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Nighttime administration of high-dose, sustained-release melatonin does not decrease nocturnal blood pressure in African-American patients: Results from a preliminary randomized, crossover trial

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ABSTRACT

Objectives: This preliminary study tested whether a high-dose, sustained-release form of melatonin reduced 24-hour blood pressure in African-Americans.
Design: Randomized, placebo-controlled, crossover pilot study of 40 self-defined African-American patients with essential hypertension.
Settings/location: Urban, academic medical center and associated outpatient clinics.
Interventions: Patients ingested either melatonin (high dose [24 mg], sustained-release formulation] or placebo in randomized order over a 4-week period.
Outcome measures: Mean nighttime and daytime systolic and diastolic blood pressures, as measured with 24-hour ambulatory blood pressure monitors. The primary outcome was mean nighttime systolic blood pressure.
Results: There were no statistically differences between melatonin and placebo conditions in mean nighttime or daytime systolic or diastolic blood pressures.
Conclusions: In contrast with studies in other populations, this preliminary study showed that nighttime dosing of continuous-release melatonin had no significant effect on nocturnal blood pressure in African Americans with essential hypertension when compared to placebo.

1. Introduction

Nocturnal hypertension is a risk factor for cardiovascular events including myocardial infarction and cerebral vascular accidents.[1] The causes of elevated nighttime blood pressure (NBP) are not completely understood. Preliminary investigations suggest that impairments in circadian rhythms,[2] poor quality of sleep,[3] sleep apnea,[4] elevated sympathetic nervous system (SNS) activity,[5] impaired vasorelaxation,[6] and increased renal absorption of sodium[7] contribute to elevated NBP.

Melatonin is an indole hormone secreted by the pineal gland and thought to reflect an output of the circadian timing system, mediated by the suprachiasmatic nucleus. Previous studies in untreated and treated hypertensive patients from the Netherlands, Italy and Israel showed a positive effect of controlled-release (CR) melatonin, at daily doses of 2–3 mg, on reducing NBP. Scheer et al demonstrated a blood pressure lowering effect in a cohort of 16 men with untreated hypertension,[8]

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Cagnacci et al showed similar results in 18 women in which half were treated hypertensives,[9] and Grossman et al confirmed the same finding in 38 treated patients.[10] Proposed explanations for mechanisms underlying melatonin's beneficial effect include the alteration of one or more of the above-mentioned determinants of NBP.[11]

Nocturnal hypertension is more common in African Americans (AA)[12] who are also at higher risk for end-organ damage due to hypertension.[13] We hypothesized that, as shown in populations of Northern European or Middle Eastern origin,[10] nighttime melatonin would lower nighttime BP in AA. We designed a study to investigate the safety, tolerability and the effects of high dose melatonin (24 mg administered at night) on NBP. Additionally, given the presumed vasorelaxation properties of melatonin,[14] new biomarkers of vasodilatation (selectins)[15] were chosen to assess biochemically the proposed vasodilatory effect of melatonin on the smooth muscle vasculature.

2. Methods

2.1. Overall Design

This was a pilot, double-blind, placebo-controlled, crossover, randomized clinical trial (see Fig. 1). The study protocol was approved by the Emory University Institutional Review Board (IRB), and all patients provided written Informed Consent. Patients were recruited from the parent NIH funded study (Pharmacogenomics Evaluation of Antihypertensive Responses [PEAR], Clinicaltrials.gov NCT01203852)[16] and also from hypertension clinics in Atlanta. This preliminary trial consisted of 4 initial weeks of treatment (placebo or melatonin) immediately followed by 4 additional weeks of the other treatment in a randomized, crossover design. Compensation of $750 per patient was offered.

Table 1
Study Exclusion Criteria.

Secondary causes of hypertension
Usage of more than two anti-hypertensive medications
Severe uncontrolled hypertension (SBP > 170 or DBP > 110)
History of Cardiovascular Disease (myocardial infarct, congestive heart failure, prior cardiac procedures)
Diabetes mellitus
Renal disease (serum creatinine > 1.5 mg/dl)
Liver disease (alanine transaminase or aspartate transaminase > 2.5 x upper limit of normal)
Pregnancy
Breastfeeding
Usage of non-steroidal anti-inflammatory medications
Usage of corticosteroids
Usage of COX-II inhibitors
Usage of warfarin
History of sleep apnea requiring treatment with continuous positive airway pressure
Active malignancies
Excess caffeinated beverage consumption (equivalent of > 3 cups of coffee per day)
Current use of melatonin

2.2. Participants

The study targeted to enroll 40 self-described AA men and women ages 18–64 years with a history of essential HTN. Presence of nighttime HTN was defined by an average nighttime SBP ≥ 115 mmHg (based on 24 hour [24 h] ambulatory blood pressure monitoring [ABPM]) at the end of monotherapy in the parent PEAR study or on screening visit for patients not in PEAR. This eligibility criterion was lowered from the original cutoff for SBP of 125 mmHg to 115 mmHg based on additional evidence that this threshold was valid for risk stratification of cardiovascular disease and in order to accelerate recruitment.[17] Non-dipping

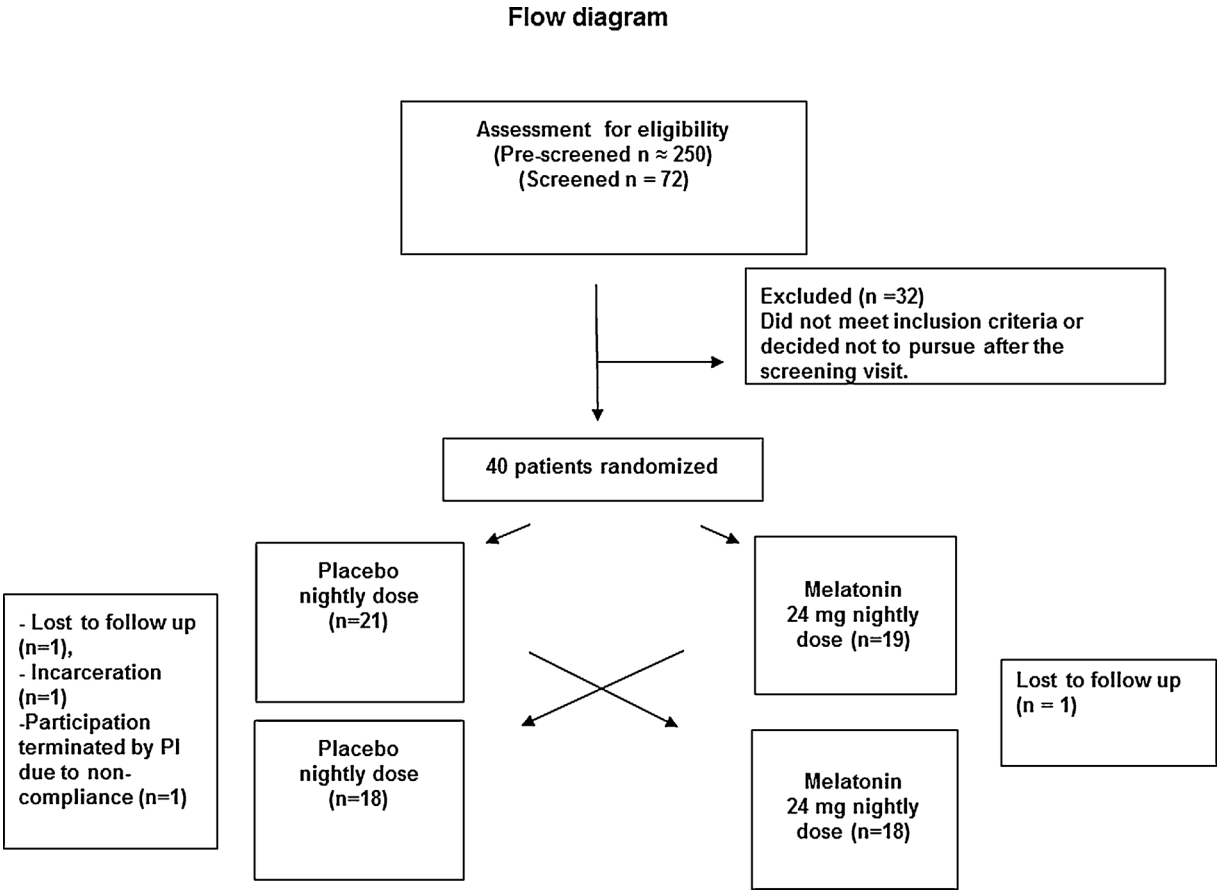

Fig. 1. Flow Diagram.

of nocturnal systolic BP (defined as nighttime: daytime BP ratio as > .90) was not an inclusion criterion for entry. Exclusion criteria are shown in Table 1. Screening included history and physical examination, routine laboratory tests (chemistry, CBC, renal function, liver function tests), 24 h ABPM and overnight in-lab polysomnography (PSG), the latter used at screening for elimination of cases with severe sleep apnea.

2.3. Randomization

Randomization occurred via permuted variable sized block randomization. Each pill bottle was blinded to both study personnel and patients and assigned a unique 3-digit number with code held by the study biostatistician in coordination with the Emory University research pharmacy.

2.4. Outcomes

The primary outcome was mean nighttime SBP at the end of 4 weeks of treatment compared to baseline. Twenty-four hour (24 h) ABPM was conducted using the guidelines of Pickering et al on behalf of the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research.[18] We used the previously validated Spacelabs (Snoqualmie, WA) 90207 monitors, programmed to record blood pressure every 30 min during throughout the 24 h. Monitors were returned to clinic at the end of the 24-hour measurement period. ABPM usually occurred within 2 days of the overnight PSG and overnight urine collection. Appropriate cuff sizes (small, medium, large and extra-large) were chosen for each participant. The Spacelabs monitors also recorded heart rate (HR) at a similar sampling rate. Coordinators were trained to place and remove the monitors in the clinic after checking simultaneous blood pressure readings by manual auscultatory method. If the average of the 6 ambulatory and 6 manual readings taken at the beginning or at the end of the ambulatory recording differed by more than 8 mm Hg, the ambulatory recording was considered "technically unsatisfactory" and repeated with a different monitor. Subjects were instructed to engage in normal activities but to refrain from vigorous physical activity and record a diary of events, including the times that they went to bed and arose from bed in the morning. The definition of “nighttime” has been widely variable in the literature based on either fixed-time hours or by individualized bedtimes and wake up times.[1,19,20] We analyzed BP data based on both fixed clock times and individualized sleep times. For the former, we defined nighttime as the period from 00:00 (midnight) through 5:59 AM, whereas daytime was defined as the period from 6:00 A.M. to 11:59 P.M. Alternatively, we also computed BP based on each participant’s time to bed and rise time as indicated by the diary.

In addition to 24 h ABPM, we collected a variety of other secondary outcomes in this pilot study, partially to inform potential sympathetic mediation pathways, if indeed melatonin was to have an effect of lowering BP, and partially to validate ingestion of melatonin. On the night of PSG, overnight urine collection provided measurements of urinary catecholamine (dopamine, adrenaline and noradrenaline) levels (ELISA assays, ALPCO Diagnostics, Salem, NH), and urinary concentration of the major metabolite of melatonin, 6-sulfatoxymelatonin (6-STM) also called 6- hydroxymelatonin sulfate (ELISA colorimetric assay, ALPCO Diagnostics, Salem, NH).[21] Urinary measurements were made from all voids collected during overnight urine collections. At 8:45 PM, all patients were asked to void and empty their bladder completely. Thereafter, all voids were collected in a specimen container until they awakened in the morning. Urinary excretion rates were calculated using the following formula and expressed in ng/min: Urinary Excretion Rate = (Urinary Concentration x Urine volume) / Duration of collection. Baseline 6-STM values < 40 ng/ml were consistent with lack of exogenous melatonin intake. Confirmation of physiologic absorption effects of exogenous melatonin ingestion was defined by 6-STM levels of > 160 ng/ml (corresponding to 4 times the upper limit of normal).

PSG was performed in private, sound-attenuated rooms without windows. Patients were allowed to choose their time to go to bed and wake up within the restrictions of the sleep lab personnel work hours (8:00 P.M.–8:00 A.M.). On sleep lab nights (1 at screening, 1 at baseline, and 1 at the end of treatment), patients went to bed and were awakened at approximately the same time throughout the study. They ingested melatonin 30 min prior going to bed. We examined two secondary outcomes from PSG, total sleep time (TST) in minutes and sleep efficiency (SE), the latter defined as the ratio of TST divided by time in bed (x100), expressed as a percentage. TST and SE were examined to determine whether improved sleep might represent a possible mediating pathway for expected improvements in BP seen with melatonin.

As a check on other potential mediational effects of melatonin on BP, we also examined two serum markers of endothelial function, e-selectin and p-selectin (ELISA assay, R&D Systems, Minneapolis, MN), made during office visits at baseline and at end of treatment.

2.5. Melatonin formulation

Participants received 24 mg of melatonin in a continuous release (CR) formulation (Douglas Laboratories, Pittsburgh, PA: ingredients included Melatonin, Dicaclium Phosphate acid, Ethocel #7, Steric acid, Magnesium stearate, MCC 102 SD, and Silica- Half-life of elimination 45 min, hepatic metabolism and renal excretion) or placebo at bed time. Dose used in this study was determined in conjunction with input from Program Officers at the National Institutes of Health.

2.6. Adverse events

Adverse events were captured via weekly phone calls to the patients, which were monitored by a Data Safety Monitoring Board (DSMB).

2.7. Statistical methods, sample size and power calculation

To derive power estimates for the proposed study, we relied upon three previously published studies of the effects of melatonin on hypertension (all represented samples derived from populations of Euro-American background). Two of these studies employed crossover designs, one for 3 weeks with a 2.5 mg sustained release formulation[8] and one for 3 weeks[9] with a 3 mg sustained release formulation, respectively, whereas the third study employed a parallel groups design in a 4-week trial with a 2.0 mg sustained release formulation.[10] The crossover trials reported mean placebo versus melatonin difference in nighttime systolic BP of

-5.6[8] and - 3.8[9] mm Hg, respectively, whereas the parallel groups study reported a baseline placebo vs melatonin difference of -6.0 mm Hg.[10] Based on pooled standard deviations of 12.05,[8] 3.15,[9] and 9.5,[10] these values yield conservative (i.e., assuming unpatched pairs for the crossover designs) effect size (d) estimates of .46, 1.20, and .63, for these three studies, respectively, suggesting at least moderate and, more likely, large effects. If we assume a mean effect size (.76), then a sample size of N = 35 was considered likely to afford 87% power to detect a difference in systolic blood pressure of 5.1 mm Hg, assuming a 2-tailed alpha of .05. To allow for the possibility of some drop outs, targeted enrollment was set at 40. The study was not powered to detect differences in diastolic blood pressure subsequent to melatonin administration.

Descriptive and statistical analyses used SAS version 9.3 (SAS Institute Inc., Carey, NC). One-way repeated measures mixed model Analysis of Variance (ANOVA) was used test the differences in outcomes across the 3 visits (baseline, placebo, and melatonin). Tukey’s comparisons were used for pairwise testing. Data were analyzed based on intent-to-treat (ITT), using bootstrapping techniques. The mixed model method allowed for the inclusion of missing data. Since catecholamine excretion rates and markers of endothelial function were

Table 2
Baseline Characteristics of Study Participants.

Characteristics	Mean (SD) or frequency (%) n = 36
Age (years)	48.9 ± 9.9
Gender (Female-Male)	25–11
BMI (kg/m^2)	29.2 ± 4.4
Nighttime systolic blood pressure (mmHg)	127.5 (2.3)*
Nighttime diastolic blood pressure mmHg)	77.6 (1.7)*
Daytime systolic blood pressure (mmHg)	138.6 (2.4)*
Daytime diastolic blood pressure (mmHg)	88.9 (1.8)*
Apnea Hypopnea Index	11.4 ± 8.5
Serum Creatinine (mg/dl)	0.93 ± 0.18
Potassium (meq/L)	3.88 ± 0.40
Albumin (mg/dl)	3.8 ± 0.2
Hemoglobin (g/dl)	13.1 ± 1.3
Serum CO_2 (meq/L)	28.2 ± 2.4
Alcohol consumer (%)	17 (50)
Smoker (%)	6 (16.7)
Diuretics (%)	21 (55)
Beta Blockers (%)	18 (47)
RAAS Blockers (%)	6 (16)

Abbreviations: BMI Body Mass Index, RAAS Renin-Angiotensin-Aldosterone System, CO2 Carbon Dioxide.
* Indicates Standard Error instead of Standard Deviation.

not normally distributed, non-parametric Friedman's ANOVAs were performed for analysis of those variables. McNemar's test was used to compare rates of side effects between placebo and melatonin. The influence of randomization order on outcomes was investigated using a two-way repeated measures mixed model ANOVA.

3. Results

Fig. 1 summarizes the enrollment flow and indicates that 40 eligible patients were randomized. Thirty-six subjects completed study procedures, and results from all participants were analyzed for each outcome, consistent with ITT principles. Non-completion was due to-non-compliance with study procedures, which included a subject started taking amphetamine-like diet pills affecting BP and whose participation was therefore terminated by investigators (n = 1), incarceration (n = 1), and loss to follow up (discontinuation of phone numbers and/or change of address) (n = 2).

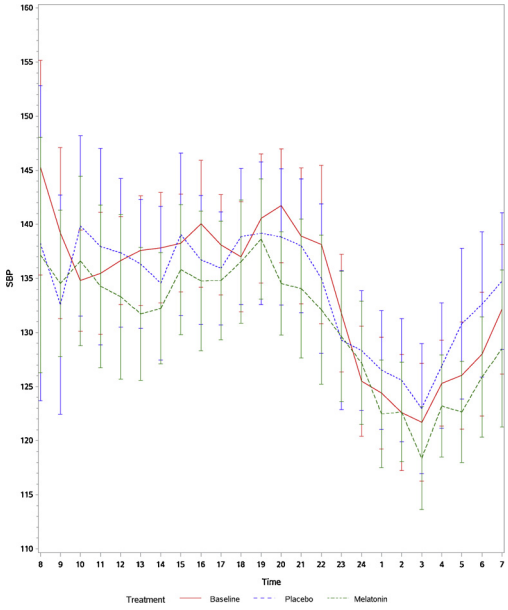

Fig. 2. Mean Hourly Ambulatory Blood Pressures for Systolic Blood Pressure.

The cohort was predominantly middle-aged, female and obese. Diuretics were commonly used. Baseline characteristics are summarized in Table 2.

Using the fixed nighttime definition, there was no difference in nocturnal or diurnal systolic blood pressure, diastolic blood pressure or heart rate between baseline, placebo or melatonin (see Table 3). The individualized definition (average bedtime = 11:30 PM [SD = 84 min]; and wake-up time = 6:45 AM [SD = 96 min]) yielded similar null results. Mean hourly 24 h systolic and diastolic BPs are presented in Figs. 2 and 3.

Examination of order effects indicated that nighttime SBP, nighttime DBP, and diurnal heart rate showed significant ($p < .05$) effects of order of administration, although pairwise contrasts indicated significant differences only for nighttime SBP. Patients receiving placebo first showed significantly lower SBP ($p = .038$) under melatonin administration relative to those receiving melatonin first ($p = .422$).

Table 3
Primary and Secondary Outcomes.

Parameters	Baseline Mean (SE)	Placebo Mean (SE)	Melatonin 24 mg/day Mean (SE)	p-value
Nighttime SBP (mmHg)	127.5 (2.3)	127.9 (2.3)	126.6 (2.3)	0.84
Nighttime DBP (mmHg)	77.6 (1.7)	77.6 (1.7)	77.2 (1.7)	0.95
Nighttime MAP (mmHg)	94.2 (1.8)	94.4 (1.8)	93.9 (1.8)	0.91
Nighttime HR (beats/min)	74.9 (1.9)	74.4 (1.9)	74.1 (1.9)	0.88
Daytime SBP (mmHg)	138.6 (2.4)	137.3 (2.4)	134.2 (2.4)	0.16
Daytime DBP (mmHg)	88.9 (1.8)	86.6 (1.8)	85.3 (1.8)	0.12
Daytime MAP (mmHg)	105.5 (1.9)	103.5 (1.9)	101.3(1.9)	0.12
Daytime HR (beats/min)	84.1 (1.8)	83.3 (1.8)	81.6 (1.8)	0.21
Asleep SBP (mmHg)	124.3 (2.4)	126.9 (2.3)	125.5 (2.3)	0.55
Asleep DBP (mmHg)	75.8 (1.6)	76.3 (1.6)	75.8 (1.6)	0.93
Awake SBP (mmHg)	137.4 (2.4)	138.1 (2.3)	134.6 (2.4)	0.25
Awake DBP (mmHg)	88 (1.8)	86.9 (1.7)	85.7 (1.8)	0.31
Urinary Dopamine excretion (ng/min)	122.7 (21.6)	130.8 (22.0)	115.6 (22.4)	0.06
Urinary Noradrenaline excretion (ng/min)	14.3 (2.7)	17.0 (2.7)	11.5 (2.7)	0.21
Urinary Adrenaline excretion (ng/min)	1.17 (0.16)	1.76 (0.17)	1.23 (0.17)	0.41
Plasma E-Selectin (ng/ml)	42.0 (2.2)	41.0 (2.2)	39.5 (2.2)	0.13
Plasma P-Selectin (ng/ml)	87.9 (9.5)	98.6 (9.5)	92.2 (9.7)	0.58
Total Sleep Time (min)	402.5 (10.6)	413.4 (10.6)	415.8 (10.9)	0.39
Sleep Efficiency (%)	87.0 (1.6)	87.8 (1.6)	89.5 (1.6)	0.35

Abbreviations: SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, HR: Heart Rate.
"Nighttime" refers to the period of 0000 (midnight) to 05:59 AM; "Daytime" refers to the period of 06:00 AM to 11:59 PM; "Asleep" and "Awake" refer to the periods adjusted to the individual's time of getting into bed and arising from bed in the morning on a particular night (see text).
p-values reflect comparison between melatonin and placebo.

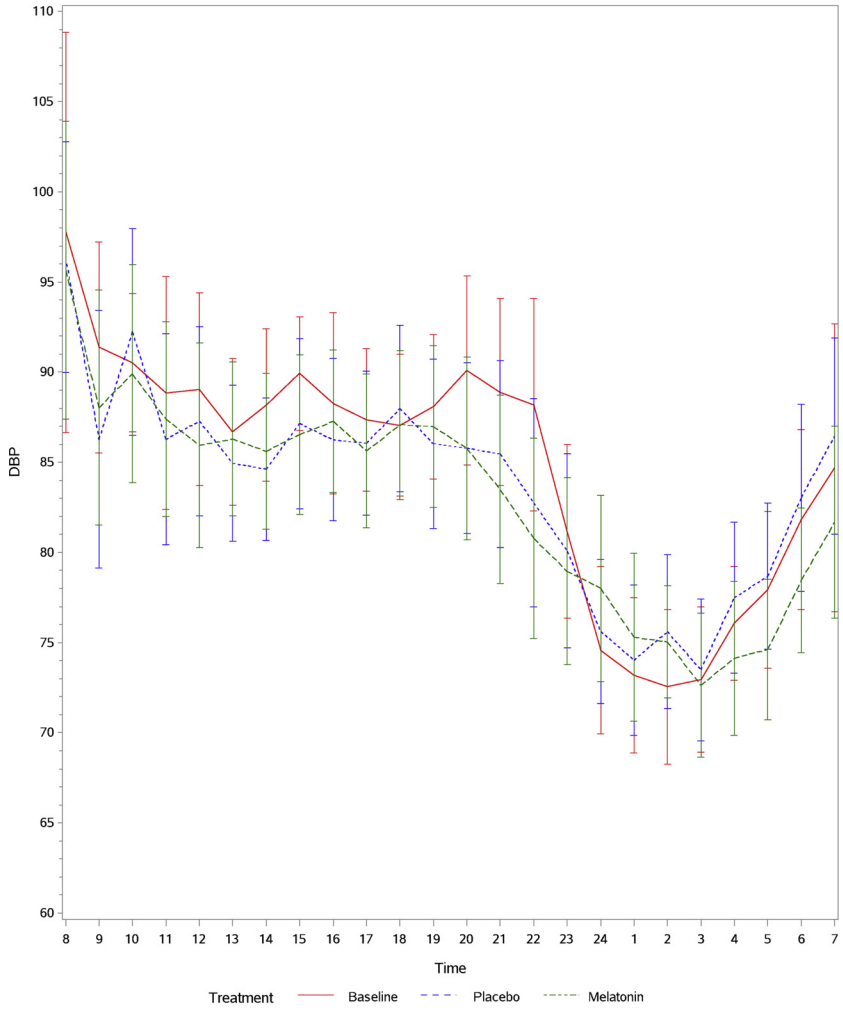

Fig. 3. Mean Hourly Ambulatory Blood Pressures for Diastolic Blood Pressure.

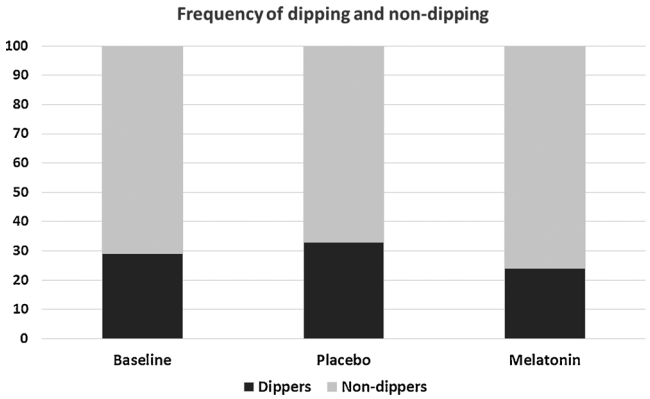

Fig. 4. Nocturnal Dipping Status.

Non-dipping was common at baseline (71% of cases) but the frequency of non-dipping was not significantly affected by melatonin compared to placebo (see Fig. 4). Non-dipping was unrelated to mean nighttime or daytime levels of SBP or DBP.

Urinary dopamine and noradrenaline excretion rates did not differ between placebo and melatonin condition. However, urinary adrenaline excretion rates were higher on placebo compared to both baseline and melatonin. Results are summarized in Fig. 5a–c.

6-STM excretion rates revealed a substantial increase during in-lab melatonin administration confirming adequate absorption and physiologic effects of exogenous melatonin. Mean excretion rates were 540 fold higher on melatonin compared to placebo (see Fig. 6).

Plasma e-selectin and p-selectin levels were not significantly different between baseline, placebo and melatonin administration.

As assessed with PSG, sleep measures (TST and SE) were not significantly different between placebo and melatonin.

There was only one serious adverse event (SAE) during the study, which was judged by the DSMB not to be related to melatonin. There were no statistically significant differences between the placebo and melatonin condition in frequency of adverse events. The most commonly occurring adverse events (presented as the proportion of patients in each condition experiencing the events) were fatigue (41.7% melatonin; 30.6% placebo), daytime drowsiness (36.1% melatonin; 30.6% placebo) and early morning awakening (38.9% melatonin; 25.0% placebo). All adverse events were considered mild to moderate and none required discontinuation of study drug in any participant.

4. Discussion

This report presents a preliminary randomized clinical trial testing whether melatonin administration reduces blood pressure in African-Americans with essential hypertension. In this pilot study, we confirmed the feasibility of conducting a trial in this population, although the number of women (derived largely from the PEAR trial, in which a relatively high proportion of African-American participants were women) in the trial could represent a bias. Our study included repeated measurements of 24-hour ambulatory blood pressures over a 2-month

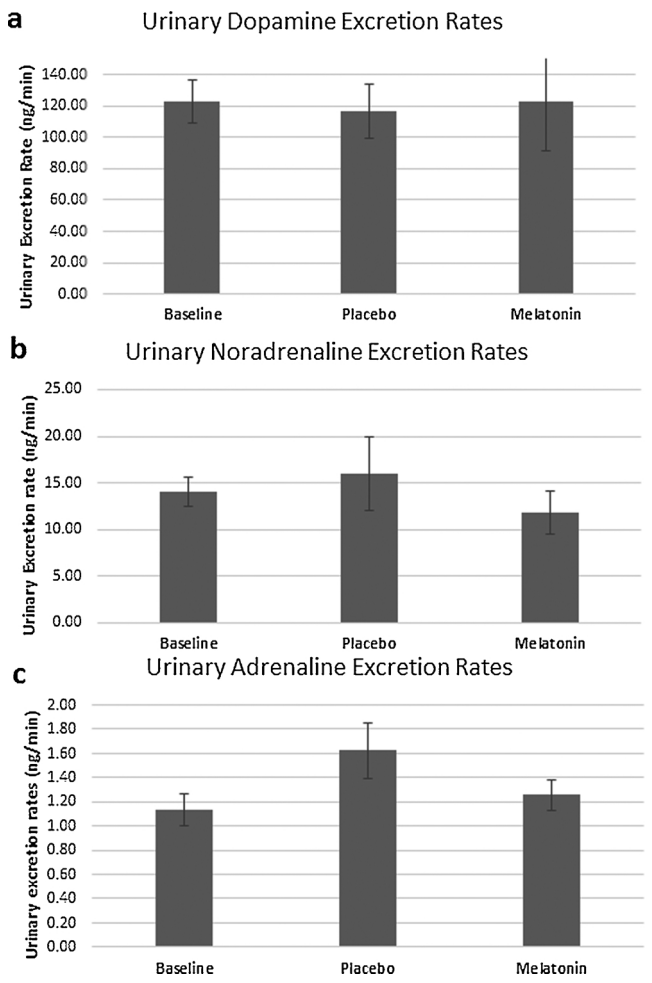

Fig. 5. Urinary Catecholamine Excretion Rates for Dopamine (a), Noradrenaline (b) and Adrenaline (c) for Baseline, Placebo, and Melatonin Conditions.

period of time, as well as examining putative mechanisms of action of melatonin's potential beneficial effects by examining both serum and urinary biomarkers and PSG. Urinary metabolites confirmed very high levels of 6STM indicating adequate absorption. Several other features of the current work should be noted as well. First, we excluded the use of calcium channel blockers, which had been linked to altered blood pressure response in previous studies with melatonin.[22] Secondly, we also used a controlled-release (c.f., a short acting) melatonin formulation, which has been reported to be particularly effective in lowering blood pressure in Caucasians.[23] Despite these enhancements and in contrast to prior data in individuals of European/Middle Eastern origin, we did not find any significant effect of controlled-release melatonin, even at a very high daily dose of 24 mg, on our primary or secondary outcomes.

Our data are not without limitations. First, our sample size was small. Second, we recorded 24-h BP only over a one-day period, whereas many studies of ABPM record for periods of 48 or 72 h, or even up to a full week. Third, our choice of inclusion of patients who were already treated with anti-hypertensive medications could have blunted the magnitude of BP response observed in an untreated population. This may be relevant since 2/3 positive studies to date[8,10] had baseline nocturnal systolic blood pressures that were 9–10 points higher than in our studies (136–137 mmHg on average), although the third[9] had an average nocturnal SBP of 116 mmHg (about 11 points lower than what we report here) and still showed an effect. Additionally, in our study only 71% of patients showed non-dipping, which may have also limited our ability to detect the blood pressure lowering effects of melatonin. Whether the differences between our results and those from the prior studies, all of which were conducted in individuals of European or Middle Eastern origin, reflect such issues with baseline levels of BP or whether the differences might reflect genetic or more broadly defined biological differences across study populations remains moot. In our population, we felt that ethical considerations excluded a high risk population of uncontrolled hypertensive patients in this pilot study.

A fourth limitation of our study involves the inclusion of patients with mild to moderate sleep apnea, which may have blunted the expected effect of melatonin. Sleep apnea is an established cause of increased SNS activity,[24] which can increase nocturnal BP.[25] Our decision to include patients with some levels of sleep apnea was made so as not to eliminate potential AA patients who would otherwise be eligible for the trial. Because of a known higher prevalence of sleep apnea in this minority population,[26] this may have worked against our detecting beneficial effects of melatonin on BP. With a larger sample size, we might have been able to analyze for sleep apnea as a baseline and/or time-dependent covariate.

A fifth point concerns our choice of a relatively high dose (24 mg nightly) formulation of melatonin CR. Previous trials of melatonin in hypertension have used daily dosages of 3 or 5 mg, though dosages as high as 100 mg have been used in trials for other medical purposes.[27]

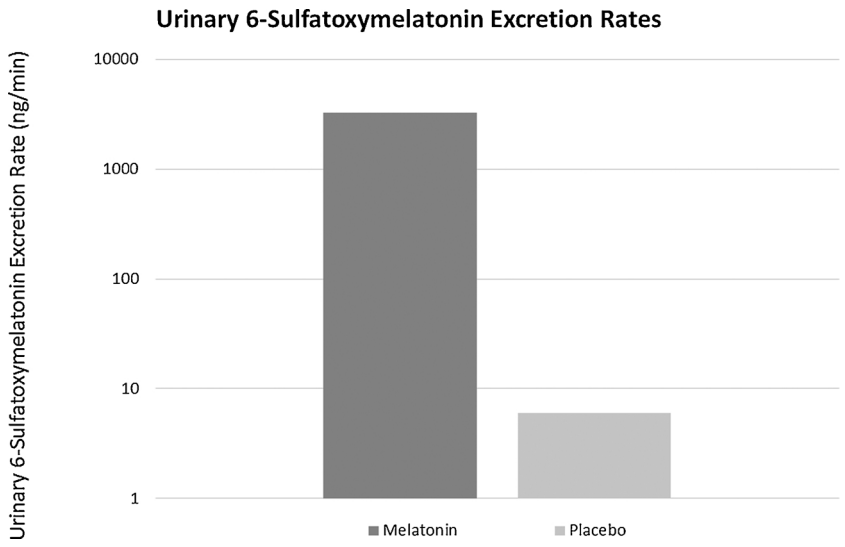

Fig. 6. Urinary 6-Sulfatoxymelatonin Excretion Rates for Baseline, Placebo, and Melatonin Conditions.

This wide range of dosages is partially explained by the low bioavailability of melatonin (15%) and rapid clearance of the molecule, suggesting that higher dosages may attain better receptor saturation.[28,29] However, this high-dose choice may have biased our results in complex and unanticipated ways. For example, studies that have examined the ability of exogenous melatonin administration to phase shift circadian rhythms in humans have noted that lower dosages may produce more potent effects than higher doses, to the extent that supra-physiologic doses may raise plasma melatonin level for 12 or more hours after ingestion, so as to differentially impact the melatonin phase response curve.[30] If the extended half-life of the 24 mg CR dose was impacting our results on this basis, we might have seen a larger BP effect during daytime than nighttime, but this did not occur. Even a low dose of 2.5 mg was reported to sustain plasma elevations as long as 14 h after nocturnal dosing in one study.[31] On the other hand, given the fact that basic science has shown that melatonin may have both vasodilatory and vasoconstrictive effects on smooth muscle,[32] it is entirely possible that our usage of a high dose CR form of melatonin might have affected BP in unforeseen ways, perhaps by differential activation of MT1 versus MT2 receptors, which appear to have different locations within the vessel wall.[33] Fortunately, we detected no increases in BP suggesting vasoconstriction associated with its usage here.

A sixth weakness of our study was that we did not adjust urine catecholamine concentrations to urine creatinine concentration. However, the relatively normal and stable levels of kidney function and muscle mass over the short period of this pilot trial argued against this as a confounder. An additional factor affecting our negative urinary catecholamine results may have been the very low urinary excretion rates of adrenaline and noradrenaline at baseline, limiting the possibility of differences subsequent to melatonin administration. We do not believe that these baseline low levels were reflective of the racial composition of our population, as previous studies showed no significant racial differences in SNS activity between AAs and Caucasians.[34]

Finally, as is often the case in crossover trials, some evidence of order effects occurred, with individuals receiving melatonin after placebo more likely to show a reduction in SBP than in those patients whose exposure to melatonin occurred first. Although statistically significant, the majority of our measures did not show order of administration effects, suggesting that crossover design did not compromise the integrity of the trial.

A relatively recent review of BP-reducing effects of nutraceuticals by Borghi and Cicero[35] cited a meta-analysis[23] encompassing several hundred participants suggesting that slow-release (106 pooled hypertensive participants), but not fast-release (110 pooled hypertensive/cardiovascular disease participants), melatonin dosed at 2–5 mg for 7–90 days resulted in lowering in both SBP and DBP. Those results are encouraging but randomized, placebo-controlled trials remain relatively sparse and/or include analyses that are difficult to place in appropriate clinical context. Clearly, neither the small sample size of our study, nor any of these other individual studies constitute samples of the size typical of Phase III intervention studies for BP reduction used, for example, in pharmacologic FDA-registration trials. If melatonin was found to have uniformly beneficial effects on lowering mean systolic blood pressure in such larger trials, the mechanism of its action is likely complex and is unlikely to involve modulation of the renin-angiotensin-aldosterone system, at least in animal models.[36] Clearly, further work is needed to understand more completely not only the mechanisms but also the viability of this alternative medicine treatment for human hypertension.

5. Conclusions

In contrast to previous studies in individuals of Euro-American or Middle Eastern background, our preliminary study does not support the use of sustained release melatonin as an antihypertensive agent in African-Americans.

Declaration of interests

None of the authors has any potential source of conflict of interest regarding this project. Dr. Bliwise has consulted to Ferring, Jazz, Merck, Eisai and Respicardia

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