A Triple Blinded Randomized Controlled Trial of Oral Melatonin in Elevated Blood Pressure Individual

NCT number: IR.TUMS.MEDICINE.REC.1397.438 Approval date: 2018-9-17

Document date: December first 2018

Introduction:

Prescription of exogenous melatonin has been proved to decrease nocturnal hypertension, the pulsatility index of internal carotid artery, platelet aggregation, and catecholamine levels (1). Melatonin effects are both receptor mediated and receptor independent. Receptor-mediated effects of melatonin comprise of membrane melatonergic receptors (MT1 and MT2) located in vascular system and heart. And also could be find in cardiomyocytes, left ventricle, and coronary arteries (2, 3).

Antioxidant and mitochondrial-protecting effects are receptor independent effects of melatonin (4). Melatonin levels decreased in pathological conditions including hypertension with no dipper pattern, (5) congestive heart failure (CHF) (6) Ischemic heart disease (4) acute myocardial infarction (7), coronary artery disease (CAD) (1) and low level of LDL-c (8). Melatonin attenuates blood pressure (BP), vascular reactivity, and circulating catecholamine versus placebo in healthy individuals (9-11). Besides, antioxidant effect, anti-inflammatory properties, and metabolic regulator activity of melatonin are also play an important role in introduction of melatonin as a potential therapeutic agent in hypertension and cardiovascular disease (CVD). Accordingly, Clinical trials have been conducted to evaluate antihypertensive effects of melatonin in different settings including:

A double-blind, placebo-controlled study in 2004 demonstrated that oral daily melatonin therapy with 2.5 Mg for 3 weeks significantly decreased systolic and diastolic BP in 16 male hypertensive patients (12). In a crossover randomized double blinded placebo controlled trial in 2005 eighteen women with normal BP or treated essential hypertension allocated to a 3-week course of slow-release 3Mg melatonin pill or placebo one hour before bedtime. They concluded that melatonin may improve the day–night rhythm of BP, particularly in women with a blunted nocturnal BP decline (13).

Effectiveness and safety of melatonin on nocturnal hypertension was investigated in an RCT in 2006. Thirty eight treated hypertensive patients underwent four weeks controlled release melatonin 2 mg or placebo two hours before bedtime. Bottom line was significant anti- hypertensive effects of controlled-release melatonin. Whereas fast-release did not control nocturnal hypertension (14)

In a placebo controlled trial effects of 1.5 Mg melatonin for two weeks in 97 hypertensive and normotensive individuals have been investigated in 2015 results have been shown that both systolic and diastolic BP was significantly mitigated (15).

In an RCT among 44 women in 2015 bedtime prescription of 6 Mg melatonin significantly decreased mean serum level of; Hs-CRP, TNF-alpha and IL-6 versus placebo (16).

Decreased level of plasma norepinephrine and blood pressure (BP) were found in an RCT study in 14 men after 90 minutes of prescribing 2 Mg melatonin versus placebo (17).

In a clinical trial in twenty healthy volunteers in 2014 to evaluate the safety and tolerability of 20, 30, 50, and 100 Mg oral doses of melatonin. Apart from transient drowsiness no adverse effects have been reported. Sleeping pattern has not been changed with melatonin prescription (18).

Therefore, melatonin is appealing in medical practice both in primary and secondary prevention arena because of lack of side effect and availability of this medication.

In a cross over double blinded trial 5Mg melatonin versus placebo was given to 47 mild to moderate hypertensive outpatients associated with Nifedipine 30 or 60 Mg a day. Results have been shown that

melatonin can impair antihypertensive effect of calcium channel blockers, suggesting caution in concomitant use of melatonin and antihypertensive agents (19).

A clinical trial in 60 coronary artery disease (CAD) patients and non- dippers has been conducted to evaluate efficacy of 5 Mg melatonin versus placebo along with previous treatment of CAD. After, completing 90 days of follow up they concluded that prescription of melatonin in patients with high normal value of BP is not recommended because of the nocturnal decrease and daytime increase in BP observed in melatonin intervention group (20).

An RCT in 63 patients with metabolic syndrome has been conducted to evaluate the efficacy of 5 Mg melatonin for two months. Results revealed that BP and lipid profile significantly decreased and anti-oxidative defence significantly improved after two months of melatonin therapy (21).

In a small sample size clinical trial in 12 young women cardiovascular effects of one Mg melatonin versus placebo has been assessed along with a fixed dose of monophasic contraceptive pill. Melatonin significantly reduced systolic and diastolic BP and pulsatility index of internal carotid artery (22).

Therefore, large scale clinical trials are needed to evaluate the efficacy of melatonin on decreasing systolic and diastolic blood pressure. Aforementioned evidences have been shown the safety and efficacy of melatonin prescription in different clinical settings. Moreover, prescription of melatonin in hypertensive patients (20) and associated with other antihypertensive medications (19) have not been recommended. Therefore, we are going to evaluate the efficacy of melatonin versus placebo in pre hypertensive individuals who have been recognized as at higher risk of developing future hypertension.

BP consists of systolic (the upper number) BP which indicates how much pressure the blood is exerting against artery walls when heart beats. And diastolic BP (the lower number) is indicative of the amount of pressure that blood is exerting against artery walls when the heart is resting between beats. Diagnosis and treatment of hypertension (HTN) depend on accurate measurement of blood pressure and also an average level of BP over a long duration. The last Classification of BP is: Normal blood pressure(systolic blood pressure(SBP) <120 mmHg or diastolic blood pressure(DBP)<80 mmHg),elevated blood pressure(SBP=120-129 mmHg or DBP<80 mmHg),hypertension (stage 1; SBP=130-139 mmHg or DBP=80-89 mmHg),(stage2; SBP>=140 mmHg or DBP>=90mmHg)(23).

Elevated BP defined as SBP=120-129 mmHg or DBP<80 mmHg), is associated with higher incidence of hypertension (HTN), cardiovascular events and other end-organ damages such as renal, cerebrovascular and ocular (24,25). It has been shown that life style intervention in elevated BP people can prevent incidence of hypertension. Elevated BP individuals who will not reach optimal BP after receiving lifestyle modification are candidate for more aggressive anti-hypertensive treatment strategies. So, lowering blood pressure in elevated BP people will provide an excellent opportunity to prevent the incidence of HTN. Therefore, we are planning to use a safe treatment option of melatonin associated with life style intervention according to ACC/AHA 2013 guideline (26) in elevated BP individuals to mitigate systolic and diastolic BP to prevent the incidence of HTN.

Ongoing researches:

IMPACT ongoing trial designed in 2014 to test intracoronary versus systemic melatonin in an RCT among patients with acute myocardial infarction (AMI) undergoing primary percutaneous cardiac intervention (27).

Objectives:

Main objective: To determine the efficacy of melatonin in attenuating blood pressure among elevated BP individuals

Specific objectives:

To determine the efficacy of melatonin in attenuation of Systolic and diastolic BP

To determine the effect of melatonin on Hs- CRP level, LDL-c, total cholesterol level and fasting blood sugar (FBS)

To determine the effect of melatonin on sleeping pattern, drowsiness

Hypothesis

Melatonin therapy can lower the systolic and diastolic BP of elevated BP individuals

Melatonin can attenuate levels of circulatory biomarkers such as Hs- CRP

Melatonin can decline the level of total Cholesterol, LDL-c and FBS

Materials, subjects and methods:

Study design: Triple blinded randomized controlled trial (RCT)

Study population: Elevated BP individuals who have systolic blood pressure of 120-129 mmHg or diastolic blood pressure of 80 mmHg

Study sample: Patients admitted in Tehran Heart Centre (THC)

Sampling method: Eligible patients will be recruited with simple random sampling

Inclusion criteria:

-Individuals with blood pressure120-129 / 80 mmHg

- Age range of 30-60

-Negative pregnancy test for women at productive age

-Baseline melatonin and biomarkers level and complete liver function tests within normal range

Exclusion criteria:

-Previous history of hypersensitivity of melatonin

- Past history of using antihypertensive treatment

- Past medical history of hypertension, cardiovascular diseases and diabetes mellitus, epilepsy and other physician documented diseases

- Use of beta-blockers, sleep aids, warfarin, flaxseed, soy and supplements

-Non- compliance

Sample size:

Sample size calculation is based on the following equation and efficacy of melatonin in reducing systolic and diastolic blood pressure published in an RCT in 2004 by Scheer F et.al:

$N= (1/1-f) (z\alpha+z\beta)^2 \ (s1^2 +s2^2)^2 \ / (X1-X2)^2$

N=160 per arm

$N_{total}= 320$

Informed consent:

Written consent form according to Helsinki Declaration will provide participants with information about intervention including: benefits and harms, cost, methods of measuring out comes, follow up intervals, physician visits, and study team. Participants who accept to randomly assign to the trial arms are going to allocate to treatment versus placebo arm.

Study design: Randomized controlled trial (RCT), parallel two arms study

Intervention plan:

Recruitment: 320 cases of elevated BP will recruit to the study based on eligibility criteria with a simple random sampling method during screening visits by the physicians from THC.

Treatment plan: Three weeks melatonin 3Mg or placebo one hour before bedtime has been planned. All of the melatonin and placebo capsules will be supplied from a single hospital pharmacy and free of charge to the participants. Melatonin and placebo capsules will be identical. Participants will receive a three weeks supply at the assignment time. Besides, all participants will receive a careful plan of adherence to a heart-healthy diet, regular exercise, avoidance of tobacco use and maintenance of a healthy body mass index (BMI) according to 2013ACC/ AHA guideline (the last version).

Comprehensive written intervention protocol will be circulating at treatment assignment time.

Treatment arms: Melatonin 3 mg versus placebo

Treatment allocation: After completing informed consent and prior to randomization, all participants undergo complete physical examination and laboratory test. Baseline melatonin level, inflammatory biomarkers and pregnancy test (for women in reproductive age) will be performed. Sleep quality, actual sleep time, and sleep latency will be recorded.

320 participants will be assigned to melatonin 3 mg versus placebo arm using balanced randomization.

Randomization scheme: Balanced randomization using computerized random digit table will be used.

Blinding: Triple blinding is planned. All participants, medical providers and outcome evaluators will be blinded about treatment arms.

Measurements:

Two ambulatory blood pressure (BP) recording have been planned while using melatonin versus placebo during three weeks intervention period. First measurement will be at recruitment time and the second one at the end of three weeks intervention.

We have also planned to measure melatonin level at baseline, inflammatory biomarkers, liver function tests, lipid profile and sleep details.

Follow up:

Duration: Three weeks

Active follow up:

Written intervention protocol will be circulating at treatment assignment time. Weekly telephone contact with participants will assess adherence to the protocol and will obtain weekly counts of the melatonin or placebo capsules, recall for ambulatory BP measurement at the end of three weeks.

Out comes:

We will assess lowering blood pressure, sleep details using Pittsburgh sleep quality questionnaire (PSQI), inflammatory biomarkers, liver function test and adherence to ACC/AHA 2013 guideline regarding heart-healthy diet (step one national cholesterol education program), regular exercise (moderate level exercise 30 minutes a day five times a week), avoidance of tobacco use and maintenance of a healthy body mass index (BMI= 21-25) at baseline and after completion of the 3 weeks follow up period. All clinical evaluations including efficacy of the treatments, side effects will be assessed by a different blinded clinician. Costs of a trial will be calculated by the research team.

All blood samples will be fasting sample which will be processed, stored and assessed by one hospital laboratory.

Laboratory methods: Standardized lab method using international or local kits will be used.

Data collection: standardized questionnaire will be used to record the results of complete physical examination by physicians, anthropometric measurement, blood pressure measurement, ECG, and biological measurement such as inflammatory biomarkers and electrolytes and outcome variables such as BP, BMI, physical activity, ECG findings. Sleep quality and details of sleep will be detected with standard questionnaire.

Data management plan:

Data coding, entry, cleaning, and analysis will be performed by data analyser team.

Data analysis protocol:

Analysis plan: Normal distribution of the variables will be tested. We are going to conduct Univariate test including Log rank test and Mann Whitney or independent sample t-test, GLM, survival analysis and multivariable model of Cox proportional hazard model (CPHM). Statistical software of PASW version 21 and SAS will be used.

References:

1. Pandi-Perumal SR, Bahammam AS, Ojike NI, Akinseye OA, Kendzerska T, Buttoo K, et al. Melatonin and Human Cardiovascular Disease. J Cardiovasc Pharmacol Ther. 2016.
2. Dominguez-Rodriguez A, Abreu-Gonzalez P, Reiter RJ. Melatonin and cardiovascular disease: myth or reality? Rev Esp Cardiol (Engl Ed). 2012;65(3):215-8.
3. Ekmekcioglu C, Thalhammer T, Humpeler S, Mehrabi MR, Glogar HD, Holzenbein T, et al. The melatonin receptor subtype MT2 is present in the human cardiovascular system. J Pineal Res. 2003;35(1):40-4.
4. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin--a pleiotropic, orchestrating regulator molecule. Prog Neurobiol. 2011;93(3):350-84.
5. Jonas M, Garfinkel D, Zisapel N, Laudon M, Grossman E. Impaired nocturnal melatonin secretion in non-dipper hypertensive patients. Blood Press. 2003;12(1):19-24.
6. Girotti L, Lago M, Ianovsky O, Elizari MV, Dini A, Perez Lloret S, et al. Low urinary 6-sulfatoxymelatonin levels in patients with severe congestive heart failure. Endocrine. 2003;22(3):245-8.
7. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia MJ, Sanchez J, Marrero F, de Armas-Trujillo D. Decreased nocturnal melatonin levels during acute myocardial infarction. J Pineal Res. 2002;33(4):248-52.
8. Dominguez-Rodriguez A, Abreu-Gonzalez P, Sanchez-Sanchez JJ, Kaski JC, Reiter RJ. Melatonin and circadian biology in human cardiovascular disease. J Pineal Res. 2010;49(1):14-22.
9. Arangino S, Cagnacci A, Angiolucci M, Vacca AM, Longu G, Volpe A, et al. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. The American journal of cardiology. 1999;83(9):1417-9.
10. Cagnacci A, Arangino S, Angiolucci M, Maschio E, Longu G, Melis GB. Potentially beneficial cardiovascular effects of melatonin administration in women. J Pineal Res. 1997;22(1):16-9.
11. Cagnacci A, Arangino S, Angiolucci M, Maschio E, Melis GB. Influences of melatonin administration on the circulation of women. The American journal of physiology. 1998;274(2 Pt 2):R335-8.
12. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension. 2004;43(2):192-7.
13. Cagnacci A, Cannoletta M, Renzi A, Baldassari F, Arangino S, Volpe A. Prolonged melatonin administration decreases nocturnal blood pressure in women. American journal of hypertension. 2005;18(12 Pt 1):1614-8.

14. Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, et al. Melatonin reduces night blood pressure in patients with nocturnal hypertension. The American journal of medicine. 2006;119(10):898-902.
15. Gubin DG, Gubin GD, Gapon LI, Weinert D. Daily Melatonin Administration Attenuates Age-Dependent Disturbances of Cardiovascular Rhythms. Curr Aging Sci. 2016;9(1):5-13.
16. Mesri Alamdari N, Mahdavi R, Roshanravan N, Lotfi Yaghin N, Ostadrahimi AR, Faramarzi E. A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. Horm Metab Res. 2015;47(7):504-8.
17. Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res. 2011;50(3):261-6.
18. Galley HF, Lowes DA, Allen L, Cameron G, Aucott LS, Webster NR. Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. J Pineal Res. 2014;56(4):427-38.
19. Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. Br J Clin Pharmacol. 2000;49(5):423-7.
20. Rechcinski T, Trzos E, Wierzbowska-Drabik K, Krzeminska-Pakula M, Kurpesa M. Melatonin for nondippers with coronary artery disease: assessment of blood pressure profile and heart rate variability. Hypertension research : official journal of the Japanese Society of Hypertension. 2010;33(1):56-61.
21. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, et al. Recommendations for blood pressure measurement in humans: an AHA scientific statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. J Clin Hypertens (Greenwich). 2005;7(2):102-9.
22. Fuchs SC, Poli-de-Figueiredo CE, Figueiredo Neto JA, Scala LC, Whelton PK, Mosele F, et al. Effectiveness of Chlorthalidone Plus Amiloride for the Prevention of Hypertension: The PREVER-Prevention Randomized Clinical Trial. J Am Heart Assoc. 2016;5(12).
23. Collier SR, Landram MJ. Treatment of prehypertension: lifestyle and/or medication. Vasc Health Risk Manag. 2012;8:613-9.
24. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. Jama. 1992;267(9):1213-20.
25. Bavikati VV, Sperling LS, Salmon RD, Faircloth GC, Gordon TL, Franklin BA, et al. Effect of comprehensive therapeutic lifestyle changes on prehypertension. Am J Cardiol. 2008;102(12):1677-80.
26. Hageman PA, Pullen CH, Hertzog M, Boeckner LS. Effectiveness of tailored lifestyle interventions, using web-based and print-mail, for reducing blood pressure among rural women with prehypertension: main results of the Wellness for Women: DASHing towards Health clinical trial. The international journal of behavioral nutrition and physical activity. 2014;11:148.
27. Liao IC, Chen SL, Wang MY, Tsai PS. Effects of Massage on Blood Pressure in Patients With Hypertension and Prehypertension: A Meta-analysis of Randomized Controlled Trials. The Journal of cardiovascular nursing. 2016;31(1):73-83.
28. Marquez-Celedonio FG, Texon-Fernandez O, Chavez-Negrete A, Hernandez-Lopez S, Marin-Rendon S, Berlin-Lascurain S. [Clinical effect of lifestyle modification on cardiovascular risk in prehypertensives: PREHIPER I study]. Revista espanola de cardiologia. 2009;62(1):86-90.
29. Papadopoulos DP, Makris TK, Papademetriou V. Is it time to treat prehypertension? Hypertension research : official journal of the Japanese Society of Hypertension. 2008;31(9):1681-6.
30. Pengpid S, Peltzer K, Skaal L. Efficacy of a church-based lifestyle intervention programme to control high normal blood pressure and/or high normal blood glucose in church members: a randomized controlled trial in Pretoria, South Africa. BMC Public Health. 2014;14:568.
31. Pongwecharak J, Treeranurat T. Lifestyle changes for prehypertension with other cardiovascular risk factors: findings from Thailand. J Am Pharm Assoc (2003). 2011;51(6):719-26.
32. Tseng CD, Yen AM, Chiu SY, Chen LS, Chen HH, Chang SH. A predictive model for risk of prehypertension and hypertension and expected benefit after population-based life-style modification (KCIS No. 24). Am J Hypertens. 2012;25(2):171-9.

33. Zhao XS, Wang R, Bin LR, Wa SQ. Intervention for prehypertension and its cardiovascular risk factors in Inner Mongolia. Genetics and molecular research : GMR. 2014;13(3):4867-82.
34. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1-45.
35. Halladin NL, Busch SE, Jensen SE, Hansen HS, Zaremba T, Aaroe J, et al. Intracoronary and systemic melatonin to patients with acute myocardial infarction: protocol for the IMPACT trial. Dan Med J. 2014;61(2):A4773.