The effect of Melatonin on Improving the benign Prostatic Hyperplasia Urinary Symptoms, a Randomized Clinical Trial

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Purpose: to investigate the effect of melatonin along with tamsulosin in improving BPH urinary symptoms.

Materials and Methods: A total of 108 men with BPH symptoms, age of ≥ 50 years, and International Prostate Symptom Score (IPSS) ≥ 8 entered into the parallel group randomized, double-blind clinical trial with balanced randomization. The treatment group received of 3mg melatonin plus 0.4mg tamsulosin and the control group received placebo plus 0.4mg tamsulosin. Patients and physicians were concealed by sealed and opaque envelopes. Symptoms were assessed at baseline and 1 month after treatment. Finally all scores at the initial and end of the study were compared and analyzed using SPSS software.

Results: This study showed that adding melatonin to the classic treatment of BPH patients with tamsulosin could significantly reduce the likelihood of nocturia by 2.39 times (95% CI: 1.07-5.32, OR = 2.39, p = 0.033) and could also reduce the frequency of urination by 2.59 times (95% CI: 1.15-5.84, OR = 2.59, p = 0.021). There was no statistically significant difference between the two groups in IPSS, intermittency, incomplete emptying, straining, urgency, and weak stream.

Conclusion: Melatonin plus tamsulosin treatment is associated with a significant improvement of nocturia and frequency in patients with benign proststic hyperplasia. However, it is necessary to do more studies.

Keywords: Benign prostatic hyperplasia; melatonin; tamsulosin; nocturia; frequency

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common issue in men older than 40, and its incidence is increased by aging which leads to obstructive and irritating symptoms.[1] In recent years, different medical treatments, including α-blocker compounds such as tamsulosin[2], 5α-reductase inhibitors such as finasteride[3], were employed as a classic treatment. If the standard treatments do not relieve the symptoms, surgery is advised to patients. It has been shown that tamsulosin monotherapy cannot be effective enough and it is suggested to treat the patients with tamsulosin in accompanying with other treatments[4]. There are studies that show improvements in urinary symptoms as well as quality of life of patients with BPH after receiving tamsulosin in combination with different agents including solifenacin and mirabegron.[5,6] Also, combination of tamsulosin plus the complementary and alternative medicine such as vitamins (C and D), herbal products (Cucurbita maxima, Capsicum annum, Polygonum capsicatum) and amino acid L Glutamine provides statistically significant benefits in terms of lower urinary tract storage related to BPH compared to tamsulosin 0.4 mg/day alone[7].

Melatonin is a hormone secreted by the pineal gland and its secretion is decreased by aging and plays a role in regulating the sleep-wake cycle.[8] It is used as a low-dose drug in dietary supplements in the improvement of insomnia with minimal side effects. Some studies have shown that melatonin increases bladder capacity and reduces bladder contractions by inhibiting the calcium channels as well as strengthening the cerebral GABAergic system.[9] On the other hand, a study revealed that melatonin effectively reduces the growth of prostate epithelial cells by amplification of p27 gene transcription over MT(1) receptor-mediated stimulation of protein kinase A and protein kinase C.[10]

As melatonin has a probable effect on growth of the prostate epithelial cells and bladder contraction, we hypothesized that adding melatonin to conventional treatment of patients with BPH may reduce their urinary symptoms. Therefore, due to the very low literature about the effect of melatonin on relief of BPH symptoms in human[11], we intend to enroll a randomized double-blind clinical trial to investigate the effect of melatonin along with standard treatment on improving the BPH urinary symptoms as well as patients' quality

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Table 1. Comparison of age, IPSS before treatment, IPSS after treatment and IPSS reduction difference in the treatment and control groups.

Group Variable[a]	Treatment (Tamsulosin+Melatonin) Mean±SD	Control (Tamsulosin+Placebo) Mean±SD	*P*-value
Age(year)	64.48 ± 6.47	63.96 ± 5.56	.843
IPSS at baseline	21.22 ± 5.89	21.44 ± 5.31	.922
IPSS after treatment	15.11 ± 15.53	16.33 ± 4.75	.556
IPSS difference	6.11 ± 2.36	5.00 ± 2.5	.348

Abbreviations: IPSS, International Prostate Symptom Score
[a] quantitative variables are compared by T_independent and U_Mann–Whitney tests

of life due to their urinary problems.

PATIENTS AND METHODS

Study population

Patients who had referred to our center were included in this clinical trial if met the inclusion criteria: physician diagnosis of BPH, older than the age of 50, complain of urinary problems and need to receive a classic treatment to control their urinary symptoms according to clinical signs and findings of sonography, PSA level and IPSS score more than 8.

The potential sources of bias for the study were eliminated by excluding patients with the following characteristics from the study: suspected patients of having prostate cancer on examination or with high PSA, urinary tract infection based on urine culture, nocturnal polyuria based on urine volume chart, urethral stenosis, history of any cancer, chemotherapy, radiotherapy, cardiopulmonary and cerebral diseases, hypertension, liver failure, and taking previous medications that affect urinary symptoms such as diuretics. Also, we were sure that patients recruited for this study did not use immunosuppressive drugs, corticosteroids, sleeping pills, and antidepressants. Included patients with BPH symptoms underwent clinical examination, PSA test, urine culture, and urine volume chart.

This study was registered in the Iranian Registry of Clinical Trials (registration number: IRCT2015011314333N27 available at https://www.irct.ir/trial/13963). This study complies with the Helsinki declaration and has been approved by the ethics committee of Kermanshah University of Medical Sciences with the number of 420/7/3960/P. Patients' enrollment flow diagram has been illustrated in Figure 1.

Study design

This study was a single center, parallel group randomized, double-blind clinical trial with balanced ran-

Table 2. Comparison of characteristics between deceased and surviving patients

Variable[a]	Response to treatment[b]	Treatment (Tamsulosin+Melatonin) Number (%)	Control (Tamsulosin+Placebo) Number (%)	*P*-value
Nocturia	Improved	36 (66.6%)	25 (46.2%)	
	Not changed	15 (27.7%)	18 (33.3%)	.045*
	Worsen	3 (5%)	11 (20.3%)	
Straining	Improved	22 (40.7%)	21 (38.8%)	.928
	Not changed	23 (42.5%)	25 (46.2%)	
	Worsen	4 (7.4%)	8 (14.8%)	
Frequency	Improved	33 (61.1%)	25 (46.2%)	
	Not changed	17 (31.4%)	15 (27.7%)	.045*
	Worsen	4 (7.4%)	14 (25.9%)	
Intermitency	Improved	33 (61.1%)	32 (59.2%)	
	Not changed	16 (29.6%)	13 (24.07%)	.529
	Worsen	5 (9.2%)	9 (16.6%)	
Weak stream	Improved	29 (53.7%)	31 (57.4%)	
	Not changed	21 (38.8%)	16 (29.6%)	.512
	Worsen	4 (7.4%)	7 (12.9%)	
Incomplete emptying	Improved	21 (38.8%)	22 (40.7%)	
	Not changed	25 (46.2%)	19 (35.1%)	.400
	Worsen	8 (14.8%)	13 (24.07%)	
Urine urgency	Improved	35 (64.8%)	30 (55.5%)	
	Not changed	15 (27.7%)	17 (31.4%)	0.554
	Worsen	4 (7.4%)	7 (12.9%)	
Quality of life due to urinary problems	Improved	30 (55.5%)	28 (51.8%)	
	Not changed	24 (44.4%)	26 (48.1%)	.542
	Worsen	0 (0%)	0 (0%)	

[a] quantitative variables were compared by Chi-square and Fisher exact tests
[b] Response to treatment was determined by IPSS and a reduction or increasing of at least one score after 1 month was considered as improvement and worsening respectively.

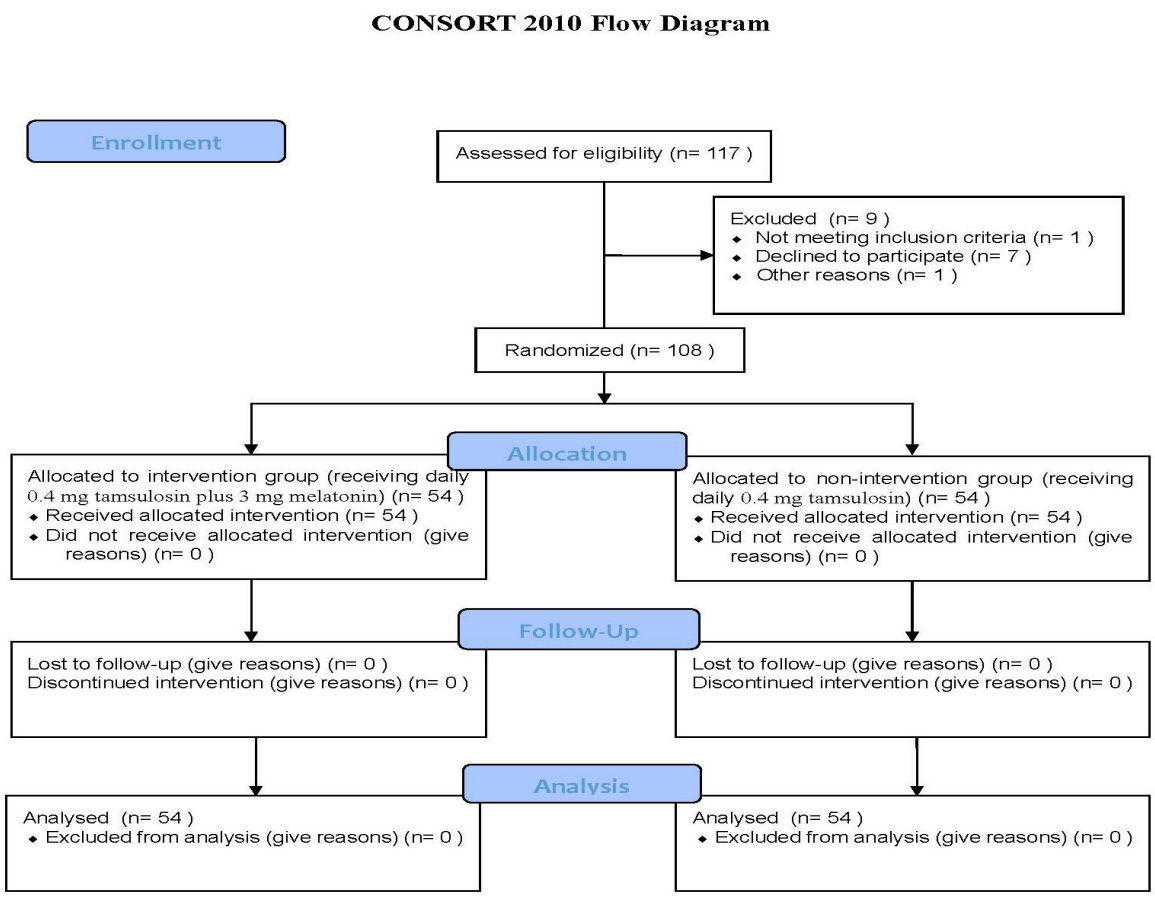

Figure 1. flow diagram of randomized clinical trial study evaluating the effect of melatonin on improving the BPH urinary symptoms

domization (1:1) which was carried out in the urology clinic of Imam Reza Hospital in Kermanshah, Iran. Based on the results obtained by Drake et al (2004), the mean value of IPSS in the melatonin and placebo groups was 27.8 ± 6.8 and 31.7 ± 7.6 respectively[11]. Considering confidence coefficient of 0.05 and study power of 80% (beta coefficient of .20), the sample size estimated in each trialed group was estimated to be 54 (totally 108).

Patients were randomly allocated to one of the two groups of the study. Randomization was carried out using computerized random numbers. Patients and physicians evaluating patients were uninformed about the allocation result. The assigned treatment for each patient was composed in a sealed and opaque envelope. After achieving eligibility criteria and obtaining written informed consent, the concealed envelopes were opened by one of the hospital employees and assigned participants to interventions. The allocated treatment was done as described below.

Intervention

During 1 month of intervention, the treatment group received classic treatment including 0.4 mg tamsulosin plus 3 mg melatonin every night. On the other hand, the Placebo group received classic tamsulosin treatment (0.4 mg) in addition to a placebo every night.

Questionnaire

Persian version of IPSS questionnaire was completed for both intervention and control groups. The reliability and validity of the Persian version of the IPSS questionnaire were confirmed previously.[12] IPSS questionnaire is utilized internationally to evaluate the symptoms of BPH and measures the urinary symptoms. The score for each part varies from 0 to 5, and the patients with IPSS $\geq$ 8 need to start treatment for their urinary symptoms [13,14]. The questionnaire was completed at the entry time and 1 month later after receiving 1 month of treatment. Comparing the initial and final questionnaires, a reduction of at least one score was considered as a sign of improvement. All participants answered a question about the quality of their urinary life at the beginning and at the end of the study. After completing the course of treatment, patients were asked about all the common side effects of tamsulosin[15] and melatonin[16].

Statistical analysis

The gathered data were analyzed by SPSS software version 19. First, the normality of variables was assessed by the Kolmogorov-Smirnov test. Thereafter, to compare quantitative variables in two groups of treatment and placebo, T_independent or U_Mann–Whitney tests were used and Chi-square or Fisher exact tests were used for qualitative variables. *P* values equal to or less than 0.05 were considered significant. The multivariable logistic regression modeling was used to assess the effects of melatonin on clinical symptoms with the presence of baseline variables of age and initial IPSS score. To design the multivariable logistic regression

model, first, each of the variables that had a significant relationship with the dependent variable in the univariate analysis (with p value of less than .1) entered the final model.

RESULTS

Comparison of the participants' data showed that there was no significant difference between age, IPSS score before and after treatment, and IPSS difference of patients in the two groups of intervention and classic treatment (**Table 1**). There was a significant difference between symptoms of nocturia and frequency of patients in the two groups. But symptoms of straining, intermittency, weak stream, incomplete emptying, urine urgency and Quality of life due to urinary problems of patients were not significantly different among patients who had received melatonin in addition to standard treatment (**Table 2**). Dry ejaculation was the only reported side effect of tamsulosin in our study, seven (12.9%) of patients in the treatment group had reported dry ejaculation whereas 8 (14.8%) of patients in the control group reported it (P = .782). Other known side effects of tamsulosin and melatonin were not found in any of the patients in this study. According to the multivariable logistic regression modeling with the presence of the parameters of patients' age and baseline IPSS, administration of melatonin could significantly reduce the likelihood of nocturia by 2.39 times (95% CI: 1.07-5.32, OR = 2.39, P = .033). Based on another multivariable logistic regression with the same baseline parameters, the use of melatonin could effectively reduce the risk for frequency of urination by 2.59 times (95% CI: 1.15-5.84, OR = 2.59, P = .021).

DISCUSSION

BPH is a common problem with increasing age in men that is accompanied by irritating and obstructive symptoms that sometimes lead to surgery due to lack of recovery. Tamsulosin is an alpha-receptor blocker that is considered a standard treatment for patients. But, the result of a recent study showed that tamsulosin alone maybe not enough for a large prostate (> 40 mg) to maintain adequate symptom relief, and it is better to start with other medical options such as combined therapy.[17]

A study by Song Y et al in 2020 showed that tamsulosin combined with solifenacin therapy was more effective in reducing the Total International Prostate Symptom Score (TIPSS), Storage International Prostate Symptom Score (SIPSS), Quality of life (QOL), and Overactive bladder symptom score (OABSS) in comparison with tamsulosin monotherapy treatment[5]. Moreover, Kang TW et al in 2020 reported that a combination of tamsulosin and mirabegron might improve the quality of life of patients presenting with persistent storage symptoms after tamsulosin monotherapy. Improved quality of life due to mirabegron compared with solifenacin could be associated with fewer adverse effects such as dry mouth and constipation.[6]

In this study, we decided to investigate the combination of tamsulosin and melatonin on the improvement of urinary problems of BPH patients. Melatonin is a hormone secreted by the pineal gland at night that regulates the sleep-wake cycle. In recent years, melatonin has been used as a short-term dietary supplement in the treatment of sleep disorders[18], which has been approved by the European Union due to its very low side effects [19]. Use of melatonin before phenylephrine reduces the contractile response of the bladder and reduces the peak contractile effect of bethanechol, KCL, and acetylcholine, and also potentiates the inhibitory effect of succinylcholine on bladder contractions, via inhibiting calcium channels[9]. Intracerebroventricular injection of melatonin increases bladder capacity and reduces its contractions through strengthening the GABAergic system[20]. Furthermore, an animal model study revealed that melatonin is a potent antioxidant which by increasing neuronal nitric oxide synthases (nNOS) and decreasing inducible nitric oxide synthase (iNOS) leads to amelioration of bladder hyperactivity [21]. Interestingly, melatonin is effective in improving chronic bladder overactivity but has no significant effect in patients with acute bladder overactivity[22]. It has been shown that melatonin is effective in inhibiting the growth and progression of prostate cancer by inducing apoptosis and preventing angiogenesis[23]. Also, it prevents prostate cancer metastasis by down-regulating matrix metallopeptidase 13 (MMP-13)[24] and delays the development of castration resistance in advanced prostate cancer by blocking androgen receptors[25].

In this study, nocturia was significantly improved in the patients who were treated with melatonin plus tamsulosin compared to patients who received only tamsulosin. It must be taken into account that in addition to the possible role of melatonin on the bladder capacity, older adults are prone to nocturnal sleep disturbance, and melatonin can improve their circadian rhythm and a good night's sleep may result in diminishing the psychological need to go to the bathroom. Pharmacological studies of melatonin in the treatment of BPH are very limited. In the only study similar to our study that carried out by Drake et al., a sample of 20 BPH patients entered a randomized, double blind, placebo controlled crossover clinical trial to detect the effect of melatonin pharmacotherapy in the treatment of BPH-related urinary symptoms. The primary endpoint was the mean change in nocturia episodes per night and secondary endpoints were mean changes in daytime urinary frequency, relative nocturnal urine volume and total IPSS. That authors have declared that parallel group design would be appropriate for their study but they could not do it because it demands a larger sample size[11].

Drake et al. showed a considerable improvement in nocturia episodes per night which is parallel to our findings. However, they could not show any significant difference between 2 groups of patients who received melatonin and who did not receive in the IPSS score, nocturnal urine volume, maximum urinary flow, and post-void residue[11]. Contradictory with Drake et al. study, in our study frequency was significantly improved in patients who received melatonin. For explanation of this inconsistency, it should be noted that in the drake et al. study patients were deprived from a standard treatment but all of the patients in our study received the standard treatment and also received a higher melatonin dose (3 mg vers. 2 mg) that can be effective in improvement of bladder contractions.

There was no statistically significant difference between the two groups in IPSS score, intermittency, incomplete emptying, straining, urgency, and weak stream in our study.

We showed that similar to other combinations of tam-

sulosin that potentiate its effect, the Quality of life due to urinary problems of our patients in the melatonin plus tamsulosin group was descriptively higher than tamsulosin monotherapy. However this difference was not statistically significant, but it could be related to the improvement of nighttime sleep and the improvement of patients' frequency and nocturia symptoms. One of the limitations of this study was the lack of eurodynamic assessment due to financial constraints that could be useful in evaluating patients. Dry ejaculation was descriptively lower in the melatonin plus tamsulosin, which may be due to the effect of melatonin on the mood of patients, but there was no significant difference between the two groups in this area. Other known side effects of tamsulosin and melatonin were not found in any of the patients in this study; it can because of the exclusion of patients with underlying problems at the beginning of the disease.

CONCLUSIONS

According to the findings of our study, the combination of melatonin and tamsulosin was drastically effective in treating the symptoms of frequency and nocturia in patients with BPH. The results achieved by this study can be used to pave the avenue of improving the symptoms of patients with BPH. We suggest conducting further pharmaceutical studies in this area to find a precise dose of melatonin as well as to assess its safety and efficacy in patients with underlying diseases.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

APPENDIX

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