Property of Melatonin of Acting as an Antihypertensive Agent to Antagonize Nocturnal High Blood Pressure: A Meta-Analysis

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Abstract: Therapy of hypertension persisting in the course of nocturnal sleep has yielded rather disappointing results . Therefore, the research has focused on drugs such as melatonin acting in such a way so as to counteract the lack of fall in blood pressure during night time sleep.

A meta-analysis has been planned by gathering only randomized controlled trials(RCTs), where melatonin was administered as a single dose at bedtime and compared with placebo.

The efficacy was the "night time variation in systolic blood pressure" and the "night time variation in diastolic blood pressure". Safety endpoint was the possible occurrence of serious adverse events.

Seven studies with 221 participants were pooled in the meta-analysis. Melatonin use was a predictor of significant decrease in nocturnal systolic blood pressure[SBP](difference in means[MD]= -5.74 mm Hg; 95% CI: -6.07 to- 5.41 mm Hg; p<0.00001).This change was generated by the very steep decrease in nocturnal SBP detected in patients treated with controlled-release(CR) melatonin (MD=-8.42 mm Hg; 95% CI: -8.82 to- 8.02 mm Hg; p<0.00001); whereas the mean change in nocturnal SBP, found in patients taking fast -release (FR)melatonin, was nonsignificant (MD=-0.06 mm Hg; 95% CI: -0.64 to 0.52 mm Hg; p=0.84). Likewise, use of melatonin was associated with a fall in DBP(MD= -0.60 mm Hg; 95% CI=-1.12 to -0.08 mm Hg), driven by the pressure changes attained by the CR melatonin. No major adverse events occurred in the examined trials. Evening administration of CR melatonin has been shown to cause a significant pressure decrease over the nocturnal sleep. Thus, the CR melatonin preparations could find a place in the antihypertensive armamentarium for promoting the physiological fall of blood pressure levels during night time sleep.

Keywords: Non-dipping, ambulatory blood pressure monitoring, melatonin.

INTRODUCTION

Melatonin is a hormone produced by the pineal gland, also called the epiphysis, located at the base of the skull, which has long been known for its ability to promote nocturnal sleep. In reality, however, a regulatory effect on the arterial pressure exerted by melatonin has never been demonstrated with certainty, so that arterial hypertension is not comprised among the indications of this pharmacologic principle [1]

In fact, melatonin is recommended as a nightly hypnotic agent [2] and also presented by someone as an anti-aging drug considering its antioxidant properties [3] However, according to some [1] melatonin could find a peculiar place in the antihypertensive armamentarium as a specific adjuvant hypotensive drug for patients with arterial hypertension already in pharmacological treatment in whom high blood pressure levels persist in the course of nocturnal sleep [4].

In fact, the fall in blood pressure during sleep, both in the healthy subject and in the patient with arterial hypertension, is a physiological consequence of attenuation in vasoconstrictor sympathetic drive.

However in some hypertensives the flexion of pressure levels during sleep is lacking and this unusual profile of the blood pressure (non-dipper "hypertensive pattern") has been related to an increased risk of cardiovascular events such as stroke and myocardial infarction [5]. The patient is defined as non-dipper if the average nocturnal systolic pressure is reduced by less than 10% compared to the daytime average.

Therefore some scholars have already proposed melatonin for a long time as a useful add-on in the patients with arterial hypertension, who on the basis of continuous blood pressure monitoring have a documented non-dipper hypertensive profile [6].

The production and subsequent secretion of endogenous melatonin in the blood stream is cyclical, being conditioned by the wake-sleep cycle, in turn influenced by the alternation of day light and night darkness. It seems that this circadian pattern of serum melatonin levels plays a useful role in the functioning of

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the neuro-vegetative system. A dysregulation of the melatonin secretion rhythm was detected in the personnel working on the intercontinental airplanes, with unfavorable repercussions on the quality and duration of sleep. However, the imbalance in melatonin secretion resulting from the rapid crossing of multiple time zones is able to generate the Jet-lag syndrome but does not seem to be able to generate an increased risk of arterial hypertension [7]. In any case, to verify if melatonin can play a role in the treatment of arterial hypertension, several randomized controlled trials have been conducted [8-14], some by means of parallel groups while other with cross-over technique. In the present meta-analysis the data of these trials were aggregated for obtaining a useful quantitative analysis (meta-analysis) aimed to elucidate a possible significant antihypertensive effect of melatonin.

METHODS

Research and Extraction of Data

We searched the PubMed, Scopus, Cochrane Library and OVID databases for randomized, placebo-controlled studies concerning exogenous melatonin and hypertension, which were published between January 1980 and December 2017. We comprised in the meta-analysis exclusively studies that compared the effect of melatonin with placebo and reported nocturnal systolic and diastolic blood pressure as measured by 24-hour ambulatory blood pressure monitoring for blood pressure assessment. Animal experimental studies as well as case reports were eliminated from the meta-analysis. Similarly, all studies not written in English, duplicated studies, non-randomized studies, review articles, editorials, and expert opinions were excluded. Eligibility assessment and data extraction were carried out independently by two investigators (RDV and AP), with discrepancies resolved by thorough and in-depth discussion between them. Search terms were “melatonin”, “blood pressure”, and “randomized controlled trials”.

Endpoints of Interest

Efficacy endpoints were the "night time variation in systolic blood pressure" and the "night time variation in diastolic blood pressure". Safety endpoint was the possible occurrence of serious adverse events.

Quality Assessment

Titles and abstracts of all identified citations were reviewed independently by two authors (RDV and AP). The same reviewers evaluated the risk of bias in randomized trials included in the meta-analysis using the Cochrane Risk of Bias Tool [15]. It evaluates individual studies for several biases: selection, performance, detection, attrition and reporting. We evaluated the quality of evidence for each outcome using GRADE criteria [15], which evaluates an outcome across studies based on risk of bias, inconsistency, indirectness, imprecision and publication bias.

We identified from each paper the patient characteristics, the melatonin formulation and dose, duration of therapy, baseline blood pressure, and nocturnal blood pressure values during treatment. For the cross-over studies, we counted the patients twice, once in the active group and once in the placebo group.

Statistical Analysis

Two continuous variables, namely “night time variation in systolic blood pressure” and “night time variation in diastolic blood pressure” were chosen as endpoints of interest. Thus, the effect size was expressed as a difference in means (MD) plus 95% confidence interval using inverse variance as the weighting method. Due to the large variety of patients, the effect size was calculated using a random effects model. Statistical heterogeneity across studies was tested using Cochran’s Q test and I^2 statistic (coefficient of variability due to inter-study variability). Statistical analyses were performed using Rev Man 5.3 software (available from the Cochrane Collaboration; http//www.cochrane.org) and Stata version 10 (Stata Corp LP, College Station, TX, USA).

RESULTS

Qualitative Analysis

On the whole, 55 articles on melatonin and blood pressure were found. 25 studies did not conform to requirements that apply to RCTs (incorrect randomization, poor description of control group, lack of assessment of blood pressure levels, selection of endpoints not pertaining to purposes of our research), while 20 trials did not test nocturnal blood pressure and were therefore excluded. Likewise two review articles and one editorial were excluded. Thus, after thorough evaluation, only seven studies satisfied the inclusion criteria and were judged suitable for inclusion in the meta-analysis (Figure **1**) [8-14].

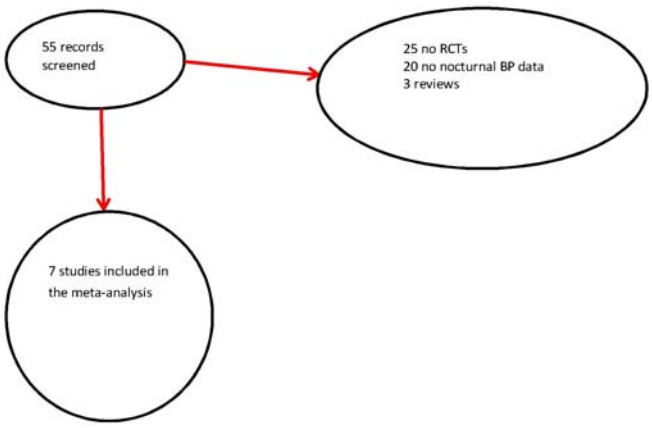

Figure 1: Flow diagram of the study selection process.

Of the seven placebo-controlled studies, six studies gathered 200 adults and one study enrolled 21 adolescents. Among the patients included in the analysis, 60 had coronary artery disease, 11 had type 1 diabetes, 51 were normotensive, and 99 had hypertension. One study reported the results separately for the normotensive and diabetic patients, and therefore was included as two separate studies in the meta-analysis [10].

In three studies, patients received either melatonin or placebo in parallel, and in the other three adult studies and the adolescent study, melatonin administration was arranged according to a cross-over design. In two of the three cross-over studies in adults, the participants received melatonin during two consecutive periods of three weeks each without interposition of a wash-out period. In the other adult cross-over study, the active drug was given for two subsequent periods of four weeks each, with interpolation of a four-week wash-out period. In the adolescent cross-over trial, the participants received the active drug for two consecutive periods of one week, separated by a one-week wash-out period.

In four studies, fast-release melatonin at a dosage of 5 mg was used, while in three other studies, controlled-release melatonin at a dosage of 2–3 mg was administered. Subgroup analyses accounting for the different pharmacodynamics of administered drug, i.e., aimed to distinguish the effects on nocturnal pressure changes in patients taking fast- release (FR) melatonin compared to those taking controlled- release (CR) melatonin, were carried out in our meta-analysis.

Risk of Bias within Included Trials

Two trials had unclear or absent allocation concealment [11-12]. One study had inadequate blinding [11] and one exhibited single-blind design [8]. Overall, loss-to-follow-up was low with a range of 0 to 6.6%.

Quantitative Analysis (Meta-Analysis)

Systolic Blood Pressure

Based on our meta-analysis, melatonin therapy was associated with a significant decrease in nocturnal systolic blood pressure [SBP] (difference in means [MD]=-5.74 mm Hg; 95% CI: -6.07 to - 5.41 mm Hg; p<0.00001) (see Figure **2**). However, this overall antihypertensive effect was driven by the very sharp fall in nocturnal SBP found in patients treated with CR melatonin (MD= - 8.42 mm Hg; 95% CI: -8.82 to- 8.02 mm Hg; p<0.00001) (Figure **2**), whereas the mean

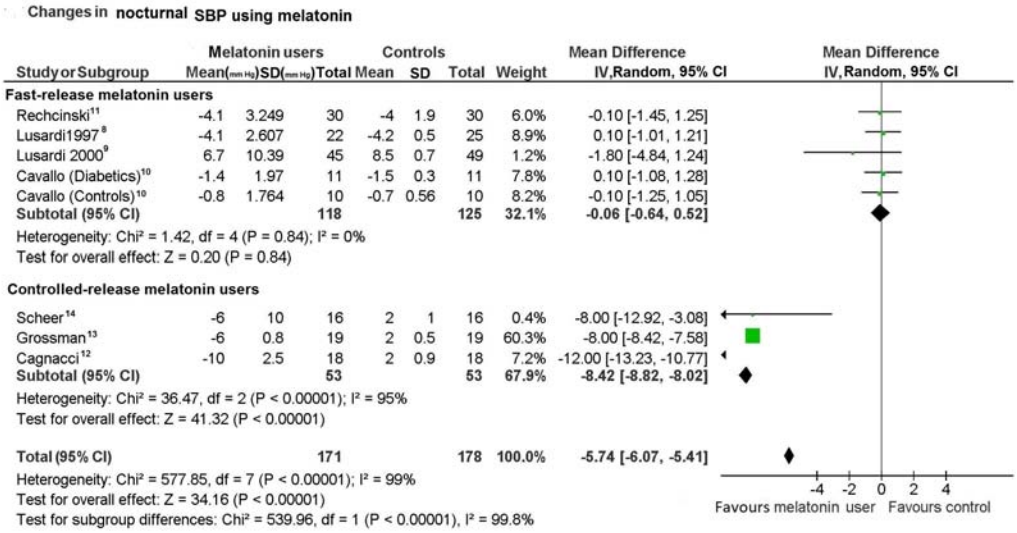

Figure 2: Melatonin-related changes in nocturnal systolic blood pressure (SBP).

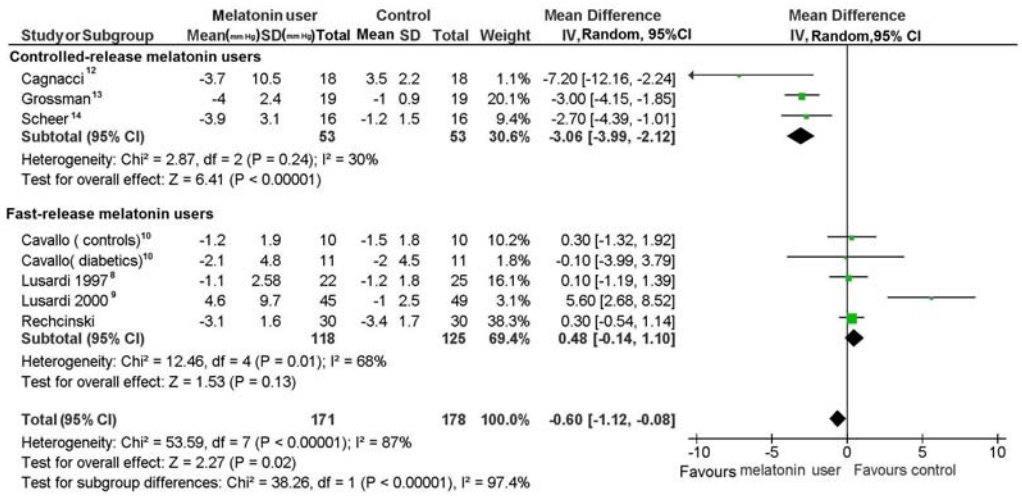

Figure 3: Melatonin-related changes in nocturnal diastolic blood pressure (DBP).

change in nocturnal SBP, detected in the group of patients taking FR melatonin was nonsignificant (MD= -0.06 mm Hg; 95% CI: - 0.64 to 0.52 mm Hg; p=0.84) (Figure **2**).

Diastolic Blood Pressure

The behavior of nocturnal diastolic blood pressure (DBP) was sensible to melatonin. Indeed, use of melatonin was associated with a slight drop in DBP: MD=-0.60; 95% CI= -1.12 to -0.08 (Figure **3**). Even in the case of DBP the overall antihypertensive effect was driven by the pressure decrease yielded with the use of CR melatonin (MD=-3.06; 95% CI: -3.99 to - 2.12 mm Hg; p<0.00001) (Figure **3**), whereas the pressure change achieved by the FR melatonin users compared to placebo was nonsignificant (MD=0.48 mm Hg; 95% CI: - 0.14 to 1.10 mm Hg; p= 0.13) (Figure **3**).

Safety Outcomes

No serious adverse events were reported. However, several side effects such as headache, drowsiness and weakness were noted in three trials. In any case, no side effects were very annoying or intense so as to induce the suspension of melatonin administration during the clinical trial period.

DISCUSSION

In our study it is important to note the usefulness of melatonin as an antihypertensive drug exclusively in the CR formulation (see Figures **2-3**). In fact, in the FR formulation, the drug administered in the evening before going to bed, would exhaust within a few hours its pharmaco-dynamic properties of orthosympathetic attenuation and relaxation of the vascular smooth muscle, instead of mimicking the action profile of endogenous melatonin which characteristically reaches its plateau of serum concentration in the last hours of the night just before dawn. The alert of the sympathetic nervous system is instead mitigated and decremented exclusively by CR melatonin preparations, which, even if taken many hours before, i.e. at bedtime, are able to exert a beneficial vascular- relaxant and anti-adrenergic effect still in the early morning. This could at least be the explanation of the finding of a significant antihypertensive effect (-8 mm Hg on average for SBP) of the CR preparations, which is not recorded for the fast release (FR) melatonin users.

For the latter, regardless of the dose taken, which varies from 0.5 to 5 mg as a single evening medication, the only valid indication seems to be insomnia, while the protective effect against nocturnal and early morning hypertension is not detected, different from the patients taking delayed-release preparations of melatonin. The only other meta-analysis that has been built on this subject, namely that by Grossman *et al.* (2011) [16] has reached conclusions similar to ours. In fact, in both meta-analyses, the respective results document a significant antihypertensive efficacy of the controlled-release melatonin compared to placebo. However, our meta-analysis exhibits some noticeable discrepancies with respect to the previous work, regarding the values of the differences in means and confidence intervals.

CONCLUSIONS

CR melatonin, not the FR melatonin could be used as beneficial add-on to antihypertensive therapy in order to antagonize nocturnal hypertension

efficaciously. Evening administration of CR melatonin has been shown to cause a significant blood pressure decrease over the nocturnal sleep. The CR melatonin preparations are different from those with fast release, could find a place in the antihypertensive armamentarium as a drug suitable for promoting the physiological fall of blood pressure levels during nighttime sleep. This study can bring an important therapeutic benefit to hypertensive patients with a non-dipper profile.

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