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Original Research Article

Effect of adjunctive melatonin on angina symptom burden and sleep quality in patients with stable angina pectoris: a randomized placebo-controlled trial

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Abstract

Purpose: *To examine the effect of adjunctive melatonin on the burden of angina symptoms and sleep quality in stable angina pectoris patients taking standard anti-anginal therapy.*
Methods: *This randomized, double-blind, placebo-controlled, parallel-group study involved adult patients (40 – 70 years) with stable angina. A total of 100 patients were enrolled, comprising 55 in melatonin group and 45 in placebo group. Participants received melatonin 5 mg or matching placebo orally once daily at bedtime for 8 weeks, alongside standard anti-anginal therapy. Angina symptoms, nitrate use, and sleep quality (PSQI) were assessed at baseline, week 4, and week 8.*
Results: *Weekly angina episodes decreased from 3.4 ± 1.7 to 1.3 ± 1.1 in melatonin group, compared with 3.3 ± 1.8 to 2.7 ± 1.6 in placebo group. Angina severity decreased significantly with melatonin, versus placebo ($p < 0.05$). Nitrate use declined from 3.0 ± 1.8 to 1.0 ± 1.1 doses/week in melatonin group and from 2.9 ± 1.7 to 2.4 ± 1.5 in placebo group. Pittsburgh Sleep Quality Index (PSQI) improved from 9.1 ± 3.0 to 6.2 ± 2.7 with melatonin, compared with 9.3 ± 3.2 to 8.7 ± 3.0 with placebo. Between-group, changes from baseline to week 8 favoured melatonin for weekly angina episodes, angina severity, and PSQI global score ($p < 0.001$).*
Conclusion: *Adjunctive melatonin at bedtime for 8 weeks is associated with improved angina symptoms, reduced nitrate use, and better sleep quality in patients with stable angina. Larger studies are needed to confirm these findings.*

Keywords: *Melatonin, Stable angina, Sleep quality, PSQI, Nitrate use, Randomized controlled trial, Chronic coronary syndrome*

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INTRODUCTION

Angina pectoris is one of the most common symptoms in chronic coronary syndrome, commonly described as recurrent chest pain or discomfort brought on by physical activity or emotional distress and eased by rest and/or short-acting nitrates. While current treatment strategies include anti-anginal medication, secondary prevention, lifestyle changes and, when indicated, revascularization, many patients still report residual anginal symptoms despite optimal medical therapy, which limit physical function and well-being. The latest guidelines stress that the goals of treatment for chronic coronary syndromes are not only to prevent major cardiovascular events, but also to improve symptom control and quality of life [1].

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The impacts of sleep disturbance are being recognized as a critical aspect of cardiovascular disease. Disturbed sleep (such as poor sleep quality, sleep fragmentation and reduced sleep duration) may lead to autonomic dysfunction, inflammation, endothelial dysfunction, fatigue, decreased functional capacity and adverse cardiovascular risk factors. In those with chronic coronary disease, sleep disturbance may also increase symptom awareness, lower exercise capacity and impact quality of life. The self-reported, validated Pittsburgh Sleep Quality Index (PSQI) questionnaire is commonly used to measure subjective sleep quality and sleep disturbances over the past month [2–5].

Melatonin is a hormone that is largely responsible for sleep regulation and the body clock. Exogenous melatonin is considered a chronobiotic agent, which can improve sleep timing and subjective sleep quality in those with disturbed sleep. Recently, the potential antioxidant, anti-inflammatory and cardiometabolic effects of melatonin have been studied, suggesting a potential role as an adjunctive therapy in patients with cardiovascular disease. Thus, testing melatonin in stable angina patients may help us understand whether the benefits of improved sleep quality extend to decreased angina symptoms [6–8].

While there is some evidence for melatonin in cardiovascular disease, the majority of evidence has reported on its effects in disease states such as oxidative stress, hypertension, ischemia-reperfusion injury and the peri-operative period, rather than in stable outpatient angina. With respect to chronic coronary syndromes, the importance of melatonin as an add-on to conventional anti-anginal treatment is relatively unknown. Specifically, there is a paucity of randomized studies that have investigated the effect of melatonin on patient-centered outcomes of angina frequency, angina severity and subjective sleep quality assessed using validated instruments such as angina diaries and the PSQI. This is significant because residual angina and sleep disturbances commonly impact quality of life, but may not always be completely managed by standard anti-anginal drugs [1,2,8].

The aim of this study was to evaluate the effect of adjunctive melatonin on angina symptoms and sleep quality in patients with stable angina pectoris receiving standard anti-anginal therapy. The primary objective was to compare changes in weekly angina episode frequency between the melatonin and placebo groups. Secondary objectives were to compare changes in angina severity, short-acting nitrate use, and sleep quality assessed using the Pittsburgh Sleep Quality Index (PSQI) [5].

METHODS

Study design

The trial randomly assigned participants in a 1:1 ratio to take 8 weeks of oral melatonin or identical placebo while continuing their standard anti-anginal treatment. A parallel-group design was chosen to compare the active supplement with placebo, and to avoid potential carry-over effects that may be seen in a crossover design [9]. The duration of intervention was 8 weeks, with assessments at baseline, week 4 and week 8. Participants continued with their usual medication regimen for stable angina, which can include anti-anginal medication and/or secondary prevention medication, if indicated (Figure 1). There were no planned changes to standard therapy as part of the trial, but medication changes (as per clinical need) were documented during follow-up.

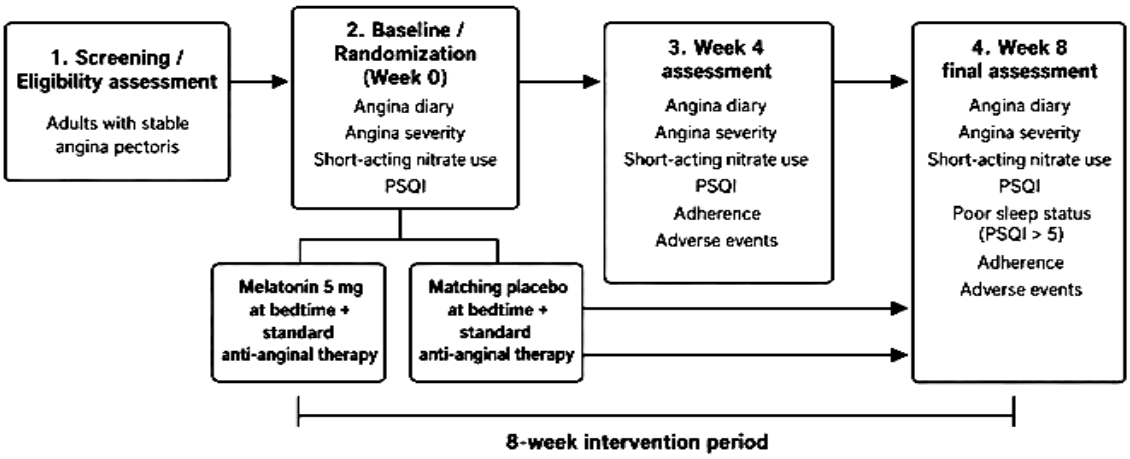

Figure 1: Study design and assessment timeline

Study setting and participants

Patients were recruited from two outpatient clinics, Dr. Mustafa Al-Sudani's Clinic and Dr. Ali Abdul-Zahra's Clinic, in Basra, Iraq, between 19 January and 16 February 2026. Participant follow-up continued until 16 April 2026. Patients were enrolled from a cardiology or internal medicine clinic that provided care for patients with stable angina pectoris. Participants were adults, 40 – 70 years old, with clinically verified stable angina (diagnosed as per Canadian Cardiovascular Society criteria) and stable background standard anti-anginal treatment for at least 4 weeks prior to entering the study. The stable background treatment criterion sought to decrease the effects of initiation or recent dose modification of anti-anginal medications [10,11]. Patients were identified from medical records in the outpatient clinic. Potentially eligible participants were approached by the research team, given information about the purposes of the research and its procedures, and invited to participate. Informed consent was obtained prior to baseline evaluation and randomization. The target population was adults with stable angina confirmed by the treating physician at cardiology or internal medicine clinics. Table 1 shows participant allocation with stable diagnosis and background medication.

Table 1: Participant enrollment and analysis population

Group	Enrolled (n)	Analyzed (n)
Melatonin	55	55
Placebo	45	45
Total	100	100

Inclusion criteria

Participants were eligible for inclusion if they fulfilled all of the criteria as listed in Table 2.

Table 2: Inclusion criteria

Criteria	Description
Age	40–70 years
Diagnosis	Clinically documented stable angina pectoris
Symptom classification	Stable angina assessed using Canadian Cardiovascular Society classification
Background treatment	Stable anti-anginal therapy for at least 4 weeks before enrollment
Consent	Ability and willingness to provide written informed consent

Exclusion criteria

Participants were excluded if they had any condition likely to affect angina symptoms, sleep quality, oxidative status, safety, or interpretation of the intervention effect (Table 3).

Table 3: Exclusion criteria

Criteria	Description
Recent acute coronary syndrome	Myocardial infarction or unstable angina within the previous 3 months
Renal impairment	Known severe renal impairment
Hepatic impairment	Known severe hepatic impairment
Recent supplement use	Use of melatonin or antioxidant supplements within the previous month
Sleep disorders	Sleep disorders requiring pharmacological treatment
Uncontrolled comorbidity	Uncontrolled hypertension or poorly controlled diabetes mellitus

These criteria were intended to protect participant safety and reduce the possibility that observed changes in symptoms or sleep quality were due to unstable disease, recent treatment changes, or external supplementation.

Randomization and blinding

Following baseline assessments, participants who qualified for the study were randomly assigned to melatonin or placebo groups in a 1:1 ratio. Randomization was conducted using a computer-generated sequence that was kept unknown to investigators responsible for recruitment, assessments and data analysis. Medication was packaged and dispensed in accordance with the code to ensure that neither the participants nor the investigators knew treatment allocation during the intervention. The trial was double-blinded. Neither the participants, treating physicians, assessors of outcomes nor laboratory staff knew which group participants had been assigned to. Melatonin and placebo capsules looked, were packaged, and were taken the same way [9]. Blinding was important because the primary outcome (weekly angina episode frequency) and secondary patient-reported outcomes (angina severity, short-acting nitrate use, and PSQI score) could be influenced by participants' knowledge of treatment allocation.

Intervention

Melatonin was a product of Oxford Pharma, London, United Kingdom. The matching placebo capsules contained starch and were prepared in the pharmacy. The pharmacist in charge coded both the melatonin and placebo capsules to maintain blinding. Melatonin 5 mg was given orally before bed for 8 weeks to the intervention group. The timing of administration was selected based on the physiological circadian actions of melatonin in regulating sleep and wakefulness, and to potentially enhance its beneficial effects on sleep. Those in the control group also took a placebo capsule once daily at bedtime for 8 weeks. Participants in both groups continued their usual anti-anginal therapy. Concomitant medications included beta blockers, calcium channel blockers, long-acting nitrates, antiplatelet agents, statins and renin-angiotensin system blockers at the discretion of the physician. Pill count and participant reporting were used to monitor compliance during follow-up visits. Participants were asked not to take any other melatonin or antioxidant supplements while in the study.

Outcomes

In the current manuscript, the emphasis was on the clinical and patient-oriented, rather than the biochemical. The primary clinical outcome was change in the frequency of angina episodes per week from baseline to week 8. The frequency of angina episodes was determined from a standard angina diary which patients kept at home and was reviewed with the research team at subsequent visits [12]. Secondary outcomes were change in angina severity, change in short-acting nitrate use per week, change in global Pittsburgh Sleep Quality Index (PSQI) score, proportion of poor sleepers (PSQI score > 5), and safety/tolerability (Table 4). Angina severity was assessed using an 11-point Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). Severity scores were recorded in the patients' angina diaries. Safety was determined via systematic questioning, spontaneous reporting of adverse events, assessment of intercurrent illness and medication changes at each visit [13].

Table 4: Study outcomes and assessment schedule

Outcome	Measurement tool	Baseline	Week 4	Week 8
Weekly angina episodes	Standardized angina diary	Yes	Yes	Yes
Angina severity	Standardized angina diary	Yes	Yes	Yes
Short-acting nitrate use	Angina diary/self-report	Yes	Yes	Yes
Sleep quality	PSQI global score	Yes	Yes	Yes
Poor sleep status	PSQI > 5	Yes	No/optional	Yes
Adherence	Pill count and self-report	No	Yes	Yes
Adverse events	Structured interview and spontaneous reporting	No	Yes	Yes

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA) .Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages.

RESULTS

Participant flow

A total of 150 patients with stable angina pectoris were enrolled in the study. One half of these were randomized to receive melatonin and one half to receive placebo, as an adjunct to anti-anginal therapy. Over the course of the trial, some patients were not included in the final analysis due to loss to follow-up, withdrawal of consent, significant protocol deviation, non-adherence, or lack of post-baseline data. The study initially aimed to recruit 150 patients with stable angina pectoris. However, 100 patients were actually enrolled and included in the study: 55 in melatonin group and 45 in placebo group. All statistical analyses were performed using data from these 100 participants. No intention-to-treat analysis was conducted.

Baseline characteristics

The baseline characteristics of both melatonin and placebo groups are illustrated in Table 5.

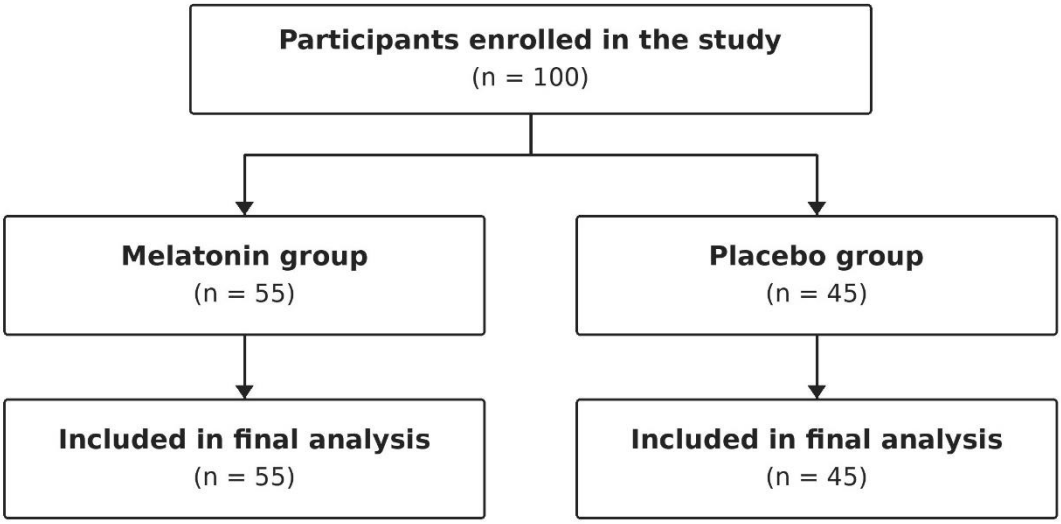

Figure 2: CONSORT participant flow diagram

Table 5: Baseline characteristics of the final analyzed population

Characteristic	Melatonin group (n = 55)	Placebo group (n = 45)
Age, years, mean ± SD	58.4 ± 7.3	57.9 ± 7.8
Male sex, n (%)	33 (60.0)	28 (62.2)
BMI, kg/m², mean ± SD	29.4 ± 3.6	29.1 ± 3.9
BMI ≥ 30 kg/m², n (%)	24 (43.6)	19 (42.2)
Duration of angina, years, mean ± SD	5.9 ± 3.4	6.2 ± 3.7
Hypertension, n (%)	38 (69.1)	32 (71.1)
Diabetes mellitus, n (%)	23 (41.8)	20 (44.4)
Dyslipidemia, n (%)	42 (76.4)	35 (77.8)
Current smoker, n (%)	15 (27.3)	11 (24.4)
Beta-blocker use, n (%)	44 (80.0)	37 (82.2)
Calcium channel blocker use, n (%)	28 (50.9)	22 (48.9)
Long-acting nitrate use, n (%)	31 (56.4)	26 (57.8)
ACE inhibitor / ARB use, n (%)	37 (67.3)	31 (68.9)
Statin use, n (%)	48 (87.3)	40 (88.9)
Antiplatelet therapy, n (%)	52 (94.5)	42 (93.3)
Weekly angina episodes, mean ± SD	3.4 ± 1.7	3.3 ± 1.8
PSQI global score, mean ± SD	9.1 ± 3.0	9.3 ± 3.2
Poor sleep, PSQI > 5, n (%)	46 (83.6)	37 (82.2)

Angina symptom outcomes

Figure 3 illustrates the changes in weekly angina episodes over the 8-week intervention. From baseline to week 8, mean weekly angina episodes decreased by 2.1 episodes in melatonin group compared with 0.6 episodes in placebo group. Mean angina severity decreased by 2.3 and 0.8 points, respectively. The reported between-group comparisons favored melatonin for both outcomes ($p < 0.001$ for each). Short-acting nitrate use decreased by a mean of 2.0 and 0.5 doses per week, respectively. Detailed results are presented in Table 6.

Sleep quality outcomes

Both groups had poor sleep quality at baseline, with mean PSQI global scores greater than the typical cut-off of 5. At baseline, the PSQI scores in melatonin and placebo groups were 9.1 ± 3.0 and 9.3 ± 3.2, respectively, suggesting similar levels of subjective sleep disturbance at the beginning of the study. Over time, melatonin group showed improvement in PSQI scores. The mean score decreased to 7.6 ± 2.8 at week 4 and further to 6.2 ± 2.7 at week 8. By comparison, placebo group demonstrated a small improvement in PSQI scores: 9.0 ± 3.1 at week 4 and 8.7 ± 3.0 at week 8 (Table 7).

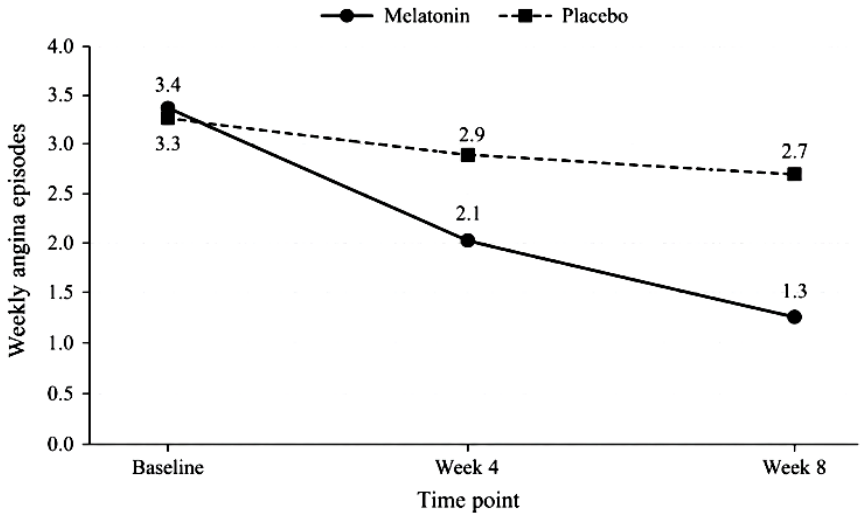

Figure 3: Change in weekly angina episodes over time

Table 6: Angina symptom profile at baseline, week 4, and week 8

Outcome	Time point	Melatonin group (n=55)	Placebo group (n=45)	Interpretation
Weekly angina episodes	Baseline	3.4 ± 1.7	3.3 ± 1.8	Comparable baseline burden
	Week 4	2.1 ± 1.4	2.9 ± 1.7	Greater early reduction with melatonin
	Week 8	1.3 ± 1.1	2.7 ± 1.6	Sustained improvement with melatonin
	Mean change, Week 8 − baseline	−2.1 ± 1.6	−0.6 ± 1.5	Between-group difference favored melatonin, p < 0.001
Angina severity score	Baseline	6.1 ± 1.4	6.0 ± 1.5	Comparable baseline severity
	Week 4	4.7 ± 1.5	5.7 ± 1.6	Greater symptom relief with melatonin
	Week 8	3.8 ± 1.6	5.2 ± 1.7	Lower final severity with melatonin
	Mean change, Week 8 − baseline	−2.3 ± 1.7	−0.8 ± 1.5	Between-group difference favored melatonin, p < 0.001
Short-acting nitrate use, doses/week	Baseline	3.0 ± 1.8	2.9 ± 1.7	Comparable baseline use
	Week 4	1.7 ± 1.4	2.9 ± 1.7	Reduced rescue use with melatonin
	Week 8	1.0 ± 1.1	2.4 ± 1.5	Marked reduction with melatonin

Values are mean ± SD

Table 7: Pittsburgh Sleep Quality Index outcomes

Outcome	Time point	Melatonin group (n = 55)	Placebo group (n = 45)	Interpretation
PSQI global score, mean ± SD	Baseline	9.1 ± 3.0	9.3 ± 3.2	Comparable poor sleep quality
	Week 4	7.6 ± 2.8	9.0 ± 3.1	Greater early improvement with melatonin
	Week 8	6.2 ± 2.7	8.7 ± 3.0	Sustained improvement with melatonin
	Mean change, Week 8 − baseline	−2.9 ± 2.3	−0.6 ± 2.0	Between-group difference −2.3 points; p < 0.001
Poor sleepers, PSQI > 5, n (%)	Baseline	46 (83.6)	37 (82.2)	Similar baseline proportion
	Week 8	33 (60.0)	35 (77.8)	Fewer poor sleepers after melatonin

Values are mean ± SD

Safety and tolerability

The most frequently reported adverse events in melatonin group were daytime sleepiness, dizziness or light-headedness, headache, and vivid or unusual dreams. These were in line with the expected effect profile of melatonin and did not raise a safety alert. Gastrointestinal symptoms and cardiovascular events were rare and equally distributed between groups. There were no deaths, and few serious adverse events, which were not considered to be related to the study medication.

Table 8: Adverse events during the 8-week intervention. N (%)

Adverse event	Melatonin group (n=55)	Placebo group (n=45)
Any adverse event	18 (32.7)	15 (33.3)
Daytime sleepiness	7 (12.7)	3 (6.7)
Dizziness/light-headedness	5 (9.1)	4 (8.9)
Headache	4 (7.3)	3 (6.7)
Vivid/unusual dreams	4 (7.3)	1 (2.2)
Nausea	3 (5.5)	2 (4.4)
Dyspepsia / abdominal discomfort	2 (3.6)	2 (4.4)
Palpitations	2 (3.6)	2 (4.4)
Symptomatic hypotension	2 (3.6)	3 (6.7)
Unstable angina requiring hospitalization	1 (1.8)	0 (0.0)
Heart failure hospitalization	0 (0.0)	1 (2.2)
Pneumonia requiring hospitalization	0 (0.0)	1 (2.2)
Death	0 (0.0)	0 (0.0)
Discontinuation due to adverse event	2 (3.6)	3 (6.7)

The comparable overall adverse-event rate between groups supports the short-term tolerability of melatonin 5 mg once daily at bedtime in this stable angina population. Although daytime sleepiness and vivid dreams were more frequent with melatonin, these events were generally mild and did not produce a clinically significant increase in treatment discontinuation.

DISCUSSION

In this double-blind, placebo-controlled study, treatment with adjuvant melatonin for 8 weeks resulted in a greater improvement in angina frequency, angina severity, use of short-acting nitrates, and sleep quality than placebo in patients with stable angina pectoris who were on standard anti-anginal therapy. This was not an isolated improvement, but was consistent across a range of patient-reported outcomes. There was a greater reduction in weekly angina episodes in melatonin group, with a reduction of about two episodes per week by Week 8, while placebo group only showed a gentle improvement. This level of improvement is important from a clinical perspective because the number of angina episodes impacts the ability to perform daily tasks, exercise capacity and quality of life in patients with chronic coronary syndromes [1,2,7]. The reduction in diary-recorded short-acting nitrate use was consistent with the reported improvement in angina symptoms; however, nitrate use was self-reported and therefore does not provide independent objective confirmation of treatment benefit. The use of rescue nitrates is highly associated with the frequency and severity of angina attacks; therefore, its reduction in melatonin group underlines the clinical relevance of the improvement in angina symptoms. Similarly, the reduction in angina severity suggests that melatonin might not have merely reduced the frequency of anginal episodes but also the degree of chest pain.

Moreover, melatonin had a significant impact on sleep quality, as indicated by the improvement in the PSQI global score. This is plausible given that melatonin is a chronobiotic hormone that regulates the circadian cycle and sleep-wake cycle. Better sleep may lead to improvements in fatigue, emotional stress response, autonomic imbalance and increased awareness of angina symptoms, all of which may play a role in chronic cardiovascular disease. But the current analysis cannot determine that the improvement in sleep was the cause of improvement in angina symptoms; the two improvements may be related to the effects of melatonin on sleep, vascular tone, oxidative stress, or neurohumoral balance [7,14,15].

The current results need to be considered in the context of current therapy for stable angina. Current guidelines for chronic coronary syndromes advocate for patient-specific anti-anginal treatment (beta-blockers, calcium channel blockers, nitrates, ranolazine, ivabradine, trimetazidine) and revascularization (where feasible), with symptom relief and protection against events as the key priorities. Melatonin is not typically regarded as an anti-ischemic agent like traditional anti-anginal medications; therefore, its potential benefits might be related to ameliorating sleep disruption, circadian misalignment, and possibly oxidative and endothelial dysfunction that are not completely addressed by conventional medication [1,8].

Prior studies of melatonin in cardiovascular disease have primarily evaluated its role in mechanistic and cardioprotective effects, such as oxidative stress, endothelial dysfunction, blood pressure, lipids, arrhythmia, atherosclerosis, and ischemia-reperfusion. Other research has explored melatonin as a hypnotic agent in patients with insomnia, circadian dysfunction or neurological disorders, rather than stable angina. This limits our ability to compare directly because few studies have examined melatonin in stable outpatient angina with outcomes of symptom diaries, nitrate consumption and PSQI. The current study therefore provides a patient-focused aspect by considering whether melatonin improves symptoms and sleep quality in stable coronary disease, rather than just biochemical or acute ischemia [7,8].

The current study has numerous strengths, such as the randomized, double-blind, placebo-controlled design and inclusion of a matching placebo, stable background anti-anginal medication, and clinically relevant outcomes measured at various time points. The angina diaries and PSQI facilitated assessment of symptoms from the patient's point of view. However, the study has limitations. This was a short-term study, with a moderate sample size, and subjective assessment of symptoms and sleep. Objective testing for ischemia, actigraphy, or polysomnography was not used. The study enrolled and analyzed 100 patients rather than the initially planned sample of 150. This smaller-than-planned sample may have reduced statistical power and the precision of the estimated treatment effects. No intention-to-treat analysis was performed. This study needs to be replicated in larger (multicenter) samples, with longer follow-up, objective sleep and ischemia measures, and mediation analyses to determine whether improvement in sleep contributes directly to improvement in angina.

The results indicated that melatonin could be a valuable adjunct in some patients with stable angina who remain symptomatic and have poor quality sleep despite conventional treatment. The fact that melatonin can be taken at bedtime, is inexpensive, and has relatively few short-term adverse effects makes it a compelling supplement, especially in the presence of sleep disturbance. But melatonin should not be offered as an alternative to evidence-based, anti-anginal and secondary prevention therapies. Evidence-based cardiovascular drug therapies, secondary prevention, lifestyle changes and appropriate revascularization remain the mainstays of current chronic coronary syndrome guidelines. Further study centered on routine clinical practice is needed, particularly to confirm efficacy and identify the optimal population for use, and longer-term cardiovascular safety in patients [1,7].

CONCLUSION

Melatonin 5 mg taken once at night for 8 weeks as adjunctive treatment to background anti-anginal therapy was associated with improved angina frequency, severity, nitrate use and subjective sleep quality over placebo in patients with stable angina pectoris. The fact that all symptoms (frequency of angina, severity of angina, nitrate use) and the PSQI score improved suggests melatonin may have important benefits that are relevant to patients. These benefits may be due to improved circadian physiology, enhanced sleep quality, and/or direct cardiovascular actions, but cannot be confirmed by this analysis. Larger, well-conducted, multi-center trials that include longer follow-up and objective measures of sleep and ischemia are required before melatonin can be recommended for routine use as an adjunctive therapy in stable angina.

DECLARATIONS

Acknowledgement/Funding
None.

Ethical approval

This research was approved by the institutional research ethics committee of the College of Pharmacy, University of Thi Qar, Iraq (Ethical reference number IQ.UTQ.PHARM.2025.005 on 19/01/2026).

Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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