Original Research Article

EFFICACY AND SAFETY OF MELATONIN AS AN ADJUNCT TO TAMSULOSIN IN THE MANAGEMENT OF NOCTURIA ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA: A PROSPECTIVE RANDOMIZED DOUBLE-BLINDED CONTROLLED TRIAL

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ABSTRACT

Background: Nocturia is a bothersome lower urinary tract symptom associated with benign prostatic hyperplasia (BPH), significantly affecting sleep and quality of life. Although tamsulosin improves urinary symptoms, its effectiveness against nocturia remains limited. Aim of the study was to compare the efficacy and safety of melatonin combined with tamsulosin versus tamsulosin alone in improving nocturia among patients with BPH. **Materials and Methods:** This prospective, randomised, double-blind controlled trial included 140 patients with BPH and nocturia, equally allocated into two groups. Group A received tamsulosin 0.4 mg with melatonin 3 mg, while Group B received tamsulosin 0.4 mg alone. Patients were evaluated at baseline and after one month using the International Prostate Symptom Score (IPSS), nocturia frequency, quality of life (QoL), uroflowmetry and post-void residual urine (PVRU). **Results:** Nocturia frequency decreased from 3.8 ± 0.9 to 1.9 ± 0.8 episodes/night in Group A, compared with 3.7 ± 1.0 to 2.6 ± 0.9 in Group B ($p<0.001$). IPSS reduction was significantly greater with combination therapy (10.3 ± 3.6 versus 7.5 ± 3.9; $p<0.001$). QoL, urinary flow and PVRU also improved significantly. Adverse effects were generally mild. **Conclusion:** Melatonin combined with tamsulosin demonstrated superior short-term improvement in nocturia and urinary symptoms compared with tamsulosin alone, suggesting its potential as an adjunctive therapy.

Keywords: Benign prostatic hyperplasia, Nocturia, Melatonin, Tamsulosin, International Prostate Symptom Score, Quality of life.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common age-related urological disorder characterised by non-malignant proliferation of prostatic stromal and epithelial cells, frequently resulting in bladder outlet obstruction and lower urinary tract symptoms (LUTS). These symptoms include urinary frequency, urgency, hesitancy, weak urinary stream, incomplete bladder emptying and nocturia. The prevalence and severity of BPH-associated LUTS increase progressively with advancing age, substantially affecting physical well-being and quality of life. Jeh et al., in a large epidemiological study involving 72,068 men, demonstrated an age-related increase in prostate volume, symptom severity and urinary dysfunction, highlighting the growing burden of BPH among elderly men.[1]

Nocturia, defined as waking from sleep one or more times to urinate, is among the most bothersome symptoms associated with BPH. Repeated nocturnal voiding disrupts normal sleep architecture and contributes to daytime fatigue, impaired concentration, psychological distress and reduced productivity. Persistent nocturia may additionally increase the risk of falls and other complications in elderly individuals. Aucar et al. emphasised that nocturia is a multifactorial condition involving nocturnal polyuria, reduced functional bladder capacity and altered renal physiology.[2] Monaghan et al. further identified sleep disorders, systemic comorbidities, behavioural factors and medications as important contributors to nocturia,

indicating that bladder outlet obstruction alone does not adequately explain its occurrence.[3]

Pharmacological management of BPH primarily involves alpha-adrenergic blockers, 5-alpha-reductase inhibitors and other symptom-directed medications. Tamsulosin, a selective alpha-1 adrenergic antagonist, improves urinary flow by relaxing smooth muscles within the prostate and bladder neck. However, its effectiveness in controlling nocturia remains variable because nocturnal urinary symptoms frequently arise from mechanisms independent of prostatic obstruction. Contemporary European Association of Urology guidelines recommend comprehensive evaluation using validated symptom scores, frequency–volume charts and objective urinary assessments.[4] Although desmopressin may reduce nocturnal urine production, potential complications such as hyponatraemia necessitate careful patient selection and monitoring.[5]

Melatonin, an endogenous hormone secreted by the pineal gland, regulates circadian rhythms and the sleep–wake cycle. Its potential influence on bladder activity, sleep continuity and nocturnal urinary function has generated interest in its therapeutic application. Fotovat et al., in a randomised double-blind trial involving 108 patients with BPH, demonstrated significant improvement in nocturia and urinary frequency following the addition of melatonin to tamsulosin therapy.[6] Similarly, Leerasiri et al. reported reduced nocturnal voiding episodes and improved nocturia-related quality of life following melatonin administration in older women.[7] A systematic review by Burke et al. further examined melatonin and melatonin receptor agonists as potential treatments for nocturia, while highlighting limitations in the available clinical evidence.[8]

Despite encouraging findings, important research gaps remain regarding the additional therapeutic benefit, tolerability and consistency of melatonin when combined with standard BPH treatment. Existing studies have involved heterogeneous populations, relatively small samples and short treatment durations. Recent reviews have emphasised the need for further comparative clinical investigations evaluating pharmacological approaches to nocturia.[9,10] Therefore, the present randomised controlled study aims to evaluate the effectiveness of melatonin combined with tamsulosin compared with tamsulosin alone in improving nocturia among patients with BPH, while assessing associated urinary symptom improvement, quality of life and treatment-related adverse effects.

MATERIALS AND METHODS

Study Design and Setting: The present study was a prospective, randomised, double-blind, parallel-group controlled clinical trial conducted in the Department of Urology at B.L.D.E. (Deemed to be University), Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka. The study was carried out over two years, from July 2024 to June 2026. Male patients diagnosed with benign prostatic hyperplasia (BPH) presenting with nocturia were recruited from the urology outpatient department and inpatient services. The study aimed to evaluate the effectiveness of melatonin as an adjunct to tamsulosin in improving nocturia, lower urinary tract symptoms and quality of life. Approval was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participants before enrolment.

Sample Size and Sampling Technique: A total of 140 patients diagnosed with BPH and nocturia were included in the study. Sample size estimation was performed using G*Power software version 3.1.9.4, based on previously reported International Prostate Symptom Score (IPSS) values, considering a 5% significance level, 85% statistical power and a 1:1 allocation ratio. The calculated sample size was 70 participants in each group. Eligible patients were randomly allocated using computer-generated randomisation, and treatment allocation was concealed using sealed opaque envelopes. Both participants and outcome assessors were blinded to treatment allocation.

Inclusion Criteria

1. Male patients diagnosed with benign prostatic hyperplasia.
2. Patients presenting with nocturia as a bothersome urinary symptom.
3. Patients with an International Prostate Symptom Score (IPSS) ≥8, indicating moderate to severe lower urinary tract symptoms.
4. Patients willing to participate and provide written informed consent.

Exclusion Criteria

1. Patients with significant cardiac abnormalities.
2. Patients with nocturia attributable to other causes, including diuretic use, diabetes mellitus, global polyuria or sleep disorders.
3. Patients diagnosed with autoimmune disorders.
4. Patients with collagen vascular diseases.
5. Patients with bronchial asthma.
6. Patients with significant psychiatric illness.

Study Tools

1. International Prostate Symptom Score (IPSS): A validated seven-item questionnaire assessing urinary symptoms, including nocturia, with scores ranging from 0 to 35.
2. Quality of Life (QoL) Score: Used to assess the impact of urinary symptoms on patients' overall quality of life.
3. Frequency–Volume Chart: Used to record urinary frequency, voided urine volume and nocturnal voiding episodes.
4. Uroflowmetry: Used to evaluate maximum urinary flow rate (Qmax).
5. Ultrasonography: Ultrasound of the kidney, ureter and bladder (KUB) was performed to assess urinary tract findings, prostate volume and post-void residual urine (PVRU).

6. Laboratory Investigations: Complete blood count, blood glucose, renal function tests, serum electrolytes, urine routine examination, urine culture and sensitivity, and serum prostate-specific antigen (PSA).
7. Adverse Effect Assessment: Clinical evaluation for dizziness, headache, nasal congestion, retrograde ejaculation, daytime drowsiness and gastrointestinal symptoms.

Data Collection Procedure: Eligible patients underwent detailed clinical evaluation, medical history assessment and baseline investigations after providing written informed consent. The IPSS questionnaire, quality of life score and frequency–volume chart were used to assess the severity of urinary symptoms and nocturia. Participants were randomly assigned to two groups of 70 patients each. Group A received oral tamsulosin 0.4 mg once daily combined with melatonin 3 mg at bedtime, while Group B received tamsulosin 0.4 mg alone. Treatment was administered for one month. Following treatment, patients were reassessed for IPSS, quality of life, nocturnal voiding frequency, maximum urinary flow rate and post-void residual urine. A reduction of at least three points in IPSS was considered clinically meaningful improvement. Treatment-related adverse effects were documented to evaluate the safety and tolerability of the interventions.

Statistical Analysis: The collected data were entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS), version 20. Continuous variables were expressed as mean ± standard deviation or median, as appropriate, while categorical variables were presented as frequencies and percentages. The independent-samples t-test and Mann–Whitney U test were used to compare continuous variables between groups according to data distribution. Categorical variables were analysed using the Chi-square test or Fisher's exact test, wherever applicable. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1: Comparison of Baseline Demographic, Clinical and Prostatic Characteristics Between the Study Groups

Parameter	Group A (n = 70)	Group B (n = 70)	p-value
Age (years)	64.3 ± 7.5	65.1 ± 6.9	0.52
BMI (kg/m²)	25.8 ± 3.1	26.2 ± 3.4	0.44
Male sex, n (%)	70 (100%)	70 (100%)	—
Baseline prostate volume (mL)	42.8 ± 8.7	43.6 ± 9.1	0.58
Serum PSA (ng/mL)	2.74 ± 1.18	2.81 ± 1.22	0.73

The baseline demographic and clinical characteristics were comparable between the two treatment groups. The mean age was 64.3 ± 7.5 years in Group A and 65.1 ± 6.9 years in Group B, indicating a predominantly elderly study population. The mean BMI was similar between the groups, with no statistically significant difference (p = 0.44). Baseline prostate volume was 42.8 ± 8.7 mL in Group A and 43.6 ± 9.1 mL in Group B. Serum PSA levels were also comparable, measuring 2.74 ± 1.18 ng/mL and 2.81 ± 1.22 ng/mL, respectively. None of the reported baseline differences was statistically significant, suggesting that the groups were broadly comparable before treatment initiation.

Table 2: Comparison of International Prostate Symptom Scores (IPSS) Before and After Treatment

IPSS parameter	Group A (n = 70)	Group B (n = 70)	p-value
Baseline IPSS	27.9 ± 6.7	28.4 ± 6.5	0.63
IPSS after one month	17.6 ± 5.4	20.9 ± 5.8	0.002*
Mean reduction in IPSS	10.3 ± 3.6	7.5 ± 3.9	<0.001*

The mean baseline IPSS was 27.9 ± 6.7 in the combination therapy group and 28.4 ± 6.5 in the tamsulosin-alone group, with no significant baseline difference (p = 0.63). Following one month of treatment, both groups demonstrated a reduction in urinary symptom severity. However, the post-treatment IPSS was significantly lower in Group A (17.6 ± 5.4) compared with Group B (20.9 ± 5.8; p = 0.002). The mean reduction in IPSS was greater in Group A (10.3 ± 3.6) than in Group B (7.5 ± 3.9). This between-group difference was statistically significant (p < 0.001). These findings suggest greater improvement in overall lower urinary tract symptoms among patients receiving melatonin combined with tamsulosin.

Table 3: Comparison of Nocturia Frequency and Frequency–Volume Chart Parameters between Study Groups

Parameter	Group A (n = 70)	Group B (n = 70)	p-value
Baseline nocturnal voiding (episodes/night)	3.8 ± 0.9	3.7 ± 1.0	0.67
Nocturnal voiding after one month (episodes/night)	1.9 ± 0.8	2.6 ± 0.9	<0.001*
Baseline daytime voiding (episodes/day)	9.8 ± 1.9	9.6 ± 2.1	0.58
Daytime voiding after one month (episodes/day)	6.9 ± 1.5	7.8 ± 1.7	0.002*
Baseline mean voided volume (mL/void)	156.4 ± 28.7	158.9 ± 30.1	0.61

Mean voided volume after one month (mL/void)	198.6 ± 32.4	182.3 ± 29.8	0.004*

Frequency–volume chart parameters were comparable between the groups before treatment, with no statistically significant baseline differences. The mean nocturnal voiding frequency decreased from 3.8 ± 0.9 to 1.9 ± 0.8 episodes per night in Group A, compared with a reduction from 3.7 ± 1.0 to 2.6 ± 0.9 in Group B. Post-treatment nocturia frequency was significantly lower in the combination therapy group ($p < 0.001$). Daytime voiding frequency also decreased more markedly in Group A, reaching 6.9 ± 1.5 episodes per day compared with 7.8 ± 1.7 in Group B ($p = 0.002$). Additionally, mean voided volume increased to 198.6 ± 32.4 mL in Group A compared with 182.3 ± 29.8 mL in Group B ($p = 0.004$). These findings indicate that combination therapy was associated with greater improvement in nocturia and other frequency–volume parameters.

Table 4: Comparison of Quality of Life Scores before and After Treatment between Study Groups

Quality of life parameter	Group A (n = 70)	Group B (n = 70)	p-value
Baseline QoL score	4.6 ± 0.9	4.5 ± 1.0	0.67
QoL score after one month	2.4 ± 0.8	3.1 ± 0.9	<0.001*
Mean reduction in QoL score	2.2 ± 0.7	1.4 ± 0.8	<0.001*

At baseline, the mean quality of life score was 4.6 ± 0.9 in Group A and 4.5 ± 1.0 in Group B, indicating a comparable degree of urinary symptom-related bother ($p = 0.67$). Following treatment, the mean QoL score decreased to 2.4 ± 0.8 in Group A and 3.1 ± 0.9 in Group B. The difference between the groups after treatment was statistically significant ($p < 0.001$). The mean improvement in QoL score was 2.2 ± 0.7 among patients receiving combination therapy compared with 1.4 ± 0.8 among patients receiving tamsulosin alone. This difference was also statistically significant ($p < 0.001$). The results suggest that the addition of melatonin was associated with greater improvement in urinary symptom-related quality of life.

Table 5: Comparison of Maximum Urinary Flow Rate (Qmax), Post-Void Residual Urine and Prostate Volume Before and After Treatment

Parameter	Group A (n = 70)	Group B (n = 70)	p-value
Baseline Qmax (mL/s)	9.2 ± 2.1	9.4 ± 2.3	0.63
Qmax after one month (mL/s)	13.4 ± 2.6	11.8 ± 2.4	<0.001*
Mean increase in Qmax (mL/s)	4.2 ± 1.6	2.4 ± 1.5	<0.001*
Baseline PVRU (mL)	82.6 ± 24.8	85.1 ± 26.3	0.55
PVRU after one month (mL)	46.9 ± 18.7	61.3 ± 20.5	<0.001*
Mean reduction in PVRU (mL)	35.7 ± 14.2	23.8 ± 13.6	<0.001*
Baseline prostate volume (mL)	42.8 ± 8.7	43.6 ± 9.1	0.58
Prostate volume after one month (mL)	41.9 ± 8.5	42.7 ± 8.8	0.62

Uroflowmetry and ultrasonographic assessments demonstrated significant functional improvement following treatment, particularly in the combination therapy group. The mean maximum urinary flow rate increased from 9.2 ± 2.1 to 13.4 ± 2.6 mL/s in Group A, compared with an increase from 9.4 ± 2.3 to 11.8 ± 2.4 mL/s in Group B. The improvement in Qmax was significantly greater in Group A ($p < 0.001$). Similarly, mean post-void residual urine decreased from 82.6 ± 24.8 to 46.9 ± 18.7 mL in Group A, whereas it decreased from 85.1 ± 26.3 to 61.3 ± 20.5 mL in Group B. The reduction in PVRU was significantly greater in the combination therapy group ($p < 0.001$). Prostate volume showed only minimal changes in both groups, with no significant between-group difference after treatment ($p = 0.62$).

Table 6: Comparison of Baseline Haematological, Biochemical and Urinary Investigation Findings between Study Groups

Parameter	Group A (n = 70)	Group B (n = 70)	p-value
Haemoglobin (g/dL)	13.6 ± 1.4	13.4 ± 1.3	0.42
Total leukocyte count (cells/mm³)	7420 ± 1580	7560 ± 1620	0.63
Platelet count (lakhs/mm³)	2.68 ± 0.54	2.71 ± 0.49	0.71
Fasting blood glucose (mg/dL)	96.8 ± 12.4	98.2 ± 11.9	0.53
Postprandial blood glucose (mg/dL)	132.5 ± 21.7	135.4 ± 22.3	0.48
Blood urea (mg/dL)	28.4 ± 6.5	27.9 ± 6.1	0.64
Serum creatinine (mg/dL)	1.02 ± 0.21	1.05 ± 0.24	0.49
Serum sodium (mEq/L)	139.6 ± 3.8	138.9 ± 4.1	0.34
Serum potassium (mEq/L)	4.3 ± 0.5	4.2 ± 0.6	0.41
Serum chloride (mEq/L)	102.4 ± 4.6	101.9 ± 4.2	0.52
Normal urine findings, n (%)	64 (91.4%)	66 (94.3%)	0.51
Mild pyuria (≤5 WBC/HPF), n (%)	4 (5.7%)	3 (4.3%)	0.70
Trace proteinuria, n (%)	2 (2.9%)	1 (1.4%)	0.56
Haematuria, n (%)	0 (0%)	0 (0%)	—
Sterile urine culture, n (%)	67 (95.7%)	68 (97.1%)	0.65

Positive urine culture, n (%)	3 (4.3%)	2 (2.9%)	0.65

Baseline haematological, biochemical and urinary investigations showed comparable findings between the two study groups. Mean haemoglobin levels were 13.6 ± 1.4 g/dL in Group A and 13.4 ± 1.3 g/dL in Group B, without a statistically significant difference. Blood glucose concentrations, renal function parameters and serum electrolyte levels were also similar between groups ($p > 0.05$). Routine urine examination revealed normal findings in 91.4% of Group A and 94.3% of Group B, while mild pyuria and trace proteinuria were observed in a small proportion of patients. Urine cultures were sterile in 95.7% and 97.1% of patients, respectively. Overall, no statistically significant between-group differences were reported for the investigated baseline laboratory parameters, indicating comparable laboratory profiles before treatment.

Table 7: Comparison of Treatment-Related Adverse Effects between Study Groups

Adverse effect	Group A (n = 70), n (%)	Group B (n = 70), n (%)	p-value
Dizziness	6 (8.6%)	5 (7.1%)	0.75
Headache	4 (5.7%)	3 (4.3%)	0.70
Nasal congestion	3 (4.3%)	2 (2.9%)	0.65
Abnormal ejaculation	5 (7.1%)	4 (5.7%)	0.72
Daytime drowsiness	7 (10.0%)	2 (2.9%)	0.08
Gastrointestinal discomfort	2 (2.9%)	1 (1.4%)	0.56
No adverse effects	43 (61.4%)	53 (75.7%)	0.07

Treatment-related adverse effects were generally mild and occurred in both groups during the one-month follow-up period. Dizziness was reported in 8.6% of Group A and 7.1% of Group B, while headache occurred in 5.7% and 4.3%, respectively. Abnormal ejaculation was observed in 7.1% of patients receiving combination therapy compared with 5.7% receiving tamsulosin alone. Daytime drowsiness was more frequent in Group A (10.0%) than Group B (2.9%), although this difference did not reach statistical significance ($p = 0.08$). No adverse effects were reported by 61.4% of Group A and 75.7% of Group B ($p = 0.07$). None of the individual adverse-effect comparisons was statistically significant, although the numerical increase in daytime drowsiness warrants attention.

Table 8: Correlation between Urinary Symptom Severity, Nocturia Frequency, Quality of Life and Urological Parameters

Variable 1	Variable 2	Correlation coefficient (r)	p-value
IPSS score	Nocturia episodes	0.62	<0.001*
IPSS score	QoL score	0.71	<0.001*
IPSS score	Qmax	−0.48	<0.001*
IPSS score	PVRU	0.39	0.002*
Nocturia episodes	QoL score	0.65	<0.001*
Qmax	PVRU	−0.44	<0.001*
Prostate volume	PVRU	0.31	0.010*

Correlation analysis demonstrated significant associations between urinary symptom severity, nocturia frequency, quality of life and objective urological parameters. A strong positive correlation was observed between IPSS and nocturia episodes ($r = 0.62$, $p < 0.001$), indicating that greater nocturia frequency was associated with higher urinary symptom scores. IPSS also demonstrated a strong positive correlation with QoL score ($r = 0.71$, $p < 0.001$), suggesting greater impairment in quality of life among patients with more severe symptoms. A moderate negative correlation was observed between IPSS and Qmax ($r = −0.48$, $p < 0.001$), indicating an association between greater symptom severity and reduced urinary flow. Nocturia frequency was positively correlated with QoL score ($r = 0.65$, $p < 0.001$), highlighting the relationship between nocturnal voiding and symptom-related bother. Additionally, Qmax was negatively correlated with PVRU ($r = −0.44$), whereas prostate volume was positively correlated with PVRU ($r = 0.31$). These findings demonstrate interrelationships among subjective urinary symptoms, functional urinary parameters and quality of life.

Table 9: Multivariable Regression Analysis of Factors Associated with Urinary Symptom Severity and Treatment Response

Panel A. Multiple Linear Regression Analysis for Predictors of IPSS Score

Predictor variable	Unstandardised coefficient (B)	Standard error	Standardised β	p-value
Age (years)	0.08	0.04	0.16	0.040*
BMI (kg/m²)	0.12	0.07	0.10	0.090
Nocturia episodes/night	1.85	0.28	0.54	<0.001*
Qmax (mL/s)	−0.74	0.19	−0.31	<0.001*
Prostate volume (mL)	0.06	0.03	0.18	0.030*

PVRU (mL)	0.03	0.01	0.22	0.010*

Panel B. Logistic Regression Analysis for Predictors of Treatment Response

Predictor variable	Odds ratio (OR)	95% confidence interval	p-value
Treatment group (combination vs tamsulosin alone)	2.48	1.22–5.03	0.010*
Baseline IPSS score	1.07	1.01–1.14	0.030*
Nocturia episodes/night	1.63	1.21–2.19	0.001*
Qmax (mL/s)	0.86	0.74–0.98	0.020*
Prostate volume (mL)	1.02	0.99–1.05	0.110
PVRU (mL)	1.01	1.00–1.02	0.070

Multivariable linear regression analysis identified nocturia frequency, maximum urinary flow rate, prostate volume, post-void residual urine and age as statistically significant predictors of IPSS score. Nocturia episodes showed the strongest reported standardised association with symptom severity ($\beta = 0.54$, $p < 0.001$), whereas Qmax demonstrated a significant inverse association ($\beta = -0.31$, $p < 0.001$). Logistic regression analysis indicated that patients receiving melatonin combined with tamsulosin had higher odds of treatment response compared with those receiving tamsulosin alone (OR = 2.48, 95% CI: 1.22–5.03; $p = 0.01$). Baseline IPSS, nocturia frequency and Qmax were also significantly associated with treatment response. In contrast, prostate volume ($p = 0.11$) and PVRU ($p = 0.07$) were not statistically significant predictors in the logistic model. These findings suggest that baseline symptom characteristics and treatment allocation may be associated with the likelihood of clinical improvement.

DISCUSSION

The present prospective randomised controlled study evaluated the efficacy and safety of melatonin combined with tamsulosin compared with tamsulosin alone in improving nocturia among 140 patients with benign prostatic hyperplasia (BPH). Both treatment groups demonstrated improvements in urinary symptoms after one month; however, the combination therapy group showed greater reductions in nocturnal voiding frequency, International Prostate Symptom Score (IPSS), quality of life (QoL) score and post-void residual urine (PVRU), together with greater improvement in maximum urinary flow rate (Qmax). These findings suggest a potential additional therapeutic benefit of melatonin in BPH-associated nocturia, although the short follow-up period limits conclusions regarding long-term efficacy.

The baseline characteristics were comparable between the groups, with mean ages of 64.3 ± 7.5 and 65.1 ± 6.9 years in the combination and monotherapy groups, respectively. Prostate volume, BMI and serum prostate-specific antigen levels were also similar. The predominance of older patients reflects the age-related nature of BPH and its associated urinary symptoms. Kuhlmann et al. (2021), analysing data from the REDUCE clinical trial, demonstrated that dutasteride produced modest reductions in nocturia over two and four years but did not significantly improve sleep quality. Their findings suggest that treatment directed primarily at prostatic pathology may not adequately address the sleep-related mechanisms contributing to nocturia.[11]

The principal finding of the present study was a greater reduction in nocturnal voiding episodes following combination therapy. Mean nocturia frequency decreased from 3.8 ± 0.9 to 1.9 ± 0.8 episodes per night in the melatonin–tamsulosin group, compared with 3.7 ± 1.0 to 2.6 ± 0.9 episodes in the tamsulosin-alone group ($p < 0.001$). These values represent approximate reductions of 50.0% and 29.7%, respectively. The findings are consistent with Fotovat et al. (2022), who reported improvements in nocturia and urinary frequency following the addition of melatonin to tamsulosin in patients with BPH.[6] Similarly, Leerasiri et al. (2023) investigated melatonin for nocturia and provided further evidence supporting its potential therapeutic usefulness, although their study involved older women rather than men with BPH.[7]

The present study also demonstrated significantly greater improvement in overall urinary symptom severity with combination therapy. Mean IPSS decreased from 27.9 ± 6.7 to 17.6 ± 5.4 in Group A, compared with 28.4 ± 6.5 to 20.9 ± 5.8 in Group B. The mean reduction was 10.3 ± 3.6 versus 7.5 ± 3.9 points, respectively ($p < 0.001$). This finding suggests that the addition of melatonin may provide symptomatic benefits beyond those obtained with alpha-adrenergic blockade alone. Nevertheless, because nocturia constitutes one of the seven IPSS items, improvements in nocturia contribute directly to reductions in the total symptom score. Gupta et al. (2023), in an Indian retrospective study involving 335 patients with BPH, evaluated the effectiveness of alpha-blocker monotherapy using IPSS, Qmax and residual urine volume. Their findings support the clinical utility of alpha-blockers in improving urinary symptoms and provide an important Indian comparison for the present trial.[12]

The significant improvement in quality of life further supports the clinical relevance of combination therapy. Mean QoL scores decreased from 4.6 ± 0.9 to 2.4 ± 0.8 in Group A and from 4.5 ± 1.0 to 3.1 ± 0.9 in Group B ($p < 0.001$). Since nocturia contributes to repeated sleep interruptions and subsequent daytime impairment, reducing nocturnal voiding may improve perceived well-being. Lenfant et al. (2023), in a meta-analysis of 12 randomised trials evaluating antimuscarinics combined with alpha-blockers, reported only modest improvements in urinary frequency, accompanied by increased risks of urinary

retention and other adverse effects.[13] These findings highlight the importance of investigating adjunctive therapies with different mechanisms of action.

The present study also demonstrated improvements in functional urinary parameters. Qmax increased from 9.2 ± 2.1 to 13.4 ± 2.6 mL/s in Group A, compared with 9.4 ± 2.3 to 11.8 ± 2.4 mL/s in Group B. Similarly, PVRU decreased from 82.6 ± 24.8 to 46.9 ± 18.7 mL and from 85.1 ± 26.3 to 61.3 ± 20.5 mL, respectively ($p < 0.001$). However, these findings should not be interpreted as definitive evidence that melatonin directly improves bladder outlet obstruction. Su et al. (2023), in a network meta-analysis of 15 randomised trials, demonstrated that several adjunctive medications improved persistent storage symptoms among patients receiving alpha-blockers, with desmopressin showing favourable effects on nocturia.[14]

This supports an individualised approach to persistent nocturnal urinary symptoms.

Correlation analysis in the present study demonstrated significant positive associations between IPSS and nocturia frequency ($r = 0.62$), IPSS and QoL score ($r = 0.71$), and nocturia frequency and QoL score ($r = 0.65$). Multivariable analysis identified nocturia frequency, Qmax, prostate volume and PVRU as significant correlates of symptom severity. Furthermore, combination therapy was associated with higher odds of treatment response (OR = 2.48; 95% CI: 1.22–5.03; $p = 0.01$). These findings suggest that nocturia contributes substantially to overall symptom burden, although the inclusion of nocturia within the IPSS requires cautious interpretation of their statistical association. Regarding safety, adverse effects were generally mild and statistically comparable between groups. Daytime drowsiness occurred more frequently with combination therapy (10.0% versus 2.9%; $p = 0.08$), suggesting the need to monitor sedative effects. Burke et al. (2024) similarly identified potential benefits of melatonin-based interventions but emphasised the limited and heterogeneous available evidence.[8]

Okumura et al. (2025) additionally demonstrated that adjustment of bedtime improved nocturia and uninterrupted sleep duration in older adults, supporting the relevance of sleep–wake regulation in nocturia management.[15] The principal limitations of the present study include its single-centre design, relatively modest sample size and short follow-up period. Moreover, objective sleep-quality measurements, circadian hormone profiles and longer-term safety outcomes were not evaluated. Future multicentre randomised trials incorporating sleep assessments, nocturnal urine production measurements and extended follow-up are necessary to establish the clinical utility of melatonin as adjunctive treatment.

CONCLUSION

The present study demonstrated that melatonin combined with tamsulosin was associated with significantly greater improvement in nocturia frequency, overall urinary symptoms, quality of life, maximum urinary flow rate and post-void residual urine compared with tamsulosin alone among patients with benign prostatic hyperplasia. The combination therapy was generally well tolerated, although daytime drowsiness occurred more frequently in the melatonin group. These findings suggest that melatonin may represent a useful adjunctive treatment for patients experiencing persistent nocturia despite conventional alpha-blocker therapy. However, further large-scale, multicentre studies with longer follow-up are required to confirm its sustained effectiveness, safety and clinical applicability.

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