The Efficacy of Oral Melatonin in Improving Sleep in Cancer Patients with Insomnia: A Randomized Double-Blind Placebo-Controlled Study

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ABSTRACT

Background: The natural hormone melatonin has sleep inducing properties. Insomnia in cancer patients is common. So far, melatonin has been seldom tried for the improvement of sleep in patients with malignancies. Keeping this in mind, we planned and conducted a double-blind study to test the efficacy of melatonin in promoting sleep in patients with malignancies suffering from insomnia.

Objective: To assess the hypnotic efficacy of oral melatonin in cancer patients with insomnia.

Materials and Methods: After Ethical Committee approval, 50 patients (age range 20–65 years) from our pain clinic "NIVARANE" who met the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria for primary insomnia were randomized to receive melatonin 3 mg or placebo at 7 pm orally every day for 14 days from our pharmacist. After 1, 7, 14 days, the patients were reviewed with the Athens insomnia scale oral questionnaire to document the subjective sleep quality. The patients and we, the investigators were blinded to the study drug.

Results: There were 2 drop outs (one from each group) as they failed to complete visit on day 14. Significant differences in favor of melatonin treatment were found in clinically relevant improvements in insomnia (46.53%; $P = 0.00001$ vs. 11.30%; $P = 0.1026$) There was improvement in sleep from 1 to 7 days (19.91%; $P = 0.00001$ vs. 0.98%; $P = 0.2563$). More significant improvements were seen between 7 and 14 days (33.24%; $P = 0.00001$ vs. 10.42%; $P = 0.1469$).

Conclusion: We conclude that daily intake of oral melatonin 2 h before bedtime improves sleep induction and quality in cancer patients with insomnia.

Key words: Malignancies, Melatonin, Oral administration, Sleep, Sleep disorders

INTRODUCTION

Sleep is vital to all human functioning and sleep disturbance is a significant problem for cancer patients.[1,2] The prevalence, type, and severity of sleep complaints in a cancer population have been difficult to judge. The prevalence estimates range from 24% to 95%.[3]

Insomnia is a complaint regarding the quantity, quality, or sleep timing at least 3 times a week for at least 1 month according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 4th Edition.[4]

The sequels of insomnia include daytime fatigue and reduced alertness, irritability, and impaired concentration and all these symptoms having a major negative impact on the quality of life.[5]

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Insomnia can exacerbate cancer-associated medical conditions such as pain, psychiatric comorbidities, fatigue, use of opioids (which could contribute to daytime sedation and sleep-related breathing disorders), and stimulating or alerting drugs.[6]

Insomnia is a frequently overlooked problem in cancer practice, and patients may fail to report it, assuming it to be a normal and temporary reaction to a cancer diagnosis or treatment.[7] The treatment should be multimodal including both nonpharmacological and pharmacological approaches.[8]

Nonpharmacological options include an emphasis on sleep hygiene, and cognitive behavioral interventions;[9] nevertheless; it is better to add medications to nonpharmacological therapy. Drugs commonly used in the management of sleep disturbances include the benzodiazepine (BDZ) group of drugs, BDZ-like drugs such as zolpidem and zaleplon, sedating antidepressants such as amitriptyline and nortriptyline and sedating antihistamines. All these drugs have several associated side effects. Long-term treatment with medication alone is not the optimal treatment strategy for patients with insomnia. It is better combined with the behavior changes to improve sleep patterns.[4]

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone chemically related to serotonin. It is produced by the pineal gland in the midbrain. Melatonin exhibits both hypnotic and chronobiotic properties and thus has been tried for inducing sleep and treating sleep disorders of children, adults, and elderly people.[6,10] Melatonin is different from BDZs and their derivatives in that it exerts a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep inducing effect, quite mild.[11]

With this background, we planned and conducted a study for evaluating the efficacy of oral melatonin in improving sleep in patients with malignancies suffering from insomnia.

MATERIALS AND METHODS

We conducted this study over a period of 6 months at our pain and palliative care clinic "NIVARANE" from January to June 2014 after Institutional Ethical Committee approval. Fifty cancer subjects after obtaining consent were selected if they satisfied the inclusion criteria. The inclusion criteria included age between 20 and 65 years, cancer patients with sleep complaints more than a month, any stage and type of cancer and patients who were not on sleep medications for a minimum of 2 weeks. Pregnant/lactating females, mentally impaired patients, patients with a history of psychiatric disorders, mental impairment or on antipsychotic treatment, having language or communication difficulties, other sleep disorders and with liver and renal dysfunction were excluded from the study.

A prospective double-blind study was conducted on 50 patients (n = 25) who were randomly assigned to Group A or B by the fishbowl technique. Patients were given either tablet melatonin 3 mg (Meloset from Aristo pharmaceuticals) or placebo (multivitamin tablets – Supradyn from Abbott Healthcare pharmaceuticals) by our pharmacist. The tablets in both groups were wrapped in similar looking envelopes which were given to the patients. Both the tablets were colored light yellow and similar looking. The patients were instructed to take the tablets every day for 14 days, 2 h before routine bedtime. They were evaluated with the Athens insomnia scale (AIS) oral questionnaire for assessing subjective sleep quality either through phone or in person. Both patient and we (evaluators) were blinded to the drug given by the pharmacist. The identity of the drug group was revealed to us at the end of the study.

The AIS is a self-assessment psychometric instrument designed for quantifying sleep difficulty. It consists of 8 items: The first 5 pertain to sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality; while the last 3 refer to well-being, functioning capacity, and sleepiness during the day. The items are measured on 0–3 numeric rating scales. Patients are asked to rate the severity of their insomnia at 0 being "no problem" and 3 being "did not sleep at all."[12]

At a cut-off score of 10, the positive predictive value of the scale in the general population reaches about 90% without the negative predictive value becoming lower than 94%.[13]

RESULTS

After conducting a pilot study, the sample size n = 25 was found to be adequate with respect to improvement in the quality of sleep,[14] with the power of the study being 90% and an alpha error of 5%. The data collected were tabulated using Microsoft Excel worksheet and the data were analyzed using Statistical Package for the Social Sciences version 20.0 Inc., Chicago, IL, US. The parametric data regarding improvement in sleep in the two groups were compared using the paired t-test.

At the end of the study period, the study groups were revealed. Group A belonged to tablet melatonin 3 mg and Group B belonged to the placebo group.

Both groups were comparable in age and sex ratio. There was one drop out in each group. One patient had lost the drug, and one patient did not come for follow-up. 44% of the patients and 40% patients in Group B had stage one cancer in Group A and B, respectively followed by 32% and 36% of the patients belonging to stage 2 cancer respectively. Stage 3 and 4 together comprised of 24% in both groups [Table 1].

Fifty-four percent of the total sample had cancer of head and neck like carcinoma base of tongue, carcinoma larynx, etc., followed by cancer cervix 12%. The remaining 14% of the patients had ovarian, gastrointestinal, breast cancers, and sarcomas.

On comparison of the AIS scores of the two groups in improving sleep at days 1, 7, 14 by paired *t*-test, there was a significant improvement ($P < 0.05$) in sleep in patients receiving Group A when taken for 1 week and 14 days when compared to Group B [Table 2].

When the AIS scores of 1st week, 2nd week, and through the 14 days period were compared individually it was found that there was a significant improvement ($P < 0.05$) in sleep in Group A patients in the 1st week as well as in the 2nd week and after 14 days of taking the drug when compared to Group B patients. However, the improvements in sleep were highly significant in Group A in the 2nd week of drug intake ($P = 0.00001$) [Table 3].

When an intragroup comparison of Group A was done it showed the percentage of changes in the improvement of sleep was 19.91% in the 1st week, 33.24% in the 2nd week, and 46.53% throughout the 2 weeks. This improvement in sleep was highly significant ($P = 0.00001$).

When an intragroup comparison of Group B was done the percentage of change in improvement of sleep was 0.98%, 10.42%, and 11.30% when the drug was taken for the 1st week, 2nd week and throughout the 2 weeks period. This improvement was insignificant as the ($P > 0.05$) [Figure 1].

Table 1: Patient demographics in the two groups (Group A and Group B)

Patient characteristics	Group A	Percentage	Group B	Percentage	Total	Percentage
Sex						
Male	13	52.00	13	52.00	26	52.00
Female	12	48.00	12	48.00	24	48.00
Age (years)						
≤50	5	20.00	11	44.00	16	32.00
51-60	9	36.00	9	36.00	18	36.00
≥61	11	44.00	5	20.00	16	32.00
Mean age	55.20		49.64		52.42	
SD age	7.63		11.69		10.17	
Drop outs	1		1		2	
Stage I and II cancer	19		6		25	
Stage III and IV cancer	19		6		25	

Group A: Tablet melatonin 3 mg; Group B: Placebo; SD: Standard deviation

Table 2: Comparison of mean athens insomnia scale scores of two groups (Group A: Melatonin 3 mg and Group B: Placebo) in improving sleep at days 1,7,14 by *t*-test

Variable	Group	Mean AIS score±SD	*t*	*P*
1 day	A	17.88±2.03	2.4136	0.0197*
	B	16.28±2.62		
7 days	A	14.32±1.49	−3.0714	0.0035*
	B	16.12±2.52		
14 days	A	9.56±2.58	−4.5562	0.00001*
	B	14.44±4.69		

*P<0.05. AIS: Athens insomnia scale; SD: Standard deviation

Table 3: Comparison of athens insomnia scale scores of two groups (Group A: Melatonin 3 mg and Group B: Placebo) in improvement of sleep with respect to duration of drug intake by paired *t*-test

Time period with respect to drug intake	Group	Mean AIS score±SD	*t*	*P*
1st week	A	3.56±2.58	6.3591	0.00001*
	B	0.16±0.69		
2nd week	A	4.76±2.26	2.5490	0.0141*
	B	1.68±5.60		
Throughout 14 days	A	8.32±3.77	4.9059	0.00001*
	B	1.84±5.42		

*P<0.05. AIS: Athens insomnia scale; SD: Standard deviation

DISCUSSION

Oral melatonin undergoes extensive first pass metabolism with varying bioavailability. It is a highly lipophilic substance with a consequent high volume of distribution. More than 90% of circulating melatonin is cleared by the liver. Exogenous melatonin is rapidly absorbed and peak plasma levels are reached in 60–150 min. The elimination half-life of melatonin is about 12–48 min. Hence, there are minimal residual effects the next morning. Its bioavailability from an oral dose ranges from 10% to 56%.[4,15]

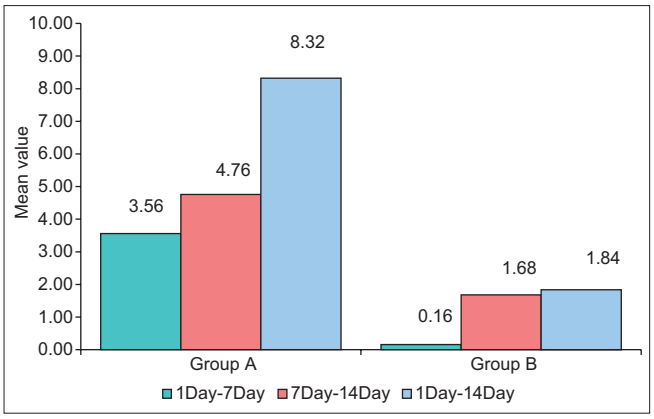

Figure 1: Comparison of two groups (Group A and Group B) with changes efficacy of oral melatonin in improving sleep from 1 day to 7th day and 14th day

Circulating melatonin can reach all body tissues and crosses the blood-brain barrier to modulate brain activity. Melatonin has a hypnotic/sedative effect when administered orally. This may be due to its circadian rhythm regulation effect. The sedative effect of melatonin is due to modulation of gamma-aminobutyric acid ($GABA_A$) receptors in the brain through its action on melatonin receptors (MT1 and MT2). Binding of melatonin to the MT1 receptor appears to affect the $GABA_A$ receptor through the G-coupled protein pathway. This enhances the binding of GABA to the $GABA_A$ receptor, which is similar to how other drugs such as BDZs exert their anesthetic effects.[16,17]

Melatonin is available in the form of syrups, capsules, and tablets. The tablets have melatonin doses ranging from 0.3 to 5 mg. An oral dose of melatonin, 3 mg was taken as this preparation was easily available in the market and it is within the safe dose range (a maximum dose of 20 mg has been published in literature).[18] Several researchers[19,20] have used melatonin tablets in dose ranges from 0.3 mg to 50 mg orally. The drug was administered 2 h prior to routine bedtime in our study like in other studies[14,21] as the exogenous melatonin when administered is rapidly absorbed and peak plasma levels are reached in 60–150 min. The body levels of melatonin as a naturally occurring hormone follow a circadian course, being stimulated by the evening onset of dim light and suppressed by bright light. The evening rise in melatonin precedes the rise in sleepiness by about 1.5–2 h.[5] The use of BDZs or other hypnotics during our study and in the preceding 2 weeks or five half-lives, whichever was longer, and throughout was prohibited as done in other studies.[22,23] This was necessary to wash out the residual effects of the hypnotic drugs.

We chose 2 weeks as the period of drug intake. The same period has been chosen by some other researchers.[14] It also allows for synchronization of melatonin levels with the circadian cycle.[22] This probably was also the reason for the highly significant improvement in sleep that was observed when the drug was taken for the entire period of 2 weeks in our study. The Pittsburgh Sleep Quality Index (PSQI) has been used in many studies[14] for the assessment of insomnia. It consists of 19 self-rated questions and five questions rated by the bed partner or room-mate[24] which would have been time-consuming and extensive for the poorly educated patient to comprehend and answer. The daily sleep diary has been used by a few researchers.[14,23] Unfortunately, a major part of our study population had a poor educational background. Hence, it would have been difficult for them to maintain a sleep diary. Actigraphy has also been used to monitor the sleep in a recent study.[20] Since getting objective monitors was not feasible to us, we could not use them.

Though melatonin has been publicized as a cure for many sleep problems, the literature on its treatment for insomnia in cancer patients is limited. Currently, there is only one study conducted on the effect of melatonin on sleep in cancer patients with insomnia;[20] nonetheless, we have compared our study results with studies on melatonin in the treatment of insomnia in noncancer patients.

Our study results were congruent with the results of the study done by Innominato *et al.*[20] in breast cancer patients with insomnia. They found that bedtime melatonin was associated with a significant improvement in a marker of objective sleep quality, sleep fragmentation and quantity, subjective sleep, fatigue severity, global quality of life, and social and cognitive functioning scales when given regularly for 2 months.[20] However, they used a higher dose of 5 mg melatonin and used actigraphy for objective sleep monitoring. We used a lower dose of 3 mg and used the AIS, which is a subjective scale for sleep assessment. Studies suggest that a placebo does, in fact, elicit biological and behavioral responses in humans and therefore, the use of a placebo itself can be considered therapeutic and an effective method of treatment.[21]

Our study results agree with the results of the studies done by Wade *et al.*,[14] Haimov *et al.*,[25] who administered oral melatonin in elderly insomniacs and observed significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency and quality of life. However, these studies[14,25] used prolonged release formulations. We administered single dose tablet formulations of melatonin. A meta-analysis done by Ferracioli-Oda *et al.*[26] concluded with the same

observations along with additional information viz- the effects of melatonin on sleep are modest but do not appear to dissipate with continued melatonin use. Our study did not agree with the results obtained by Almeida Montes *et al*.[10] who concluded that melatonin did not produce any sleep benefit in elderly insomniacs. It may be because the doses they used were 0.3 mg and 1 mg which were less compared to our study dose.

In addition to sleep induction and maintenance, melatonin produces various effects viz- analgesia, anti-inflammatory and immunological effects, anti-oxidative effects, chronobiosis, and antihypertensive effect.[22] Melatonin lowers the toxicity of chemotherapeutic agents such as cisplatin, etoposide, anthracyclines, and 5-fluorouracil. It reduces the severity of treatment-related adverse events such as myelosuppression, neurotoxicity, nephrotoxicity, and asthenia. It is also effective in the treatment of major depression and has oncostatic properties.[6] All these properties of melatonin could prove to be beneficial in patients suffering from cancer.

We did not observe any adverse effects of melatonin in our patients. Most other researchers[23,24] too, have not observed significant side effects and considered it to have a relatively benign side-effect profile compared to other agents.[26] It would be apt to note at this juncture that even if adverse effects such as a headache, dizziness, nausea, and vomiting had occurred in our patients, it would have been difficult to attribute them to melatonin intake. These effects commonly occur in cancer patients due to various other reasons.

Our study had several limitations. These include points like the inclusion of all stages of cancer in the study. In advanced stages of cancer, insomnia could be related to pain caused by tumor invasion like mass impinging on nerve roots. Patients in the early stages of cancer may have increased depression, anxiety, and fatigue levels following the diagnosis of cancer leading to insomnia. Depressive mood is the main factor influencing the quality of life.[27] The inclusion of patients suffering from a plethora of cancers was another limitation. The insomnia rates have been found to be variable in different cancer types; nevertheless, breast cancer patients are known to have high insomnia rates possibly because of the disruption of sleep due to increased frequency and severity of hot flashes associated with breast cancer treatment.[28] We could not standardize all these factors in our study. We did not stratify the effects of melatonin on insomnia as improvement in sleep onset and sleep maintenance, but we propose to do this in further studies.

Currently, subjective and objective measures are recommended for measuring sleep-wake disturbances in patients with cancer. Objective sleep monitors such as actigraphy and polysomnography for a more objective sleep measurement were not available to us. We had to thus resort to a subjective scale for sleep assessment.

In cancer populations, the causes of insomnia are multifactorial and include predisposing, precipitating, and perpetuating factors. Predisposing factors include female gender, older age, personal or family history, mood, or anxiety disorders; precipitating factors include cancer treatments that alter levels of inflammatory cytokines or disrupt circadian rhythms, side-effects of cancer treatment, menopausal symptoms, co-occurring symptoms like pain and medications used to manage treatment side–effects, such as corticosteroids; and perpetuating behavioral factors such as excessive daytime sleeping, long-term use of medications, and maladaptive cognitions, i.e., inaccurate appraisal of sleep difficulty and quality and daytime impairments.[7] We were not able to standardize all these factors in our study due to technical problems.

We suggest further research on this topic using prolonged release/sublingual formulations. Furthermore, we recommend robust studies with larger sample sizes than ours and long-term studies of longer duration than ours with more stringent inclusion criteria to evaluate the safety and efficacy of oral melatonin in cancer patients. Spouses/caregivers of cancer patients experience and share much of the suffering of the patients and have resultant insomnia.[2] Hence, studies on the use of melatonin in these caregivers would be beneficial.

CONCLUSION

We conclude that regular daily intake of oral melatonin 3 mg 2 h before bedtime along with nonpharmacological measures improves sleep induction and the quality of sleep in cancer patients with insomnia.

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Conflicts of interest

There are no conflicts of interest.

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