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Research Article

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Melatonin Versus Zinc for Sleep Disorders in Cirrhotic Patients: A Randomized Double-Blind Pilot Trial

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Abstract

Given the absence of an established gold standard for managing sleep disturbances in patients with cirrhosis, the present randomized double-blind trial was conducted to evaluate the efficacy and safety of melatonin (5 mg/night) versus zinc (50 mg/night) in alleviating sleep disorders within this population. A total of 42 eligible participants were enrolled and randomly assigned to receive either melatonin or zinc. The Pittsburgh Sleep Quality Index (PSQI) was evaluated at baseline and again after one month of treatment. All participants tolerated the interventions well, and no dropouts occurred during the study period. Statistical analysis revealed that PSQI scores significantly improved in both treatment groups compared with baseline ($p = 0.001$ for both the melatonin and zinc groups). However, there was no statistically significant difference between the two interventions in PSQI scores at the end of the trial ($p = 0.936$). Based on the observed efficacy and tolerability, both melatonin at 5 mg nightly and zinc at 50 mg nightly may be considered as viable options for addressing sleep disorders in individuals with cirrhosis.

Keywords: Melatonin; Zinc, Sleep disorder; Cirrhosis; Clinical trial.

1. Introduction

Sleep-wake disturbances are common in cirrhotic patients and contribute to a diminished quality of life (QoL). The prevalence of sleep disorders in cirrhosis, as assessed by questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), ranges from 48% to 81% [1]. The exact mechanism underlying sleep disturbances in patients with cirrhosis has not been fully elucidated, and various factors have been proposed, including melatonin dysregulation, muscle cramps, restless legs syndrome, frailty, malnutrition (such as zinc deficiency), and hepatic encephalopathy [2]. Melatonin is a neurohormone secreted by the pineal gland and is also present in other organs, such as the gastrointestinal tract [3]. As melatonin is metabolized in the liver, sleep disorders in cirrhotic patients may be attributed to dysfunction in melatonin metabolism [4]. In a randomized clinical trial, De Silva et al. evaluated the effect of melatonin administration in cirrhotic patients.

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Volunteers received 3 mg of melatonin daily or a placebo for 14 days. After a 7-day washout period, patients were crossed over to melatonin or a placebo for an additional 14 days. Patients in the melatonin arm had significantly lower PSQI scores than both pretreatment ($P < 0.001$) and post-placebo ($P < 0.001$) scores. Regarding safety, the occurrence of adverse effects was similar in both arms [5].

Malnutrition is a prevalent complication and occurs in 20%–50% of cirrhotic patients [6]. It has been reported that a higher PSQI score was associated with a higher risk of malnutrition in cirrhotic patients [2]. In healthy people, some trace elements have been successfully used to improve sleep disorders with minimal adverse effects [7]. Research indicates that a zinc deficiency can alter glutamate levels, potentially interfering with sleep and leading to insomnia. Additionally, zinc plays a crucial role in the production of melatonin, which is essential for maintaining the circadian rhythm and sleep cycle. Evidence suggests that zinc supplementation may enhance melatonin production, potentially improving sleep duration and quality. Moreover, zinc deficiency has been linked to dysregulation of other sleep-related hormones, such as growth hormones, which may further exacerbate sleep disturbances [8]. Zhang et al. have evaluated the relationship between serum trace element concentrations and sleep quality in cirrhotic patients. They concluded that elevated copper levels and reduced zinc levels are significant risk factors for sleep disorders in cirrhotic patients [9]. Low zinc levels have also been proposed as a nutritional deficiency in cirrhotic patients [10]. Due to negative side effects, routine sedative hypnotic medications are generally not advised for the treatment of sleep disorders in patients with cirrhosis. A clinical trial assessed the relationship between the use of benzodiazepines and the onset of hepatic encephalopathy in a cohort of 865 cirrhotic patients. While cirrhotic patients who had taken benzodiazepines for only one or two days did not show an increased risk of developing hepatic encephalopathy, those who started using benzodiazepines for a duration of three to ten days exhibited a significantly heightened risk of developing hepatic encephalopathy [11].

Given the significant roles of melatonin and zinc in addressing sleep issues, we are unaware of any clinical trials that have compared these dietary supplements for the treatment of sleep disorders associated with cirrhosis. The objective of this study is to assess and compare the efficacy and safety of administering melatonin and zinc in improving the sleep quality of patients with cirrhosis.

2. Patients & Methods:

A randomized, double-blind clinical trial has been designed to assess the efficacy and safety of melatonin versus zinc in improving sleep among patients with cirrhosis. This trial has received ethical approval from the Ethics Committee of the School of Pharmacy, Nursing, and Midwifery at Shahid Beheshti University of Medical Sciences (Approval Code: IR.SBMU.PHARMACY.REC.1403.087, approval date: 07/20/2024). Furthermore, the study has been officially registered in the Iranian Clinical Trial Registry Database under the registration code IRCT20121021011192N18 (approval date: 06/24/2024).

The inclusion criteria for the study encompassed patients aged 18 years or older with a confirmed diagnosis of cirrhosis who reported sleep disturbances. The exclusion criteria were as follows: 1) a history of allergy to melatonin or zinc, 2) renal failure, defined as a creatinine clearance below 30 mL/min, 3) refusal to provide informed consent for participation in the trial, 4) pregnancy and breastfeeding, and 5) individuals engaged in shift work. Prior to enrolment, all patients were required to sign a consent form and retained the right to withdraw from the study at any time.

The melatonin (5 mg) and zinc (equivalent to 50 mg elemental) tablets were repackaged in identical containers to ensure blinding, preventing both physicians and patients from knowing the specific contents of each bottle. At baseline, demographic characteristics, clinical and laboratory data, and PSQI scores were assessed for all participants. Subsequently, eligible patients were randomly assigned to one of two groups. One group received a nightly oral dose of 5 mg melatonin, while the other received zinc sulphate tablets containing elemental zinc equivalent to 50 mg per night for 4 weeks. Melatonin and zinc tablets were repackaged in bottles of similar shape (A and B bottles), and the prescriber, along with the individual collecting the data, assessed the outcomes while remaining blinded throughout the trial. Randomization was performed using a computer-generated block randomization method specific to each

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study centre. If any participants reported serious side effects potentially related to melatonin or zinc, the medication was discontinued, and these individuals were excluded from the trial. Patient adherence to the prescribed medications was monitored through weekly telephone assessments. According to the standard definition of medication adherence, patients who missed more than 80% of their prescribed doses were classified as non-adherent and were therefore excluded from the trial. After four weeks, the PSQI scores were reassessed for all participants. Additionally, patients were asked to report any side effects experienced throughout the trial.

All the data were expressed as mean ± SD, when appropriate. Statistical Package for the Social Sciences version 22 (SPSS 22.0.) was used for statistical analysis. T-test, Mann-Whitney test, and chi-square test were used for the analysis, and P<0.05 was considered statistically significant. This clinical trial is the inaugural study comparing the effects of melatonin and zinc on sleep disturbances in individuals with liver cirrhosis. Consequently, a pilot sample size of 42 participants, with 21 assigned to each treatment group, was deemed essential.

3. Results and Discussion

Over a period of 4 months, 42 eligible patients successfully completed the trial (21 in the melatonin arm and 21 in the zinc arm). The trial flowchart is shown in **Figure 1**. The demographic characteristics of the study participants are presented in **Table 1**. No statistically significant differences were observed between the melatonin and zinc groups with respect to mean age, sex distribution, smoking status, alcohol consumption, Child-Turcotte-Pugh score, education level and marital status (p = 0.702.0.538, 0.505, 0.343, 1, 0.24, 0.545 respectively). At baseline, the PSQI scores were 16.7 ± 1.6 in the melatonin group and 17.0 ± 1.4 in the zinc group. No statistically significant difference was observed between the two groups ($p = 0.43$). At the conclusion of the trial, PSQI scores decreased to 7.8 ± 3.7 in the melatonin group and 7.1 ± 3.9 in the zinc group. A within-group comparison of PSQI scores before and after treatment revealed a statistically significant improvement in both groups ($p = 0.001$ for each).

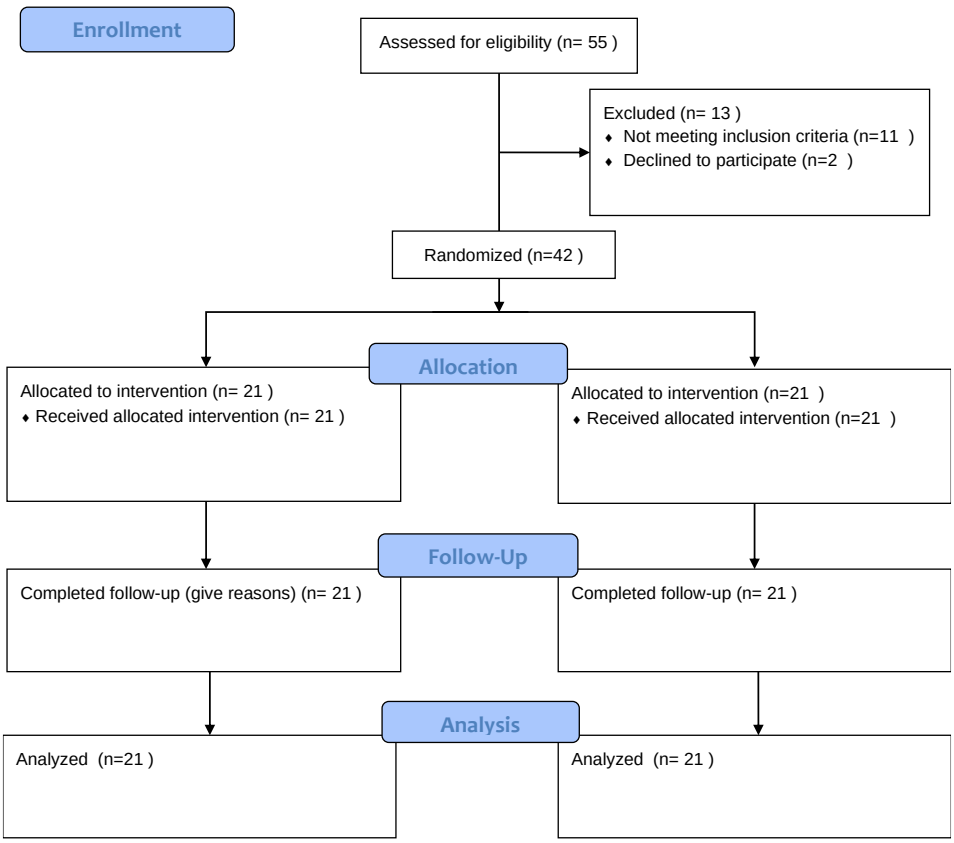

Figure 1. flowchart of the trial.

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Table 1. demographic data of the participants

		Melatonin group (n=21)	Zinc group (n=21)	P value
Mean Age (years) (±SD)		57.2 ± 10.4	56 ± 11.1	0.702
Sex distribution	Female	9	12	0.538
	Male	12	9	
Smoking status	No	13	16	0.505
	Yes	8	5	
Alcohol use	No	17	20	0.343
	Yes	4	1	
Child-Turcotte-Pugh score	A	18	17	> 0.99
	B	3	4	
	C	0	0	
Education level	Under diploma	3	1	0.24
	Diploma	8	14	
	Bachelor above	10	6	
Marriage status	Married	19	20	0.545
	Single	2	1	

Additionally, at the conclusion of the trial, comparative analysis of PSQI scores between the melatonin and zinc groups revealed no statistically significant difference ($p = 0.936$). The values for each PSQI component are presented and compared in **Table 2**. At baseline, no statistically significant differences were observed between the two groups across the individual PSQI components—namely, subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. These results remained consistent at the end of the trial, with no significant differences detected across the seven components between the two groups. During the first week of the trial, one patient in the melatonin group reported a headache, and one patient in the zinc group experienced abdominal pain. These adverse effects were likely related to the administered medications but subsided within one week. Notably, no participants withdrew from the study throughout the trial period.

3.1. Discussion

Given the clinical relevance of sleep disturbances in patients with liver cirrhosis, the present trial was conducted to evaluate the potential efficacy of melatonin and zinc in mitigating these disorders. The PSQI was used to systematically assess sleep-related parameters in the study population. The instrument comprises 19 self-administered items designed to assess various dimensions of sleep over the preceding month, including subjective sleep quality, sleep behaviours, and the presence of sleep disturbances. Lower scores on the PSQI indicate better sleep quality and quantity, suggesting more favourable sleep outcomes [12]. Our findings indicate that a 1-month administration of melatonin (5 mg) and zinc (50 mg) led to improved patient-reported satisfaction with sleep disturbances and medication tolerance in a prior clinical trial investigating melatonin. In that trial, 2 out of 70 participants discontinued participation due to adverse effects attributed to the intervention. However, the study authors did not specify the nature of the reported adverse effects [4]. In the present trial, one case of headache associated with melatonin administration and one case of abdominal pain were reported during the first week. No statistically significant difference was observed between the two treatments ($p = 0.936$). Previous clinical trials have demonstrated a favourable safety profile of melatonin at doses exceeding 5 mg/day, consistent with the dosage used in our study. Somnolence, the most frequently reported adverse effect, can be effectively mitigated through administration at bedtime. Collectively, these findings support the conclusion that melatonin is a safe and well-tolerated therapeutic agent [13]. In a systematic review evaluating the efficacy and safety of zinc supplementation, which encompassed six clinical trials involving a total of 1,009 patients, no adverse events attributable to zinc were reported across any of the included studies [14]. Both study arms were comparable with respect to key demographic and lifestyle variables, including mean age, sex distribution, smoking habits, and alcohol consumption. Several of these variables have been identified in the literature as being associated with sleep disorders. For instance, conditions such as insomnia, circadian rhythm sleep-wake disorders, and parasomnias are commonly observed in older adults. They are linked to an overall decline in sleep quality with advancing age [15].

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Table 2. Amounts of seven component scores of PSQI in two groups.

		Melatonin group (n=21)	Zinc group (n=21)	P vaue
Subjective sleep quality (±SD)	Baseline	2.6 ± 0.4	2.8 ± 0.4	0.18
	End of the trial	0.6 ± 0.7	0.8 ± 0.7	0.40
	P value	0.001	0.001	
Sleep latency (±SD)	Baseline	2.8 ± 0.4	2.8 ± 0.3	0.68
	End of the trial	1.2 ± 0.7	1.1 ± 0.6	0.67
	P value	0.001	0.001	
Sleep duration (±SD)	Baseline	2.4 ± 0.5	2.6 ± 0.4	0.22
	End of the trial	1.4 ± 0.6	1.3 ± 0.6	0.63
	P value	0.001	0.001	
Sleep efficiency (±SD)	Baseline	2.4 ± 0.5	2.5 ± 0.5	0.54
	End of the trial	1.4 ± 0.6	1.3 ± 0.6	0.46
	P value	0.001	0.001	
Sleep disturbance (±SD)	Baseline	2.0 ± 0.5	2.2± 0.5	0.35
	End of the trial	1.2 ± 0.5	1.3 ± 0.7	0.47
	P value	0.001	0.001	
Use of sleep medications (±SD)	Baseline	1.5 ± 0.5	1.1 ± 0.7	0.10
	End of the trial	0.4 ± 0.8	0.1 ± 0.3	0.09
	P value	0.001	0.001	
Daytime dysfunction (±SD)	Baseline	2.7 ± 0.4	2.7 ± 0.3	0.73
	End of the trial	1.1 ± 0.6	1.4 ± 0.9	0.34
	P value	0.001	0.001	

Furthermore, a recent review by Grigoriou et al. demonstrated that smoking adversely affects sleep architecture by reducing slow-wave and rapid eye movement sleep, thereby impairing overall sleep quality [16]. Given the equivalence of the two study arms on these parameters, they are unlikely to confound the interpretation of our findings. Although a previous study has compared melatonin with a placebo in patients with liver cirrhosis [4], to the best of our knowledge, no published research has addressed the efficacy and safety of zinc in the management of sleep disorders among this population. Our trial is the first to compare melatonin and zinc in this context directly. In the aforementioned melatonin–placebo study, only the total PSQI score was reported, with no analysis of individual components.

In contrast, our findings demonstrate improvement across all seven PSQI components following one month of intervention. However, no statistically significant differences were observed between the melatonin (5 mg/night) and zinc (50 mg/night) groups in any of the individual components. In an animal study, Harman and Serpek reported that zinc supplementation was associated with a quantitative increase in melatonin levels [17]. Prior research suggests a bidirectional relationship between zinc and melatonin. Zinc appears to play a role in both the synthesis and physiological activity of melatonin, while melatonin has been shown to enhance zinc absorption [18]. Although zinc and melatonin levels were not assessed in the present trial, it is plausible that these agents exerted a synergistic effect within the study context. Previous research has demonstrated a correlation between sleep disorders and QoL [19]. QoL was not assessed in the present study population; therefore, future investigations should concurrently evaluate both sleep disturbances and QoL outcomes in cirrhotic patients. The present pilot trial is subject to several limitations, including its single-centre design, limited sample size, short assessment duration, and the absence of serum melatonin or zinc measurements and QoL evaluations. Future large-scale, multicenter clinical trials incorporating these parameters are warranted to address these limitations and thereby strengthen the reliability and generalizability of the findings.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Authors Contributions

Conceptualization 1,4 Data curation 2, 4 Formal analysis 3 Investigation 4 Methodology 1,2,4 Project administration 1,2 Resources 3,4 Software 2,3,4 Supervision 1,4 Validation 1 Visualization 4 Writing original draft 3,4 writing review and editing 3.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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