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ORIGINAL RESEARCH

Melatonin premedication dose impact response in oncosurgical patients: A double blinded randomized controlled trial

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ABSTRACT

Background: Preoperative anxiety (an unpleasant tension brought on by a patient's anxiety about hospitalisation, anaesthesia, and surgery) is exacerbated by the fact that cancers are life-threatening and by the related fear of recurrence or death.Therefore, this study aimed to evaluate the impact of preoperative oral melatonin on anxiolysis, sedation, sleepiness, and hemodynamic response to intubation, as compared to a placebo control group. **Materials &Methods:** The study was carried out on 60 cancer patients between the ages of 18 and 60 who had ASA physical status Grades 1 and 2 and receiving elective oncological procedures under general anesthesia. The patients were randomly assigned into two groups (Group-C and Group-M) by computer generated random number.Ramsay sedation score, Stanford sleepiness scale, Haemodynamic parameters such as HR, SBP, DBP and MAP were recorded. **Results:** The mean age in group M was 39.9 years and in C group was 45.1 years. There were 21 males and 9 females and 24 males and 6 females. The height was 157.1 cm and 155.8 cm, weight was 53.7 cm and 55.3 cm, HR variability was 83.3 beats/min and 82.2 beats/min, SBP was 118.8 and 116, DBP was 82.4 mm Hg and 84.6 mm Hg in group M and C respectively. The difference was non- significant ($P > 0.05$). Before premedication and 90 minutes after premedication, Ramsay Sedation score in group M was 2.0 and 3.3 respectively and in group C was 1.97 and 2.1 respectively. The difference was significant ($P < 0.05$). Before premedication and 90 minutes after premedication, Stanford sleepiness scale in group M was 1.37 and 4.57 respectively and in group C was 1.03 and 1.40 respectively. The difference was significant ($P < 0.05$). **Conclusion:** Compared to placebo, oral melatonin provides increased sedation and sleepiness while maintaining greater hemodynamic stability during endotracheal intubation. However, when used alone for anxiolysis, melatonin appears to be comparable to placebo. Further research is necessary to establish the optimal and safe dosage of oral melatonin for achieving anxiolytic effects in cancer patients.

Keywords: Anxiety, Oncosurgical, Ramsay Sedation score

INTRODUCTION

The management of cancer involves both positive and unpleasant experiences, anxiety and fear, desire to find relief from the condition.[1] Preoperative anxiety (an unpleasant tension brought on by a patient's anxiety about hospitalisation, anaesthesia, and surgery) is exacerbated by the fact that cancers are life-threatening and by the related fear of recurrence or death.[2] Any patient before surgerywill likely feel anxious. Yet, it is more noticeable in cancer patients when they are prepped for surgery compared to the general population or people with chronic conditions. Preoperative anxiety negatively impacts the patient's intraoperative and postoperative results.[3] Melatonin (N-acetyl-5-methoxytryptamine) regulates the circadian rhythm and is a hormone produced chiefly

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by the pineal gland. Melatonin appears to act in a way that is similar to other anaesthetic drugs by modulation of Gamma-Aminobutyric Acid (GABA) receptors in the brain.[4]

Hence, preoperative counseling and premedication in anaesthesiology treatment make lowering preoperative anxiety a top priority. It was hypothesized that oral melatonin administered as a premedication would induce anxiolysis with minimal adverse effects.[5]Therefore, this study aimed to evaluate the impact of preoperative oral melatonin on anxiolysis, sedation, sleepiness, and hemodynamic response to intubation, as compared to a placebo control group. The primary endpoint of the study was preoperative anxiolysis, while secondary endpoints included sedation, sleepiness, and hemodynamic response to intubation.

MATERIALS & METHODS

The study was carried outon 60 cancer patients between the ages of 18 and 60 who had ASA physical status Grades 1 and 2 and receiving elective oncological procedures under general anaesthesia after obtaining written informed consent.The study was conducted in the Department of Onco - Anaesthesia and Critical Care, State Cancer Institute, Gauhati Medical College, Guwahati.

The patients were randomly assigned into two groups (Group-C and Group-M) by computer generated random number. Before the surgery: Patient was evaluated in the Pre anesthesia clinic routinely and on the day of surgery 90 min before induction, patients of both the groups are counselled and given premedication as on the opaque sealed envelopes by the anesthesiologist not involved in the study, patients in group C are given ondansetron as oral tablet and patients in group M are given melatonin at 0.5 ml/kg , VAS score, Ramsay sedation score, Stanford sleepiness scale, Haemodynamic parameters such as HR, SBP, DBP and MAP were recorded using multi-parameter patient monitoring system just before premedication, 90 min after premedication.Results thus obtained were subjected to statistical analysis. P value < 0.05 was considered significant.

RESULTS

Table I Demographic data

Parameters	GroupM(Oral melatonin 0.5 mg/kg)(n=30)	GroupC(Placebo) (n=30)	Pvalue
Age(years)	39.90±10.88	45.17±10.02	0.05
Sex,(Male:Female ratio)	21:9	24:6	0.37
Height,(cm)	157.10±8.23	155.87±5.46	0.496
Weight,(Kg)	53.73±10.87	55.37±10.39	0.55
HRvariability,(beats/minute)	83.37 ±11.90	82.23±9.25	0.68
SBP in mm of mercury	118.8±11.76	116±10.86	0.35
DBP in mm of mercury	82.4±7.86	84.6±8.86	0.32

Table I shows that mean age in group M was 39.9 years and in C group was 45.1 years. There were 21 males and 9 females and 24 males and 6 females. The height was 157.1 cm and 155.8 cm, weight was 53.7 cm and 55.3 cm, HR variability was 83.3 beats/min and 82.2 beats/min, SBP was 118.8 and 116, DBP was 82.4 mm Hg and 84.6 mm Hg in group M and C respectively. The difference was non- significant (P> 0.05).

Table II Sedation (Ramsay sedation score)

Group	Before premedication (Mean±SD)	90 Minutes after premedication (Mean±SD)	Difference (Mean±SD)	Pvalue
GroupM	2.00±0.00	3.30±0.11-1.30±0.11 <0.001	-1.30±0.11	<0.001
GroupC	1.97±0.03	2.17±0.07	-0.20±0.07	0.012*

Table II shows that before premedication and 90 minutes after premedication, Ramsay Sedation score in group M was 2.0 and 3.3 respectively and in group C was 1.97 and 2.1 respectively. The difference was significant (P< 0.05).

Table III Stanford sleepiness scale

Group	Before premedication (Mean±SD)	90 Minutes after premedication(Mean±SD)	Difference (Mean±SD)	P value
GroupM	1.37±0.09	4.57±0.38	-3.20±0.30	<0.001
GroupC	1.03±0.03	1.40±0.22	-0.37±0.19	0.06*

Table III shows that before premedication and 90 minutes after premedication, Stanford sleepiness scalein group M was 1.37 and 4.57 respectively and in group C was 1.03 and 1.40 respectively. The difference was significant (P< 0.05).

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DISCUSSION

Pre-operative anxiety and the intubation process can trigger harmful stress responses that negatively impact patients both during and after the operation. While benzodiazepines, opioids, and barbiturates are commonly used to manage these concerns, they can have serious side effects and should only be used when absolutely necessary. For cancer patients, who are already vulnerable to unpredictable reactions, safe pre-medications with minimal side effects are crucial. Recent research has explored the potential of oral melatonin for various applications, including reducing anxiety before and after surgery and as an adjunct to anesthetic medications.[6] This study aimed to compare the effectiveness of oral melatonin to a placebo as a pre-medication for cancer patients undergoing general anesthesia. The findings did not reveal any significant reduction in anxiety with melatonin compared to the placebo. However, the study did show that melatonin led to noticeable sedation and improved hemodynamic stability in patients compared to the placebo group. These results suggest that while melatonin may not be effective in reducing preoperative anxiety, it can induce sedation and stabilize vital signs in patients undergoing surgery.

Previous research has demonstrated that melatonin can significantly reduce anxiety compared to a placebo. However, the current study's findings contradict these earlier results, showing no significant difference in anxiety reduction between melatonin and placebo. This inconsistency is supported by the work of Capuzzo M et al[7] and Isik B et al[8], who also found no significant anxiolytic effect of melatonin compared to placebo. Some researchers have suggested that lower doses of melatonin and the older age of participants may contribute to the diminished anxiolytic effects observed in certain studies.

It is well-established that the anxiolytic effects of melatonin may be diminished in older individuals. While a higher dose of melatonin (0.5 mg/kg) was administered in this study, it did not result in significant anxiolytic effects. Given the heightened susceptibility to anxiety in cancer patients, particularly the elderly, the anxiolytic impact of melatonin may have been further reduced in this population.

Further investigation is necessary to determine the most effective and safe dosage of oral melatonin as a premedication for its anxiolytic properties in cancer patients. The current body of research on this topic is limited, necessitating additional studies to establish optimal dosing regimens and assess potential side effects.

Consistent with previous research, this study observed a higher sedation score in the melatonin group compared to the placebo group. However, studies by Isik B et al.[8], Sury MRJ[9] did not report significant sedative effects of melatonin. This discrepancy may be attributed to the heterogeneous nature of the pediatric populations undergoing MRI in these studies, which often included children resistant to conventional sedation methods. In contrast, a study by Dollins AB et al. found that melatonin improved sleepiness.

Similar to the findings of this study, the melatonin group exhibited improved sleepiness compared to the placebo group. While the sedation and sleepiness scores were elevated in the melatonin group, these effects were not detrimental. Patients remained calm and easily arousable from their mild sedation state. Importantly, they did not experience any difficulties with intubation, as all patients had undergone normal preoperative airway assessments.

The relatively low sedation and sleepiness observed in the placebo group could have potentially led to increased hemodynamic parameters. In contrast to the findings of JockovichM et al[9], who did not observe beneficial effects of a 1 mg melatonin dose on sleep, the current study, utilizing higher doses of melatonin, demonstrated improved sleepiness in the melatonin group compared to the placebo group. However, unlike previous studies that directly compared melatonin to midazolam, the present study did not include midazolam as a comparator. These studies consistently reported the highest degree of sedation for midazolam compared to both melatonin and placebo. This highlights the less precise monitoring requirements for patients receiving oral melatonin, who typically experience mild sedation, compared to those receiving midazolam, who often require deep sedation.

Gupta P et al[10] observed that oral melatonin induced stable hemodynamic profiles 60-120 minutes post-premedication. Consistent with these findings, the current study also demonstrated a reduced increase in blood pressure in response to endotracheal intubation in the melatonin group compared to the placebo group. Mohamed AA et al[11] previouslyinvestigated the impact of preoperative melatonin administration on the hemodynamic response to direct laryngoscopy and tracheal intubation, concluding that melatonin significantly attenuated these responses. In alignment with these findings, the present study observed a greater decrease in blood pressure in the melatonin group compared to the placebo group. Furthermore, similar to the study by Gupta P et al., the current study revealed a more pronounced attenuation of heart rate response to endotracheal intubation in the melatonin group compared to the placebo group.

The current study employed a 0.5 mg/kg dose of oral melatonin in adult cancer patients, resulting in minimal adverse effects compared to lower doses or sublingual administration used in previous studies. Currently, the body of research examining the effects of melatonin in cancer patients remains limited.

CONCLUSION

Compared to placebo, oral melatonin provides increased sedation and sleepiness while maintaining greater hemodynamic stability during endotracheal

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intubation. However, when used alone for anxiolysis, melatonin appears to be comparable to placebo. Further research is necessary to establish the optimal and safe dosage of oral melatonin for achieving anxiolytic effects in cancer patients.

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