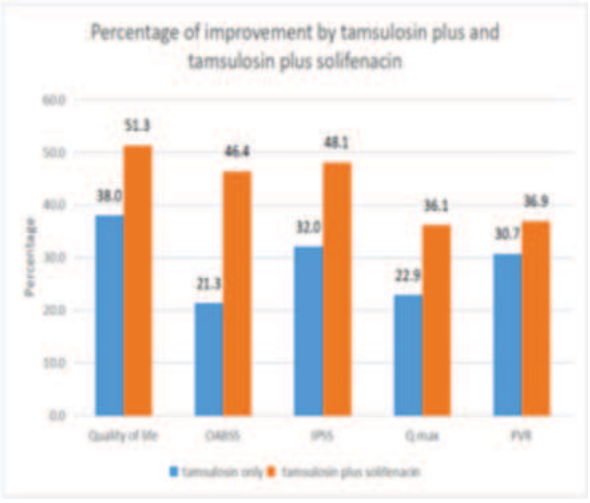


Table -8 : Comparison Of PVR Between Group 1 And 2



	Group 1	Group 2	p-value
Before	18.1 ± 2.0	18.1 ± 2.1	0.98
After	12.3 ± 2.4	9.4 ± 2.5	<0.001

	Group 1	Group 2	p-value
Before	34.8 ± 13.2	35.5 ± 14.1	0.81
After	24.1 ± 9.1	22.4 ± 9.2	<0.01



DISCUSSION

Lower urinary tract symptoms (LUTS) in older men are most commonly caused by benign prostatic hyperplasia (BPH), with storage LUTS, which includes urgency, frequency, urge incontinence, and nocturia, often occurring in about 50% of cases. Overactive bladder (OAB) linked to BPH is primarily caused by a confluence of myogenic and neurogenic mechanisms as well as changes in the bladder mucosal sensitivity. In this study, we investigated the effects of combining tamsulosin, a uroselective alpha-1 receptor blocker that acts on the urethra, bladder neck, prostate, and smooth muscles, with solifenacin, an anticholinergic drug that targets muscarinic receptors M2 and M3 on the bladder. The main objective was to determine whether this combination medication could outperform tamsulosin monotherapy in improving quality of life (QoL) and various other parameters.

A total of 90 patients participated in the study, with 45 patients in the control group receiving tamsulosin alone and 45 patients in the observation group receiving a combination of tamsulosin and solifenacin. The mean age of the patients in the control group was 59.4±4.8 years, and in the observation group, it was 59.4±4.6 years. The baseline characteristics, including the International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), Quality of Life (QoL), Qmax, and post-void residual volume (PVR), showed no statistically significant differences between the two groups (P>0.05).

Following the 12-week treatment period, both groups exhibited significant improvements in IPSS, OABSS, and QoL scores (P<0.05). However, the observation group, which received the combination therapy, demonstrated significantly greater improvements compared to the control group. Specifically, reductions in daytime urination frequency, night urination frequency, urgency, and urge incontinence were more pronounced in the observation group (P<0.05). The Qmax and PVR also improved in both groups, but the changes in PVR were not statistically different between the two groups (P>0.05).

Regarding adverse reactions, the incidence was slightly higher in the control group (15.6%) compared to the observation group (89%), although this difference was not statistically significant (P>0.05). The most common side effects included dizziness, thirst, blurred vision, and dysuria, with no reports of acute urinary retention in either group.

Table 9 Summary Of Key Features In Recruited Studies (Ordered by Year)

Author	Sample Size	Dose	Follow-Up Period	Region
Kaplan (2009)	202 (Combination), 195 (Mono)	T (0.4 mg) + S (10 mg), T (0.4 mg + placebo)	4 weeks	USA
Seo (2011)	30 (Combination), 30 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	3 months	Korea
Yamaguchi (2011)	210 (Combination), 215 (Mono)	T (0.2 mg) + S (2.5 or 5 mg), T (0.2 mg)	12 weeks	Korea
Liang (2012)	55 (Combination), 53 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	4 weeks	China
Xiang (2012)	20 (Combination), 20 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	8 weeks	China
Kerrebroeck (2013)	339 (Combination), 327 (Mono)	T (0.4 mg) + S (6 or 9 mg), T (0.4 mg)	12 weeks	Europe
Lee (2014)	76 (Combination), 80 (Mono)	T (0.4 mg) + S (5 mg), T (0.4 mg)	12 weeks	Korea
Ko (2014)	94 (Combination), 93 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	12 weeks	Korea
Song (2016)	51 (Combination), 76 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	2 weeks	China
Marcus (2016)	339 (Combination), 327 (Mono)	T (0.4 mg) + S (6 or 9 mg), T (0.4 mg)	12 weeks	Europe
Xing (2016)	48 (Combination), 41 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	12 weeks	China
Yuan (2017)	32 (Combination), 32 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	4 weeks	China
Lee (2017)	44 (Combination), 55 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	12 weeks	Korea
Duan (2018)	34 (Combination), 34 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	12 weeks	China
Chen (2019)	53 (Combination), 53 (Mono)	T (0.2 mg) + S (5 mg), T (0.2 mg)	12 weeks	China
Kirill (2018)	93 (Combination), 87 (Mono)	T (0.4 mg) + S (10 or 5 mg), T (0.4 mg)	10 months	Russia

Note: T: Tamsulosin, S: Solifenacin & Superscripts used to distinguish studies with similar author names.

Table 10 Characteristics And Outcomes Of Studies Assessing Combined Tamsulosin And Solifenacin Treatment

Author	Study Type	Participants	Trial Design	Outcome Measures	Effectiveness of TAM + SOL	Safety
Kaplan et al.	12-week, double-blind, randomized, placebo-controlled	397	Initial phase: 4 weeks of TAM 0.4 mg, followed by 12 weeks of TAM 0.4 mg + SOL 5 mg or placebo	PVR, daily urination, PPBC, UPS, IPSS	TAM + placebo: Reduced urgency episodes, improved PVR and QoL with fewer adverse events	Adverse effects were minimal, dry mouth reported most frequently (7% TAM + SOL vs. 3% placebo).
Masumori et al.	12-week, nonrandomized, no placebo	48	First 2 weeks: TAM 0.2 mg, followed by 12 weeks of TAM 0.2 mg with SOL 5 mg	PVR, QoL, IPSS, OABSS	IPSS, QoL, and OABSS scores significantly improved with SOL treatment	No adverse events or change in PVR observed
Yamaguchi et al.	12-week, double-blind, randomized, placebo-controlled	638	Initial 2-week phase: TAM 0.2 mg or placebo, followed by 12 weeks of TAM 0.2 mg + SOL (2.5 mg or 5 mg)	PVR, daily urination, nocturia, urgency episodes, IPSS, QoL	Improvement in total and storage IPSS scores, QoL, and reduction in nocturia and urgency episodes	AUR was reported in 1.9% of patients receiving SOL 5 mg
Kaplan et al.	12-week, double-blind, randomized, placebo-controlled	192	12 weeks of placebo, SOL 6 mg + TAM, SOL 9 mg + TAM	PVR, Qmax, PPBC, IPSS, QoL	Significant improvement in Qmax, QoL, and IPSS scores with combined therapy versus placebo	PVR change at the end of the treatment was significant in combined therapy

Lee et al.	12-week, randomized, no placebo	156	Phase 1: 4 weeks of TAM 0.2 mg, Phase 2: 8 weeks of TAM 0.2 mg + SOL 5 mg	IPSS, OABSS, PPBC, urgency episodes	Significant improvement in IPSS, OABSS, and QoL with combined therapy	AUR observed in 1 patient upon SOL addition
Shin et al.	12-week, randomized, no placebo	405	Washout period followed by 4 weeks of TAM, then 4 weeks of TAM + SOL 5 mg	PVR, IPSS, OABSS	Notable improvements in PVR, storage IPSS, and QoL observed across different treatment phases	Overall tolerable with no major adverse effects
Yun et al.	4-week, randomized, no placebo	344	Patients grouped based on storage or voiding issues; treatment with TAM 0.2 mg alone or TAM 0.2 mg + SOL 5 mg	IPSS (voiding, storage), QoL	Storage group: significant improvements in IPSS and QoL. Voiding group: better outcomes versus TAM monotherapy	Clinically insignificant minor PVR increase
van Kerrebroeck et al.	12-week, double-blind, randomized, placebo-controlled	937	2-week placebo period followed by 12 weeks of treatment with TAM + SOL at various dosages	IPSS, QoL, PVR, daily urination frequency, urgency episodes, nocturia	Improved storage and total IPSS scores, QoL, and PPBC compared to TAM alone. Post-hoc analysis highlighted effectiveness in moderate-severe symptoms	Low incidence of AUR, minimal and clinically insignificant PVR increase

Notes:

l **Abbreviations**: TAM, tamsulosin; SOL, solifenacin; IPSS, International Prostate Symptom Score; QoL, quality of life; OABSS, Overactive Bladder Symptom Score; AUR, acute urinary retention; PVR, post-void residual volume; PPBC, Patient Perception of Bladder Condition; QoL, Quality of Life Index.

l *The effectiveness results only highlight statistically significant findings.* Our findings demonstrate that the addition of solifenacin to tamsulosin resulted in a significant enhancement in QoL for patients in Group 2, with scores improving from 4.31 ± 0.44 to 2.1 ± 0.45 ($P < 0.001$). This improvement is consistent with the results reported by Van Kerrebroeck et al. (2013), who also observed significant QoL benefits with this combination therapy. Similarly, Group 1, which received tamsulosin alone, showed improvement in QoL from 4.16 ± 0.55 to 2.58 ± 0.48 ($P < 0.001$), aligning with findings from Chapple et al. (2013).

In terms of the Overactive Bladder Symptom Score (OABSS), the combination therapy in Group 2 demonstrated superior efficacy, with OABSS decreasing from 9.7 ± 1.40 to 5.2 ± 1.04 ($P < 0.001$). This significant reduction is in agreement with studies by Masumori et al. (2010) and Yamaguchi et al. (2011), who also reported similar improvements upon the addition of solifenacin to tamsulosin. Furthermore, the combination therapy proved more effective in reducing the International Prostate Symptom Score (IPSS), as Group 2 exhibited a greater reduction compared to Group 1. These results echo the findings of Kaplan SA et al., who reported a lower incidence of nocturia, urgency, and urge incontinence, alongside improved IPSS, with the combined treatment.

The study also highlighted the effectiveness of the combination therapy in improving Q max, where Group 2 saw an increase from 8.3 ± 2.0 to 11.3 ± 2.8 ($P < 0.001$). This improvement is in line with Hui Wang et al. (2017), who documented similar enhancements in Q max after introducing solifenacin to tamsulosin treatment.. Lastly, post-void residual volume (PVR) was significantly reduced in Group 2, with values decreasing from 35.5 ± 14.1 to 22.4 ± 9.2 ($P < 0.001$), further supporting the efficacy of the combination therapy. These findings correlate with those of Hui Wang et al. (2017), who also observed a substantial reduction in PVR following the addition of solifenacin.

Finally, compared to tamsulosin alone, the combination of solifenacin and tamsulosin provides a more successful treatment for storage LUTS in BPH patients, resulting in notable improvements in Q max, PVR, OABSS, IPSS, and quality of life. These findings provide credence to the idea that combination therapy is a good option for patients who do not get sufficient symptom alleviation from tamsulosin monotherapy.

ADVERSE EFFECTS

Both the observational group (tamsulosin plus solifenacin) and the control group (tamsulosin only) experienced side effects in this investigation. Interestingly, neither group had any incidences of acute urine retention. Dizziness and blurred vision were among the 15.6% of adverse events that occurred in the control group. By contrast, the observational group saw a reduced rate of adverse events (8.9%), with symptoms such as dry mouth, blurred vision, and dizziness being noted.

According to statistical analysis, there was no discernible difference between the two groups' total incidence of adverse responses ($P=0.34$). Patients tolerated both treatment plans well, suggesting a good safety record for the tamsulosin and solifenacin combination therapy.

LIMITATIONS

This study contains limitations of short term follow up, potential selection bias, lack of placebo group and insufficient consideration of adverse effects and confounding variables may impact the reliability and generalizability of the findings.

CONCLUSION

Our study's results show that patients with benign prostatic hyperplasia (BPH) who mostly experience storage lower urinary tract symptoms (LUTS) benefit greatly from the combination of solifenacin and tamsulosin. Quality of life (QoL), the Overactive Bladder Symptom Score (OABSS), and the International Prostate Symptom Score (IPSS) were among the important clinical outcomes that the combination medication improved over the short-term follow-up period more effectively than tamsulosin alone. According to these findings, combining solifenacin with tamsulosin may provide a more thorough method of treating storage LUTS in BPH patients, improving patient outcomes overall. To confirm these results and evaluate the combo therapy's long-term safety and effectiveness, more research with extended follow-up times is advised.

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