Melatonin reduces tachycardia in Postural Tachycardia Syndrome (POTS): A Randomized, Crossover Trial

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Methods—Patients with POTS (n=78) underwent acute drug trials with melatonin 3 mg orally and placebo, on separate mornings, in a randomized crossover design. Blood pressure, HR and
symptoms were assessed while seated and after standing for up to 10 minutes prior to, and hourly for 4 hours following, study drug administration.

**Results**—The reduction in standing HR was significantly greater two hours after melatonin compared to placebo (P=0.017). There was no significant difference in the reduction of systolic blood pressure between melatonin and placebo, either with standing or while seated. The symptom burden was not improved with melatonin compared with placebo.

**Conclusion**—Oral melatonin produced a modest decrease in standing tachycardia in POTS. Further research is needed to determine the effects of regular night-time use of this medication in POTS.

**Keywords**
tachycardia; melatonin; autonomic nervous system; sympathetic nervous system; drugs; orthostatic intolerance

**INTRODUCTION**

Postural tachycardia syndrome (POTS) is a chronic autonomic nervous system disorder that affects approximately 500,000 people in the United States. POTS is characterized by an excessive increase in heart rate (HR) with upright posture accompanied by palpitations, lightheadedness, blurred vision, shortness of breath, chest pain, and mental clouding, as well as other symptoms including fatigue, headaches, exercise intolerance and nausea.[1] This condition predominantly affects women of childbearing age,[1] and can result in significant functional disability and poor health-related quality of life.[2] While the pathophysiology of the condition is unknown and likely heterogeneous,[1] many patients with POTS have increased sympathetic nervous system tone.[3] Melatonin is an endogenous indoleamine secreted by the pineal gland, and is involved in the regulation of the circadian rhythm and acts as a signal for darkness. The cellular effects of melatonin are mediated by two G protein coupled receptors (MT1 and MT2).[4;5] In the suprachiasmatic nucleus (SCN), MT2 receptors appear to mediate phase-shift responses. These receptors induce the initiation of sleep and adjust the circadian rhythm to allow for continued sleep in response to endogenous and exogenous melatonin. Approximately 85% of an oral dose is removed by hepatic first-pass metabolism. In humans, melatonin has been studied both as a chronobiotic and hypnotic.[6;7]

In previous studies, melatonin produced varying effects on HR and blood pressure (BP) in healthy adults,[8–14] and significantly decreased standing plasma norepinephrine levels in healthy women.[9] Given the potentially sympatholytic effects of melatonin,[10] we tested the hypothesis that melatonin would significantly decrease the standing tachycardia and improve the self-reported symptom burden in patients with POTS.[3]
METHODS

Subjects

Patients with POTS referred to the Vanderbilt Autonomic Dysfunction Center between April 2004 and March 2012 were candidates for inclusion in this study. Patients met criteria for POTS in that they developed symptoms of orthostatic intolerance accompanied by HR rise ≥ 30 bpm within 10 minutes of standing in the absence of orthostatic hypotension (fall in BP ≥ 20/10 mmHg). All patients had at least a 6-month history of symptoms in the absence of additional chronic disorders known to cause orthostatic intolerance and in the absence of prolonged bed rest. All patients were at least 18 years old. The Vanderbilt University Investigational Review Board approved this study, and written informed consent was obtained from each subject before initiating the study. The data reported are a part of “The Treatment of Orthostatic Intolerance” study, which is registered with http://www.clinicaltrials.gov (NCT00262470).

Study Diet and Baseline Characterization

Study investigations were performed in the Vanderbilt Clinical Research Center. Subjects consumed a methylxanthine-free diet containing 150 mEq/day sodium and 60–80 mEq/day potassium for at least 3 days before testing. Long-term medications were discontinued 5 half-life periods before the study. Selective serotonin reuptake inhibitors (SSRIs) were not discontinued because the long functional half-life would have limited clearance prior to enrollment. Subjects taking selective serotonin norepinephrine reuptake inhibitors (SNRIs) were excluded from this study due to their effects on noradrenergic pathways. Fludrocortisone has an elimination half-life of 3.5 hours but was discontinued for at least 5 days before the study due to potentially extended hormonal effects.

Posture Study

HR, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure, and plasma catecholamines were assessed after overnight fast with the patient in the supine position and again after standing up to 30 minutes (as tolerated) as part of baseline characterization. For catecholamine measurements, blood was collected in plastic syringes and immediately transferred to chilled heparinized vacuum tubes (BD, Franklin Lakes, NJ) on ice. Plasma was centrifuged at −4°C and stored at −80°C in collection tubes with 6% reduced glutathione (Sigma-Aldrich, St Louis, MO). Concentrations of norepinephrine and epinephrine were measured by batch alumina extraction followed by high-performance liquid chromatography for separation with electrochemical detection and quantification. Plasma norepinephrine and epinephrine are reported in SI units. To convert from nmol/L to the more conventional pg/mL, multiply 169.18 for norepinephrine (1 nmol/L = 169.18 pg/mL) or by 183.2 for epinephrine (1 nmol/L = 183.2 pg/mL).

Medication Trials

All medication trials were started in the morning at least 2 hours after an early, light breakfast (to avoid acute hemodynamic effects from eating) in a post-void state. In this trial, patients with POTS were given melatonin 3 mg (Sunmark, San Francisco, CA) or placebo.
(“Cebocaps”, Forest Pharmaceuticals, New York, NY) in a randomized crossover fashion on separate days. The order of intervention was randomly assigned in a 1:1 fashion using a random number generator by one co-investigator (BKB) who then ordered the appropriate study drug, but was not involved in any outcome assessments. All included subjects underwent BOTH study drug interventions, although not all satisfactorily completed the symptoms score. The study was single-blind (patient) with blinded evaluation of the response measure (investigators). The patients were seated in a chair during the data collection except during prescribed periods of standing. Brachial oscillometric cuff BP and HR were measured with an automated vital signs monitor (Dinamap Vital Signs Monitor, Critikon Corp, Tampa, FL) and digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation, Redmond, WA). Immediately before study drug administration, and hourly for 4 hours after study drug administration, each patient was asked to stand for 10 minutes while standing HR and BP were recorded. Although the increase in orthostatic stress is not as great when the subject is standing from a seated position compared with standing from a supine position (which is used as a POTS criterion), this provides a clinically relevant and reproducible model. Subjects were not permitted to ambulate, eat, drink or go to the restroom during the study.

**Symptoms**

Patients were asked to rate their symptom burden immediately before and at 2 and 4 hours after study drug administration using the Vanderbilt Orthostatic Symptom Score (VOSS).

[17] The patients were asked to rate the severity of 9 symptoms on a scale of 0 to 10 (0 reflects absence of symptoms). The sum of the scores at each time point was used as a measure of symptom burden (lower score reflects reduced symptom burden). The 9 symptoms were mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea. This symptom score has been used previously by our center [17;18] and these symptoms were chosen because they reflect common complaints of patients with POTS.

**Missing Data**

Individual missing hemodynamic data points were interpolated by taking the within-individual mean for the parameter at the data point for the hour immediately before and immediately after the missing data point. Hemodynamic data were not interpolated if either the baseline or 4-hour (final) value was missing or if >1 consecutive hourly data point was missing. Less than 1% of the hemodynamic data points required interpolation. Only patients with paired sets of complete hemodynamic data (after interpolation) were included in these analyses.

**Sample Size Determination**

The study was powered based on a paired t-test of the standing HR 2 hours after study drug administration (primary endpoint). We sought to detect a difference of 5 bpm between the matched pairs, which was felt to be clinically meaningful based on prior studies by our group.[18] Assuming a standard deviation of 15 bpm for the difference in standing HR between the 2 interventions, we needed to study 73 subjects to show such a difference with
alpha=0.05 and power=0.8 (PS Power and Sample Size Calculation 3.0, Nashville, TN; http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

Statistical Analysis

Our primary end point was the standing HR 2 hours after study drug administration. The 2-hour time point was chosen because the peak plasma concentration of melatonin occurs ~60 minutes after dosing.[19] The primary statistical analysis involved a comparison of the change in the standing HR at 2 hours after study drug administration between melatonin and placebo. The null hypothesis was that standing HR would not be statistically different between the melatonin and placebo day.

Secondary analyses were performed with paired t-tests to compare standing HR at other time points after drug administration as well as seated HR, delta HR (ΔHR; standing minus seated), standing, seated, and delta SBP, standing and seated DBP, standing and seated MAP, and VOSS for each time point. Additionally, analyses with paired t-tests were performed comparing standing HR, seated HR, and ΔHR at baseline and each hour after study drug administration for those subjects with standing norepinephrine ≥3.55 nmol/L (600 pg/ml) in the initial posture study with those with standing norepinephrine <3.55 nmol/L (600 pg/ml). A repeated-measures analysis of variance was used to compare change-from-baseline HR (standing, seated and delta) change-from-baseline SBP (standing, seated, and delta) and change-from-baseline symptom score at one through four hours since the onset of treatment. These analyses used a generalized estimating equation approach in which the response variable (e.g. change in standing HR) was regressed against indicator covariates for time and treatment [20]. Interaction covariates were included in these models to permit non-additive effects of time and treatment on the response measure. We used the identity link function and a normal random component in these analyses. The Huber-White sandwich estimator was used to obtain a robust estimate of the variance-covariance matrix of the model’s parameters. This matrix was used to derive P values and 95% confidence intervals for the difference in response due to treatment at 1, 2, 3 and 4 hours after the onset of treatment. Values are reported as mean±standard deviation unless otherwise noted. P values <0.05 were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed with SPSS for Windows (version 19.0, IBM Corporation, Armonk, NY) and Stata for Windows (version 13.1 StataCorp College Station, TX). Prism for Windows 5 (version 5.02, GraphPad Software Inc., La Jolla, CA) was used for graphical presentation.

RESULTS

Baseline Characteristics

Study inclusion criteria were met by 78 subjects with POTS (72 female, 32±9 years). All subjects underwent paired administration of melatonin and placebo.

Baseline data are presented in Table 1. Supine heart rate was 74±13 beats per minute (bpm), and BP was 108±11/68±9 mmHg. The supine plasma norepinephrine and epinephrine values (measured in 70 subjects) were within the normal range (norepinephrine <2.81 nmol/L and
epinephrine <0.41 nmol/L) with the exception of 7 subjects with elevated norepinephrine and 2 subjects with elevated epinephrine. On standing, there was a significant increase in HR (120±25 bpm; P<0.001), plasma norepinephrine (4.63 ± 3.60 nmol/L; P<0.001), and plasma epinephrine (0.40 ± 0.65 nmol/L; P<0.001) consistent with POTS. There was no significant increase in SBP (109±22 mmHg; P=0.494), but there was an increase in DBP (72±14 mmHg; P=0.013).

**Heart Rate Effects (Table 2)**

Immediately prior to drug administration, there was no difference in seated HR between melatonin (85±12 bpm) and placebo (87±12 bpm, P=0.219). Melatonin decreased seated HR to a greater extent than placebo, and this was statistically significant at 2 hours (P=0.021) and at 3 hours (P=0.008) following study drug administration (see Figure 1).

Baseline standing HR was similar between melatonin (114±17 bpm) and placebo (117±17 bpm, P=0.118). Melatonin significantly decreased HR at 2 hours to a greater extent than placebo (P=0.017; primary endpoint for this study) and at 4 hours (P=0.009) after drug administration when compared to placebo.

At baseline, both melatonin and placebo groups (29±15 bpm vs. 30±14 bpm, P=0.394) had similar large postural increases in HR (ΔHR). There was not a significant decrease in ΔHR between melatonin and placebo.

**Blood Pressure Effects (Figure 2)**

From 1h to 4h post study drug administration, there were not statistically significant differences in seated SBP and the standing SBP (Figure 2) between the melatonin and placebo days.

**Symptoms**

Melatonin did not improve VOSS score compared to placebo. Placebo improved VOSS more than melatonin at 2 hours (P=0.031), the the 2 interventions had comparable scores at 4 hours.

**Heart Rate and Baseline Norepinephrine Concentration (Figure 3)**

Both standing HR (P=0.014) and ΔHR (P=0.044) were significantly different before melatonin administration between those with posture study standing plasma NE >600 pg/mL and those with NE <600 pg/mL. Standing HR remained significantly different between the groups at all time points after melatonin administration (1 hour P=0.014, 2 hours P=0.005, 3 hours P=0.017, 4 hours P<0.001). ΔHR was also significantly different between the groups at 2 hours (P=0.029) and 4 hours (P=0.003) after melatonin administration. There was no significant difference in baseline seated HR between the two groups (P=0.319) and this continued for all hours after study drug administration. There was no difference in VOSS at baseline (P=0.213), 2 hours (P=0.241) or 4 hours (P=0.423) after melatonin administration.
DISCUSSION

This report is the first placebo-controlled trial of melatonin in patients with POTS. We found that (1) oral melatonin 3 mg produced a modest statistically significant decrease in standing and seated HR compared to placebo in patients with POTS; and (2) melatonin did not improve the self-reported symptom burden.

Melatonin and the Sympathetic Nervous System

Melatonin plays an important role in maintaining the diurnal rhythm, acting as a signal of darkness, and it is also involved in the regulation of the cardiovascular system. The effects of melatonin are primarily mediated by two receptors: MT1 and MT2. MT1 receptor activation causes vasoconstriction[4] whereas MT2 receptor activation leads to vasodilation.

[5] Given the contradictory effects of the receptors, the effects of melatonin on blood vessels are complex and variable, causing either vasoconstriction[21] or vasodilation[22] in animals.

There is also evidence that melatonin may have central sympatholytic effects. Results from human studies on the effects of melatonin have been variable, producing combinations of either a decrease or no change in SBP, DBP, MAP, HR and plasma norepinephrine.

Proposed mechanisms of these effects include a reduction of catecholamines,[9] direct modulation of neural centers that regulate the cardiovascular system,[23;24] direct relaxation of blood vessel smooth muscle, and antioxidant mechanisms.[25;26] Melatonin is secreted from the pineal gland under the control of the SCN.[27] Melatonin also provides negative feedback to the SCN, primarily through MT1 receptors,[28] decreasing the excitability of SCN neurons.[29] This decrease in excitability may lead to a decrease in sympathetic tone through intermittent inhibitory GABA-ergic signaling of the SCN on the paraventricular nucleus (PVN),[24;30] which projects to the rostral ventrolateral medulla and decreases sympathetic tone.[24;31;32] This sympatholytic effect of melatonin could benefit patients with POTS, many of who have a hyperadrenergic state.

Melatonin decreases HR in POTS

The decrease in standing HR found in this study was not consistent with the results of two previous studies using melatonin in healthy adults. These studies found that melatonin did not decrease HR during standing or lower body negative pressure compared with placebo,[8;10] and each measured standing HR approximately 1 hour after drug administration. We found that standing HR reduction with melatonin occurred at 2 hours after drug administration, but not at 1 hour after drug administration (when the previous studies assessed HR). It is possible that the increased sympathetic tone while standing in POTS patients[3;17;33] compared to healthy subjects contributed to the different HR responses to melatonin observed in this study compared to the prior studies in healthy subjects.

Melatonin caused a moderate decrease in standing HR at 2 hours compared to placebo (102 bpm vs. 109 bpm; Figure 1). We have previously shown that a similar decrease in standing HR (7 bpm) could be associated with significant improvement in symptoms (5 point decrease in VOSS) in patients with POTS.[18] While this decrease in standing HR may not
be adequate for symptom benefit as monotherapy, melatonin could ultimately be a valuable component in a multi-drug regimen used to treat POTS.

**HR remains increased in those with increased sympathetic tone**

The association we found in this study between elevated standing NE and increased standing HR and ΔHR have been demonstrated previously in patients with POTS. In fact, it was this known association between a hyperadrenergic state and excessive standing tachycardia in POTS that led to the hypothesis that the sympatholytic effects of melatonin may be beneficial in this condition. Interestingly, however, analysis of subgroups with normal and elevated standing plasma NE reveals that melatonin did not affect these two groups differently despite the difference in sympathetic tone. One possible explanation for this finding is that the sympatholytic effect of the relatively low dose of melatonin used in this study was not sufficient to overcome the baseline differences in sympathetic tone between the two groups. Future studies with increased melatonin dose may be necessary to better understand this finding.

**Melatonin and Beta Blockers**

Beta-adrenergic antagonists, which are commonly used in the treatment of POTS,[17;34] have been shown to decrease endogenous melatonin through beta-1 adrenergic receptor blockade. Nightly melatonin excretion during treatment with beta-blockers is decreased in patients with beta-blocker induced central nervous system (CNS) side effects,[35] and sleep disturbances are the most commonly reported CNS side effect of propranolol.[36] For these reasons, melatonin supplementation has been proposed for hypertensive patients taking beta blockers.[26] We recently reported that sleep problems are a significant contributor to diminished health related quality of life in patients with POTS.[2] Taken together with the results of the present study, these data indicate that it might be valuable to study the nocturnal use of melatonin supplementation in patients with POTS.

**Melatonin Supplementation and Time of Day**

In this study, melatonin was administered in the morning in a proof of concept study to demonstrate the efficacy of melatonin in decreasing upright heart rate in POTS patients. Given the soporific and phase shifting effects of melatonin,[6;7] morning dosing does not represent a likely clinical scenario. Rather, melatonin might be a particularly useful nighttime agent in POTS patients. It is not possible to exclude the possibility that these soporific effects may have played some role in the cardiovascular effects noted in this study, either directly or indirectly through reduced sympathetic nervous system tone. Data from nighttime administration of melatonin is important because of variability in melatonin binding and receptor mRNA levels in response to light exposure and melatonin levels.[37–39] A single daytime dose of melatonin decreases blood pressure,[9;12;14] but a single nighttime dose might not have the same effect.[40] In order to determine the efficacy of melatonin supplementation in POTS, additional studies must be performed to demonstrate the effects of melatonin in POTS with repeated nighttime administration.
Symptoms

Melatonin did not improve VOSS score compared to placebo after drug administration. The reason for this finding is not clear, as we have previously found that decreases in standing HR as small as 7 bpm have been associated with significant improvement in patient reported symptoms.[18] One possible explanation for this apparent discrepancy is that the drug trial was performed in the morning when the phase shifting and soporific effects of exogenous melatonin could have masked any improvement that might have been associated with reduction in standing heart rate. These effects may have negatively influenced the other components of the patient reported symptoms score.

Study Limitations

The primary limitation of this study is that the melatonin was given in the morning and not at night. Given the soporific and phase shifting properties of melatonin, future studies of the effects of melatonin in POTS should be performed at night.

Another limitation is that this was an acute dosing study with short follow-up. Longer studies are needed to determine if the short-term HR suppression achieved in this study can be translated into long-term suppression of standing tachycardia with chronic administration or if other factors, including possible tachyphylaxis affect long-term results. The effects of higher doses of melatonin also require further study.

Plasma catecholamines were not collected before and after melatonin administration in this study. Because the effects of melatonin are likely mediated, at least partially, by a change in sympathetic tone, collecting plasma catecholamines would have helped to better understand the physiological responses observed in this trial.

Conclusions

Melatonin produced a significant, moderate decrease in standing tachycardia in patients with POTS, although it did not improve symptoms when taken in the morning. Longer studies with nighttime drug administration are needed to further evaluate the efficacy of this medication therapeutically.

Acknowledgments

We would like to thank our patients who participated in this study and to recognize the highly professional care provided by the staff of the Elliot V. Newman Clinical Research Center at Vanderbilt University.

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Reference List


Figure 1. Changes in heart rate before and after melatonin vs. placebo

Heart rate (HR) data are presented immediately before (pre), and hourly for 4 hours (4H) following study drug administration for the Melatonin 3 mg day (“Melatonin”; solid circles) and the placebo day (open squares). Peak HR after standing for a maximum of 10 minutes (Fig 1A), seated HR immediately before standing (Fig 1B) and the changes in HR from sit to stand (Fig 1C) are shown. The error bars represent the standard error of the mean. * - The analysis of variance P<0.05 for the adjusted difference in effect between melatonin and placebo for the change at each time point from baseline. bpm – beats per minute.
Figure 2. Changes in systolic blood pressure before and after melatonin vs. placebo
Systolic blood pressure (SBP) data are presented immediately before (pre), and hourly for 4 hours (4H) following study drug administration for the Melatonin 3 mg day (“Melatonin”; solid circles) and the placebo day (open squares). Standing SBP (Fig 2A), seated SBP (Fig 2B) and the changes in SBP from sit to stand (Fig 2C) are shown. The error bars represent the standard error of the mean. mmHg – millimeters of mercury.
Figure 3. Changes in heart rate for baseline norepinephrine >600pg/mL and <600pg/mL

Heart rate (HR) data are presented for subjects with baseline plasma NE <600pg/mL (solid circles) and subjects with NE>600pg/mL (open squares) immediately before (pre), and hourly for 4 hours (4H) following study drug administration for the Melatonin 3 mg day ("Melatonin"; solid circles). Standing HR (Fig 1A), seated HR immediately before standing (Fig 1B) and the orthostatic change in HR from sit to stand (Fig 1C) are shown. The error bars represent the standard error of the mean. The ANOVA interaction P values are presented for the overall differential effect of melatonin over time in the 2 subgroups. bpm – beats per minute.
Table 1
Postural vital signs and catecholamines of the subjects with Postural Tachycardia Syndrome (n=78).

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Standing</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>74 ± 13</td>
<td>119 ± 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>107 ± 11</td>
<td>109 ± 22</td>
<td>0.494</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>68 ± 9</td>
<td>72 ± 14</td>
<td>0.013</td>
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<tr>
<td>Norepinephrine (nmol/L)</td>
<td>1.38 ± 1.33</td>
<td>4.63 ± 3.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epinephrine (nmol/L)</td>
<td>0.10 ± 0.11</td>
<td>0.40 ± 0.65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bpm – beats per minute. Data are presented as the mean ± standard deviation. Reported P values are for paired t-tests comparing supine and upright parameters.
## Table 2

Differences in change in orthostatic hemodynamics and symptoms from baseline between melatonin 3mg and placebo in patients with Postural Tachycardia Syndrome (n=78).

<table>
<thead>
<tr>
<th></th>
<th>Change at 1 hour</th>
<th>Change at 2 hours</th>
<th>Change at 3 hours</th>
<th>Change at 4 hours</th>
</tr>
</thead>
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<tr>
<td><strong>Standing HR (bpm)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Melatonin - Placebo</td>
<td>−1.5 ± 1.4</td>
<td>−4.1 ± 1.7</td>
<td>−0.69 ± 1.8</td>
<td>−4.5 ± 1.7</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−4.2, 1.3)</td>
<td>(−7.5, −0.7)</td>
<td>(−4.2, 2.9)</td>
<td>(−7.9, −1.1)</td>
</tr>
<tr>
<td>P value</td>
<td>0.30</td>
<td>0.017</td>
<td>0.71</td>
<td>0.009</td>
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<tr>
<td><strong>Seated HR (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Melatonin - Placebo</td>
<td>−0.62 ± 1.2</td>
<td>−3.4 ± 1.5</td>
<td>−3.6 ± 1.4</td>
<td>−2.4 ± 1.3</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−3.0, 1.8)</td>
<td>(−6.2, −0.5)</td>
<td>(−6.3, −0.94)</td>
<td>(−5.0, 0.22)</td>
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<tr>
<td>P value</td>
<td>0.61</td>
<td>0.021</td>
<td>0.008</td>
<td>0.073</td>
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<tr>
<td><strong>Delta (Standing-Seated) HR (bpm)</strong></td>
<td></td>
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<tr>
<td>Melatonin - Placebo</td>
<td>−0.71 ± 1.5</td>
<td>−0.70 ± 1.9</td>
<td>3.0 ± 2.1</td>
<td>−2.1 ± 1.8</td>
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<td>(−4.5, 3.1)</td>
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<td>P value</td>
<td>0.65</td>
<td>0.71</td>
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<tr>
<td><strong>Standing SBP (mmHg)</strong></td>
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<tr>
<td>Melatonin - Placebo</td>
<td>0.16 ± 1.7</td>
<td>−1.2 ± 1.8</td>
<td>−3.1 ± 2.1</td>
<td>−2.7 ± 2.1</td>
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<td>95% Confidence Interval</td>
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<td>(−7.2, 1.0)</td>
<td>(−6.8, 1.3)</td>
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<td>P value</td>
<td>0.93</td>
<td>0.50</td>
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<td><strong>Sitting SBP (mmHg)</strong></td>
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<tr>
<td>Melatonin - Placebo</td>
<td>2.5 ± 1.3</td>
<td>0.90 ± 1.3</td>
<td>1.4 ± 1.6</td>
<td>0.72 ± 1.4</td>
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<td>95% Confidence Interval</td>
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<td>(−1.7, 3.5)</td>
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<td>(−2.1, 3.6)</td>
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<td>0.057</td>
<td>0.50</td>
<td>0.38</td>
<td>0.62</td>
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<tr>
<td><strong>Delta (Standing-Seated) SBP (mmHg)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin - Placebo</td>
<td>−2.3 ± 2.0</td>
<td>−2.1 ± 2.3</td>
<td>−4.4 ± 2.4</td>
<td>−3.5 ± 2.4</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−6.3, 1.7)</td>
<td>(−6.5, 2.3)</td>
<td>(−9.2, 0.4)</td>
<td>(−8.2, 1.3)</td>
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<tr>
<td>P value</td>
<td>0.057</td>
<td>0.35</td>
<td>0.070</td>
<td>0.15</td>
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<td><strong>Symptom Score (au) [n=61]</strong></td>
<td></td>
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<tr>
<td>Melatonin - Placebo</td>
<td>3.0 ± 1.4</td>
<td>1.0 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(0.27, 5.8)</td>
<td>(−1.8, 3.9)</td>
<td></td>
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</tr>
<tr>
<td>P value</td>
<td>0.031</td>
<td>0.48</td>
<td></td>
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</tr>
</tbody>
</table>

HR – heart rate; bpm – beats per minute; SBP – systolic blood pressure; au – arbitrary units; NS – not significant. Generalized Estimating Equation (GEE analysis was used to determine the P value and confidence interval for the difference in change between study drug and placebo for each time-point after study drug administration. A negative value for the “melatonin – placebo” value indicates a lower value for melatonin than placebo, or for the “delta” comparisons a larger decrease for melatonin than for placebo. Data are presented as mean±standard error of the mean. P<0.05 was considered significant.