Effects of melatonin on left ventricular ejection fraction and functional class of patients with heart failure: A randomized, double-blind, placebo-controlled trial

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BACKGROUND: Melatonin, a hormone secreted by the pineal gland, has multiple effects on circadian physiology, blood pressure, and coronary blood flow. It has also free radical scavenger and anti-oxidative activity. This study was planned to evaluate the effects of melatonin on left ventricular function of patients with heart failure. **METHODS:** In this randomized double-blind clinical trial, 60 patients with heart failure (based on clinical and echocardiography findings) admitted to two hospitals in Isfahan, Iran in 2010 received 3 mg melatonin or placebo for 2 months. New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) in each group, before and after the study were compared. Comparisons were also made between the two groups each step. The data was analyzed by appropriate statistical methods. **RESULTS:** Overall, 60 patients (41 men and 19 women) participated in this study. LVEF increased from 31.7 to 37.6 in the case group ($p < 0.001$) and from 34.1 to 35.2 in the control group ($p = 0.420$). NYHA functional class improved only in the case group ($p = 0.014$ versus 0.317). **CONCLUSIONS:** This study revealed that melatonin may have beneficial effects on patients with heart failure. However, larger studies may help to define its role in heart failure management.

KEYWORDS: Melatonin, Heart Failure, New York Heart Association, Left Ventricular Ejection Fraction

BACKGROUND

The prevalence and incidence rates of heart failure remain high. Heart failure has affected nearly 23 million people around the world. In individuals aged 55, almost 1 in 3 will develop heart failure during their remaining lifespan. Heart failure continues to be a fatal disease, with only 35% surviving 5 years after the first diagnosis.[1] Frequent articles have evaluated the role of oxidative stress in patients with heart failure and disease outcome. Oxidative stress, resulting from increased superoxide generation by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, is implicated in the pathophysiology of human heart failure.[2] Increased levels of malondialdehyde (MDA)-like activity, an index of peroxidation in patients with ischemic and non-ischemic cardiomyopathy, have been suggested to have a reverse correlation with left ventricular ejection fraction (LVEF) and direct relations with disease severity and duration.[3]

Melatonin is a hormone in the brain made from tryptophan amino acid by the pineal gland. The stimulation of synthesis and secretion of melatonin by light and darkness suggests the role of melatonin in circadian rhythm and various body functions. Some studies have reported circulating melatonin levels to be low in patients with congestive heart failure (HF). Such a decrease may precede the aggravation of heart failure.[4] Melatonin has anti-oxidative activity to which many of its therapeutic or preventive benefits are related. There have been many in vitro or animal studies on anti-oxidative effects of melatonin. It may thus be considered as an option in prevention or treatment of conditions that are associated with oxidative stress. So far, many studies have assessed the beneficial effects of melatonin on cardiovascular system. Experimental studies have documented the beneficial effects of the endogenously produced antioxidant, melatonin, in reducing tissue damage and limiting cardiac pathophysiology in models of experimental ischemia/reperfusion. In studies on rodents, melatonin has been shown to be highly effective in limiting abnormal cardiac physiology and loss of critical heart tissue resulting from ischemia/reperfusion injury.[5] Melatonin may also be useful in reducing cardiac hypertrophy in some situations and thereby limiting the frequency of heart failure.[3] It ameliorates hypertrophic growth of the myocardium and confronts cardio-toxic effects of cancer chemotherapy.[6] Overall, the findings from human and animal

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studies support the consideration of melatonin as a cardio-protective agent.[5]

To our knowledge, no previous study has evaluated melatonin in stable patients with heart failure. Based on the abovementioned data, we performed this study to evaluate the clinical effects of melatonin in patients with heart failure.

METHODS

This study was a double-blind randomized clinical trial on patients with heart failure who referred to training centers of Shahid Chamran and Khorshid Hospitals in Isfahan, Iran during 2010. For establishing a definite diagnosis of heart failure in this study, based on Framingham criteria for CHF, two major or one major and two minor criteria had to be present concurrently.[7] Patients with New York Heart Association (NYHA) functional classes II and III were included if they had LVEF less than 50% as determined by transthoracic echocardiography and had been stabile for at least 3 months (no clinical exacerbation or changes in their medications since at least 3 months before participation). On the other hand, individuals with diabetes mellitus, history of bleeding disorders or warfarin use, and NYHA functional class I and IV were not included. The participants were excluded at any time during the study in case of the incidence of ecchymosis, petechiae, or any evidence of coagulation disorder, unacceptable side effects such as severe gastrointestinal symptoms, drowsiness, and mood changes, or any clinical condition mandating melatonin stop (mild side effects were planned to be recorded).

After obtaining individual informed consents, the participants were divided into two groups of placebo or melatonin by picking up a card from a box containing 30 cards labeled A and 30 cards labeled B, respectively. We prescribed 3 mg melatonin or placebo before bedtime for 2 months for the study and the control groups, respectively. Placebo pills contained cellulose and were similar to oral melatonin in shape, size, and taste. Every week, drug consumption by the patients was assessed by counting the remaining pills. The functional classes of the patients were assessed based on questions about the amount of daily activity. The values were recorded in the questionnaires according to the NYHA classification criteria. Transthoracic echocardiography and LVEF measurement were performed using the modified biplane Simpson's method. Both study and control patients underwent echocardiography before and 2 months after taking the drugs.

The data collection tool was a questionnaire including demographic information, diseases history, duration of heart failure, NYHA functional classes, and LVEF values before and after the intervention. Change in functional class and ejection fraction (EF), before and after the study, in each group and the amount of changes between the two groups were compared. Functional class values were compared before and after the intervention in each group by Wilcoxon test and between the two groups using Mann-Whitney test. The mean LVEF values of the two groups were compared using the student's t-test. Comparisons between the LVEF values before and after the intervention in each group were performed by paired t-test. In addition, to compare EF changes within groups and between groups simultaneously, repeated-measures analysis of variance (ANOVA) was used. All analyses were conducted in SPSS18 (SPSS Inc., Chicago, IL, USA).

RESULTS

This study included 60 patients (41 men, 19 women) whose baseline characteristics are summarized in table 1 However, only 39 patients completed the study. In fact, 10 patients (4 in the case and 6 in the control group) did not follow the study for personal reasons (Figure 1) while 11 patients (4 in the case and 7 in the control group) developed side effects and did not continue the study. In the control group, one subject was affected by chest discomfort and 3 had headaches. In the case group, one patient developed rectorrhagia, two had headaches, one experienced gastrointestinal symptoms, and 2 had overnight sleep disturbance.

Improvements in LVEF were detected in 78% of the case group and 56% of the control group (p = 0.143). LVEF increased by 1.12% in the control group and by 5.82% in the case group (p = 0.021). NYHA functional class improved significantly only in the case group (p = 0.014 vs. 0.317) (Tables 2 and 3).

Table 1. Baseline data of the participants

	Control Group	Case Group	Total	P-value
Sex (Women/men)	6/10	6/17	12/27	0.447
Age	65.8 ± 12.5	63.6 ± 6.6	64.5 ± 9.4	0.949
Height	165.0 ± 10.3	165.1 ± 9.0	165.4 ± 9.4	0.832
Weight	68.6 ± 15.3	69.7 ± 8.1	69.3 ± 11.4	0.778
Body mass index	24.7 ± 4.0	25.6 ± 2.7	25.2 ± 3.2	0.421
Ejection fraction	34.1 ± 9.9	31.7 ± 8.6	32.7 ± 8.6	0.412

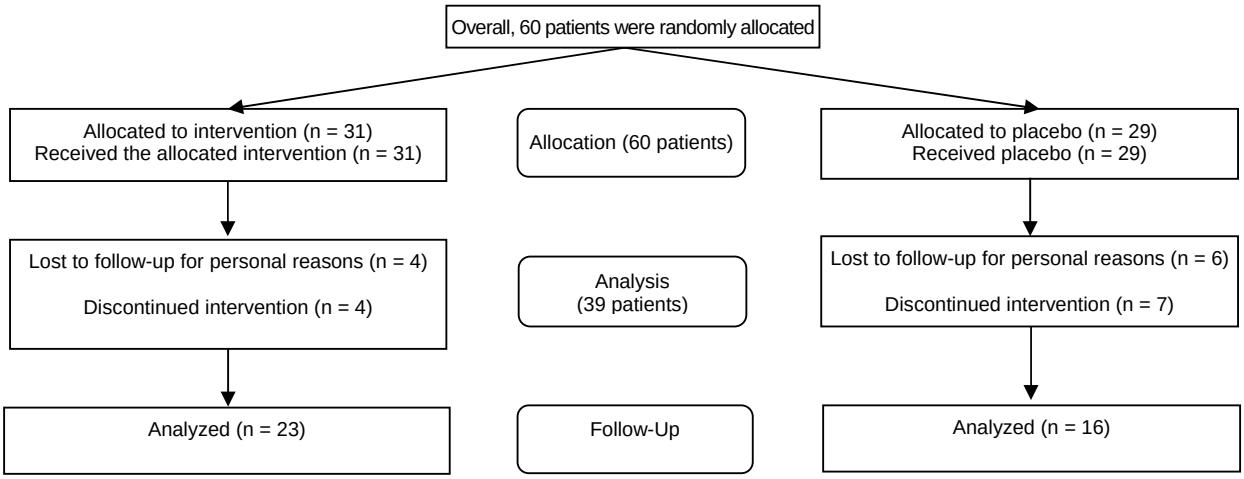

Figure 1: flow diagram of the study

DISCUSSION

To our knowledge, this was the first study to evaluate the direct effects of melatonin on patients with heart failure. The present study showed that melatonin may improve LVEF and functional class of patients with heart failure of different etiologies. As the patients were stable since at least 3 months before the study, the extra beneficial effects of melatonin were added to the patients' current medications.

Melatonin, N-acetyl-5-methoxytrypamine, is best known for its influence on circadian physiology.[8] Although initially believed to be produced exclusively in the pineal gland, recent data has indicated that melatonin is likely to be produced also in the heart.[9]

Melatonin has both receptor-mediated and receptor-independent mechanisms.[10,11] Classic melatonin membrane receptors are present in the cardiovascular system.[12] To date, 3 major melatoninergic membrane receptors have been identified in mammals. They are denoted as MT1, MT2, and MT3 receptors. Among them, MT1 and MT2 receptors share a common 7-transmembrane structure and are negatively coupled with adenylate cyclase via a pertussis toxin-sensitive G-protein.[13] In experimental studies, melatonin has been shown to increase coronary blood flow and cardiac function through the involvement of MT1/MT2 receptors, β-adrenoreceptors, and nitric oxide (NO) release.[14] The receptor-independent actions of melatonin relate to its antioxidant function.[15,16]

Reactive oxygen species mediate the downregulation of metabolically important genes such as glucose transporter type 4 (GLUT4) in the heart.[17] In human heart failure, both ventricles are targets of NADPH oxidase superoxide generation which in turn may trigger the coordinated activation of downstream signaling components. This pathway may contribute to adverse remodeling of the left and right ventricles and subsequent progression toward end-stage heart failure.[2]

Much of the tissue destruction that occurs during ischemia/reperfusion injury in the heart is the result of derivatives of oxygen including free radicals and their by-products.[5] Melatonin and several of its metabolites

Table 2. The distribution of functional classes in the two groups before and after the intervention

Functional class	Control group		Study group	
	Before	After	Before	After
I	0	1 (6.3%)	0	6 (26.1%)
II	14 (87.5%)	13 (81.3%)	20 (87.0%)	14 (60.9%)
III	2 (12.5%)	2 (12.5%)	3 (13.0%)	3 (13.0%)
P-value	0.745	0.268	0.745	0.268

Table 3. Left ventricular ejection fraction (LVEF) and its changes in the two groups before and after the intervention

Group	LVEF Before	LVEF After	LVEF Change
Control	34.1 ± 9.9	35.3 ± 6.9	1.1 ± 5.5
Case	31.8 ± 7.8	37.6 ± 7.1	5.8 ± 6.3
Total	32.7 ± 8.6	36.6 ± 7.0	3.9 ± 6.3
P-value	0.412	0.309	0.021

are potent antioxidants.[13,18,19] By this mechanism, melatonin may promote cardioprotection against ischemia/reperfusion injury.[20]

Another mechanism for explanation of beneficial effects of melatonin in our patients may be its sleep correction properties. Certain physiologic events occurring during sleep as well as long-term unsatisfactory sleep may cause or increase the risk of cardiovascular conditions such as hypertension, atherosclerosis, stroke, and cardiac arrhythmias. Human subjects whose nocturnal arterial blood pressure fails to show the normal decrement during sleep (nondippers) are also prone to sleep poorly, exhibit increased sympathetic nervous system (SNS) activity during sleep, and have an increased risk of total and cardiovascular disease mortality.[21]

Our study had some limitations. First, it was based on cardiovascular outcomes. Although such outcomes are important for clinical application of melatonin, they may not explain the exact underlying mechanism of the observed benefits. Another limitation was the high percent of loss to follow up which might have affected the comparisons between the two groups.

In conclusion, the present study showed that melatonin may be an adjunctive option to improve LVEF and functional class of patients with heart failure of different etiologies. However, larger studies would help to more clearly define its role in heart failure management.

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