DOI: 10.7860/JCDR/2021/52985.15799

Original Article

Anaesthesia Section

Dose Effect Response of Melatonin Premedication in Oncosurgical Patients: A Randomised Controlled Trial

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ABSTRACT

Introduction: Cancer patients experience higher levels of pathological anxiety than other patients. Though several studies have reported perioperative use of melatonin in alleviating preoperative anxiety with minimal side effects, research on the perioperative use of melatonin in oncology patients is scarce.

Aim: To analyse the preoperative anxiolysis, sedation, sleepiness and hemodynamic response to intubation after premedication with oral melatonin at two different doses of 0.3 mg/kg and 0.5 mg/kg body weight and comparing them with placebo.

Materials and Methods: This was randomised controlled trial on a total of 90 cancer patients aged 18-60 years undergoing elective surgeries under general anaesthesia were randomised into three groups of 30 patients each. Oral melatonin 0.3 mg/kg, oral melatonin 0.5 mg/kg, and placebo were given to patients in Groups A, B, and C, respectively. The Visual Analogue Score (VAS), Ramsay Sedation Scale (RSS), and Stanford Sleepiness Scale (SSS) were used to assess anxiety, sedation, and sleepiness before and 90 minutes after premedication. Heart rate (HR), systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures were also measured. For intragroup comparison, a paired t-test and for intergroup comparison, ANOVA (Analysis of Variance) and difference-in-differences regression analysis were performed.

Results: The three groups (group A: oral melatonin 0.3 mg/kg, group B: oral melatonin 0.5 mg/kg, group C: placebo) each having 30 patients were comparable with regard to demographic profiles with insignificant p-value. Melatonin had no significant anxiolytic impact when compared to placebo ($p>0.05$). However, melatonin offered considerable sedation and haemodynamic stability in a dose-dependent manner. Melatonin 0.5 mg/kg (group B) gave better sedation (RSS score: 3.30±0.11) and haemodynamic stability (fall in Mean Heart Rate: by 7.4 after premedication) than melatonin 0.3 mg/kg) (RSS score: 2.77±0.12; fall in mean Heart rate after premedication: by 7.76) than the placebo (RSS score: 2.17±0.07; fall in mean Heart Rate: by 0.2).

Conclusion: Oral melatonin provides better sedation and haemodynamic stability during endotracheal intubation in a dose-dependent manner when compared to placebo. But when required for sole anxiolysis melatonin was similar to placebo. Further studies are warranted to explore the safe dose for the anxiolytic effect of oral melatonin in cancer patients.

Keywords: Adjuvant, Anxiety, Haemodynamic, Preoperative, Sedation

INTRODUCTION

Anxiousness is common for any patient before surgery. However, it is more pronounced in cancer patients than the general population or those with chronic illnesses when they are posted for surgery. A mixture of positive and negative experiences is involved in cancer management, with anxiety and fear working against the hope of alleviation from the illness [1]. The life-threatening nature of cancer disorders and the associated fear of recurrence or death augments the preoperative anxiety (uneasiness or unpleasant tension secondary to patient's concern about hospitalisation, anaesthesia, and surgery). Preoperative anxiety has deleterious effects on patient's intraoperative and postoperative outcome [2]. Thus, reducing preoperative anxiety becomes an important goal for preoperative counselling and premedication in anaesthesiology management.

Premedication with benzodiazepines is a common practice for perioperative anxiety [3,4]. However, benzodiazepines are associated with several residual effects, including suppression of Rapid Eye Movement (REM) sleep [5]. For cancer patients with altered metabolic states and pathological anxiety, a note worthy alternative for benzodiazepines with few side effects will be beneficial.

Melatonin (N-acetyl-5-methoxytryptamine) regulates the circadian rhythm and is a hormone produced chiefly 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 [6]. Melatonin was found to be associated with preoperative anxiolysis [7]. With low toxicity, no residual effects, or REM sleep suppression, melatonin offers a note worthy alternative for benzodiazepines in ameliorating preoperative anxiety. Various studies have reported perioperative use of melatonin as an anxiolytic [5]; however, there are no studies on perioperative use of melatonin in oncosurgery patients [5,10].

It was hypothesised that oral melatonin when given as premedication would produce anxiolysis with minimal side effects in a dose dependent manner. Hence, the present study aimed to analyse the preoperative anxiolysis, sedation, sleepiness and haemodynamic response to intubation after premedication with oral melatonin at two different doses of 0.3 mg/kg and 0.5 mg/kg body weight compared with placebo. The primary outcome was preoperative anxiolysis and the secondary outcomes were sedation, sleepiness and haemodynamic response to intubation.

MATERIALS AND METHODS

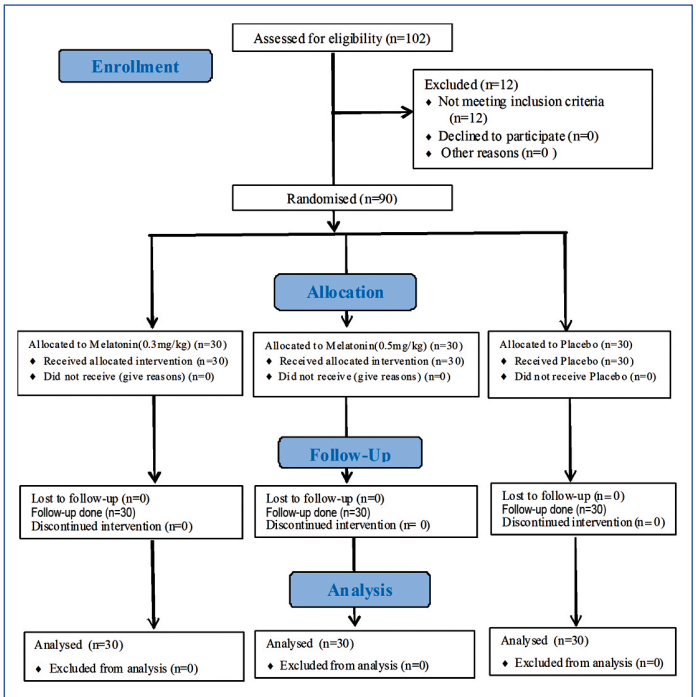
The study was carried out in Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, India, using a three-arm, single-blind, parallel-group, placebo-controlled randomised trial. The Institute Ethics committee approved the study (KCI/MEC/010/10 dtd 03 August 2018) and the study was registered in Clinical Trials Registry of India (CTRI/2018/10/015917).

Inclusion criteria: After obtaining written informed consent,a total of 90 cancer patients aged 18-60 years with American Society of Anaesthesiologists (ASA) physical status Grade 1 and 2 undergoing elective oncological surgeries under general anaesthesia were included in the present study.

Exclusion criteria: Patients who did not give written informed consent, patients with chronic hypertension, severe cardiac disease, or diabetes mellitus with autonomic neuropathy, significant hepatorenal impairment, psychiatric illness, bronchial asthma, patients on drugs like antihypertensive, antipsychotics, and antiepileptics, patients with history of allergy to drug, patients with sleep disorder, obesity, upper respiratory tract infection and anticipated difficult airway were excluded from the study.

Sample size calculation: The sample size was based on previous studies[11,12]. A sample size of 26 per group was sufficient to determine a difference in VAS score of 0.9 units between the melatonin and placebo group with a pooled standard deviation of 1 unit to provide 90% power and a-error of 0.05. To account for attrition and multiple outcomes, the sample size was increased to 30 patients/group.

Patients satisfying inclusion criteria were randomised into three groups of 30 patients each, using the computer-generated list. Patients in the three groups (Group A, B and C) received oral melatonin 0.3 mg/kg, oral melatonin 0.5 mg/kg and placebo, respectively [Table/Fig-1]. Neither the patient nor the anaesthesiologist had any role in the allocation of patient to each group.



[Table/Fig-1]: CONSORT flow diagram.

All eligible patients received pre-anaesthetic check-up and completed all the necessary investigations. The study patients received a standardised pre-anaesthetic counselling with the anaesthetist that included an explanation about the nature of the study, various scales used in the study besides explaining the anaesthetic procedure, possible complications, their management, and postoperative pain. The patients then chose sealed envelopes (carrying the label for each group) for random allocation into three groups. All of the patients were required to fast for eight hours. On arrival at the preoperative room, NPO (Nothing Per Oral) status was confirmed, preoperative assessments were made, and patients received their assigned preoperative medication with sips of water 90 minutes before surgery.

Blinding: The study was single blinded and the participants were not aware of their allocation. Following, pre-anaesthetic counselling, the patients were asked to choose the sealed envelopes that contained a label for allocation into three groups. The envelopes were not opened infront of the patients and the patients were assigned to groups based on the labels A, B, and C. The investigators assigning the intervention and assessing the outcomes were not blinded.

Outcome assessments: The primary outcome was scores from Visual Analogue Scale (VAS) for anxiety. The secondary outcomes were Ramsay Sedation Scale (RSS) score for sedation, Stanford sleepiness scale score for sleepiness and haemodynamic parameters {Heart Rate (HR), Systolic (SBP), Diastolic (DBP) and Mean Arterial (MAP) blood pressures}. All the outcomes were assessed just before and 90 minutes after premedication. Adverse effects like nausea, vomiting, dizziness, headaches were also recorded. After 90 minutes, the patient was shifted to the operating room.

Primary Outcome

Anxiety score: The VAS for anxiety was used for assessment. It is a numeric verbal rating scale consisting of 11 stick-figure ranked from 0-10 displaying various facial expressions. Participants have to place a finger on the facial expressions that match with their current state. Face A0 represents no anxiety, and face A10 represents the highest anxiety [8].

Secondary Outcomes

Ramsay sedation score: This was evaluated using RSS. It is the most simplistic tool with a numeric score from 1 to 6, based on the responsiveness of the patient. It has to be scored by the experimenter/investigator. It is a subjective tool, 1 indicating patient awake, anxious and 6 indicating patient asleep with no response to external stimulus [9].

Stanford sleepiness scale: It is a subjective measure that evaluates sleepiness at specific moments in time. It is used for research and clinical purposes. The respondents are required to select one of the seven statements that best represent their level of perceived sleepiness, with 1 representing wide awake and 7 representing sleep onset [10].

Haemodynamic parameters: Haemodynamic parameters such as HR, SBP, DBP and MAP were recorded using multi-parameter patient monitoring system just before premedication, 90 min after premedication (just before induction), immediately, and at 5, 10 and 15 minutes after intubation.

Anaesthesia Procedure

In the operation theatre, an intravenous line was secured and adequate intravenous crystalloid infusion was started for all patients. Intraoperative monitoring included Non Invasive Blood Pressure (NIBP), MAP, continuous Electrocardiography (ECG) and Peripheral Capillary Oxygen Saturation (SpO_2). Premedication, induction and maintenance of anaesthesia were standardised as per Institutional protocol. All patients were premedicated with injection Ondansetron (0.05 mg/kg) and injection Fentanyl (1.5 mcg/kg). Patients were pre-oxygenated with 100% oxygen for three minutes; general anaesthesia was induced with Propofol (titrated to loss of verbal response to command). After confirming the adequacy of ventilation, Succinylcholine (1.5 mg/kg) was administered. Patients were put on volume-controlled mode of mechanical ventilation following oral intubation and confirmation of tube position by bilateral five-point auscultation. Balance anaesthesia was maintained with nitrous oxide 50%, O_2 50% and Isoflurane. For maintenance of muscle relaxation, Vecuronium bromide 0.08 mg/kg loading dose and 0.01 mg/kg maintenance dose was given. Neuromuscular blockade was reversed using Neostigmine (0.05 mg/kg) and Glycopyrrolate (0.01 mg/kg) at the end of surgery. Once the patient started breathing spontaneously and adequately, the patient's trachea was extubated and shifted to Surgical Intensive Care Unit (SICU). Haemodynamic parameters such as HR, SBP, DBP and MAP were recorded just before premedication, 90 minutes after premedication (just before induction), immediately after intubation, 5, 10 and 15 minutes thereafter.

STATISTICAL ANALYSIS

Data were entered into microsoft excel and analysed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA). Descriptive statistics for categorical variables included frequency and percentages; means, and standard deviations for continuous variables. Categorical data

were compared using Chi-square test. Paired t-test was used for intragroup comparison; ANOVA (Analysis of Variance) and difference-in-differences regression analysis was used for intergroup comparison [13]. The p-value <0.05 was considered statistically significant.

RESULTS

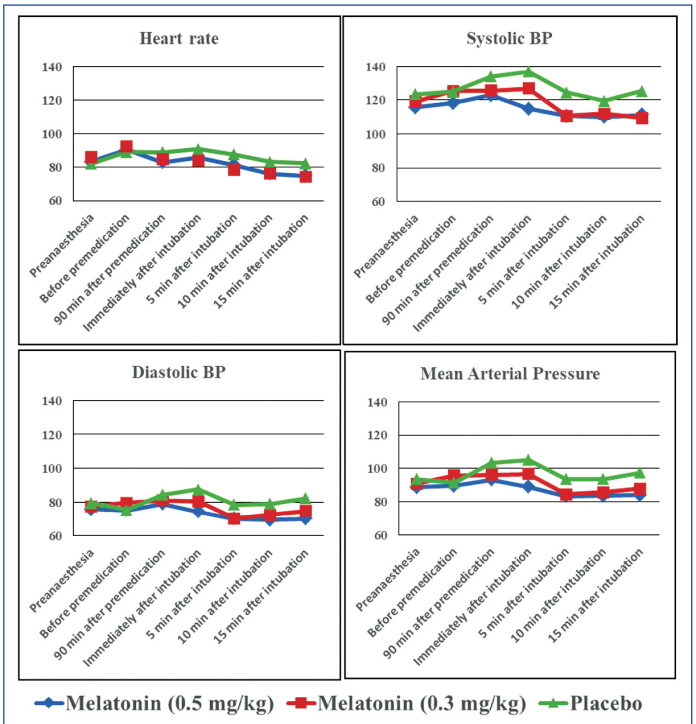
Among the 102 patients eligible for the study, 90 were included and randomised into three groups (30/group) [Table/Fig-1]. The three groups had comparable demographic profile [Table/Fig-2]. There were no dropouts in any of the groups.

Parameters	Group A (Melatonin 0.3 mg/kg) (n=30)	Group B (Oral melatonin 0.5 mg/kg) (n=30)	Group C (Placebo) (n=30)	p-value
Age (years), (Mean±SD)	43.53±13.29	39.90±10.88	45.17±10.02	0.197*
Sex, (Male:Female ratio)	21:9	21:9	24:6	0.600†
Height, (cm) (Mean±SD)	157.27±8.54	157.10±8.23	155.87±5.46	0.735*
Weight, (Kg) (Mean±SD)	57.37±9.19	53.73±10.87	55.37±10.39	0.387*
ASA grade (1:2) ratio	16:14	20:10	13:17	0.191†
Previous surgery (No:Yes)	11:19	8:22	11:19	0.871†
Heart Rate (HR)variability, (beats/minute) (Mean±SD)	86.07±10.16	83.37±11.90	82.23±9.25	0.352*

[Table/Fig-2]: Baseline characteristics demographic of study participants in three groups Group A=melatonin 0.3 mg/kg; Group B=melatonin 0.5 mg/kg; Group C=Placebo.
SD: Standard deviation; ASA: American society of anaesthesiologists; *Student t-test; †Chi-square test

Intragroup comparison, before premedication and 90 minutes after premedication, showed a decrease in VAS anxiety score and an increase in sedation and sleepiness score [Table/Fig-3]. This trend was more pronounced in Group B (melatonin 0.5 mg/kg) followed by Group A (melatonin 0.3 mg/kg), and Group C (Placebo). The change in VAS anxiety score, sedation and sleepiness score before and 90 minutes after premedication were significant (p<0.05) in all the three groups, except for the sleepiness score in the placebo group. When intergroup comparison was done using difference-in-difference analysis, the reduction in VAS score between before premedication and 90 minutes after premedication was higher in Group B (melatonin 0.5 mg/kg) as compared with Group A (melatonin 0.3 mg/kg) and Group C (Placebo). However, this reduction was not statistically significant,thus indicating that oral melatonin either in 0.5 mg/kg or 0.3 mg/kg does not produce significant anxiolysis as compared with placebo [Table/Fig-3].

The intergroup comparison of sedation and sleepiness scores (between that of before premedication and 90 minutes after premedication) showed a significant increase in sedation and sleepiness scores for Group B (melatonin 0.5 mg/kg), followed by Group A (melatonin 0.3 mg/kg) as compared with Group C (Placebo). This indicates that melatonin given as 0.5 mg/kg had greater sedation compared with melatonin (0.3 mg/kg) and the placebo group. Comparing the haemodynamic parameters using ANOVA, there was a significant decrease in mean HR after 90 minutes of premedication when compared to before premedication HR in Melatonin 0.5 mg/kg group (by 7.4) and in melatonin 0.3 mg/kg group (by 7.76) when compared to the placebo group (by 0.2), indicating a decrease in mean HR after premedication with melatonin when compared to placebo [Table/Fig-4].



[Table/Fig-4]: Comparison of haemodynamic parameters between three groups at different periods of follow-up.
BP: Blood Pressure; Group A: melatonin 0.3 mg/kg; Group B: melatonin 0.5 mg/kg; Group C: Placebo group

There was an increase in HR just immediately after intubation when compared to those of after premedication values; however, it was not significant between the groups. The mean HR was significantly higher in the placebo group (87.73±13.29 beats/minute, 83.30±13.31 beats/minute and 82.43±14.84 beats/minute at 5, 10 and 15 minutes respectively) when compared with melatonin

Group	Before premedication (Mean±SD)	90 Minutes after premedication (Mean±SD)	Difference (Mean±SD)	p-value	Groups compared	Difference-in-difference			
						Estimate	95% CI Lower limit	95% CI Upper limit	p-value
Anxiety (VAS anxiety score)									
Group A	4.23±0.38	2.13±0.31	2.10±0.23	**<0.001***	Group A Vs Group C	0.23	-0.92	1.39	0.691
Group B	3.80±0.36	1.20±0.22	2.60±0.21	**<0.001***	Group B Vs Group C	0.73	-0.42	1.89	0.213
Group C	3.76±0.32	1.90±0.30	1.86±0.16	**<0.001***	Group A Vs Group B	-0.50	-1.66	0.66	0.395
Sedation (Ramsay sedation score)									
Group A	1.93±0.05	2.77±0.12	-0.83±0.12	**<0.001***	Group A Vs Group C	-0.63	-0.94	-0.33	**<0.001***
Group B	2.00±0.00	3.30±0.11	-1.30±0.11	**<0.001***	Group B Vs Group C	-1.10	-1.40	-0.80	**<0.001***
Group C	1.97±0.03	2.17±0.07	-0.20±0.07	**0.012***	Group A Vs Group B	0.47	0.16	0.77	**0.003***
Stanford sleepiness scale									
Group A	1.07±0.05	2.90±0.33	-1.83±0.31	**<0.001***	Group A Vs Group C	-1.47	-2.37	-0.56	**0.002***
Group B	1.37±0.09	4.57±0.38	-3.20±0.30	**<0.001***	Group B Vs Group C	-2.83	-3.74	-1.93	**<0.001***
Group C	1.03±0.03	1.40±0.22	-0.37±0.19	0.06	Group A Vs Group B	1.37	0.46	2.27	**0.003***

[Table/Fig-3]: Difference-in-differences regression analysis for intergroup comparison of study parameters.
Group A=melatonin 0.3 mg/kg; Group B=melatonin 0.5 mg/kg; Group C=Placebo. *Statistically significant. VAS: Visual analogue scale; CI: Confidence interval

0.5 mg/kg group (81.30±11.37 beats/minute, 76.27±10.72 beats/minute and 74.3±10.87 beats/minute at 5, 10 and 15 minutes, respectively) and melatonin 0.3 mg/kg group (78.40±12.89 beats/minute, 76.23±12.42 beats/minute and 74.33±11.96 beats/minute at 5, 10 and 15 minutes, respectively). The p-values (ANOVA) for HR comparison between the three groups at 5, 10 and 15 minutes were 0.016, 0.04 and 0.026, respectively.

After intubation., the placebo group had significantly higher mean SBP (136.9±27.2 mm of Hg, 124.4±15.1 mm of Hg, 119.4±15.6 mm of Hg, and 125.3±19.1 mm of Hg at 0, 5, 10 and 15 minutes, respectively) than the Melatonin 0.5 mg/kg (114.9±19.9 mm of Hg,110.7±13.3 mm of Hg, 110.0±12.9 mm of Hg and 111.3±14.8 mm of Hg at 0, 5, 10 and 15 minutes, respectively) and Melatonin 0.3 mg/kg (126.7±23.1 mm of Hg, 110.7±19.3 mm of Hg, 112.0±15.3 mm of Hg, and 109.4±22.5 mm of Hg at 0, 5, 10 and 15 minutes, respectively) groups. The p-values (ANOVA) for SBP comparison between the three groups at 0 (immediate) 5, 10 and 15 minutes were 0.002, 0.001, 0.038 and 0.003, respectively.

Similarly, mean DBP were significantly higher in the placebo group (87.5±16.6 mm of Hg, 78.5±10.2 mm of Hg, 79.0±13.8 mm of Hg, and 82.2±14.7 mm of Hg at 0, 5, 10 and 15 minutes, respectively) than the Melatonin 0.5 mg/kg (74.4±15.2 mm of Hg, 70.0±11.1 mm of Hg, 69.5±12.3 mm of Hg, and 70.1±13.1 mm of Hg at 0, 5, 10 and 15 minutes, respectively) and Melatonin 0.3 mg/kg (80.5±15.3 mm of Hg, 70.3±12.5 mm of Hg, 72.3±12.0 mm of Hg, and 74.8±11.4 mm of Hg at 0, 5, 10 and 15 minutes, respectively) groups from intubation to 15 minutes after intubation. The p-values (ANOVA) for DBP comparison between the three groups at 0 (immediate) 5, 10 and 15 minutes were 0.007, 0.006, 0.015 and 0.002, respectively. The MAP was also observed significantly higher in the placebo group (105.2±19.7 mm of Hg, 93.7±9.7 mm of Hg, 93.8±12.8 mm of Hg, and 97.5±15.6 mm of Hg at 0, 5, 10 and 15 minutes, respectively) than the Melatonin 0.5 mg/kg (88.9±16.8 mm of Hg, 83.4±12.0 mm of Hg, 83.6±10.4 mm of Hg, and 84.1±11.6 mm of Hg at 0, 5, 10 and 15 minutes, respectively) and Melatonin 0.3mg/kg (96.7±18.6 mm of Hg, 84.5±14.9 mm of Hg, 85.8±11.6 mm of Hg and 88.0±12.3 mm of Hg at 0, 5, 10 and 15 minutes, respectively) groups from intubation to 15 minutes after intubation. The p-values (ANOVA) for DBP comparison between the three groups at 0 (immediate) 5, 10 and 15 minutes, were 0.004, 0.003, 0.003 and 0.001, respectively. However, there was no significant difference in mean SBP, DBP and MAP between Melatonin 0.5 mg/kg vs Melatonin 0.3 mg/kg from intubation to 15 minutes after intubation. Thus, melatonin helps in the attenuation of haemodynamic response to intubation. Melatonin at dose of 0.5 mg/kg does not have any additional adverse effect (headache, nausea) compared to Melatonin 0.3 mg/kg.

DISCUSSION

Preoperative anxiety and endotracheal intubation can cause a variety of stress responses that are both intraoperatively and postoperatively detrimental to the patient [14,15]. Benzodiazepines, opioids, and barbiturates, which are currently in use, have severe side effects and should only be used when recommended for anxiety and sedation [16]. In oncological patients, safe pre-medicants with low adverse effects are necessary since they carry the danger of unpredictable action [17]. With oral melatonin being studied for a variety of purposes, including anxiolysis in the perioperative phase and as an adjuvant to anaesthetics [18,19], the present study was undertaken to compare the effectiveness of the two doses of oral melatonin with placebo as a premedicant for patients scheduled to undergo oncological surgery under general anaesthesia. The study did not find any significant anxiolytic effect of melatonin when compared to placebo. Further, the results showed melatonin to cause significant sedation and haemodynamic stability in patients as compared to placebo. Also, melatonin in a higher dose (0.5 mg/kg) produced better sedation and haemodynamic stability in patients compared to a lower dose of 0.3 mg/kg.

Studies conducted by Khare A et al., Patel T and Kurdi MS; Ismail SA and Mowafi HA; and Ionescu D et al., had documented the significant anxiolytic effect of melatonin compared to placebo [11,12,20,21]. In contrast, the present study finding indicated melatonin not more effective than a placebo in reducing anxiety. This is quite similar to studies by Capuzzo M et al., and Isik B et al., They found no significant anxiolytic effect for melatonin compared with placebo [22,23]. It was argued that a lesser dose of melatonin and older age of the patients could contribute to the insignificant anxiolytic effects of melatonin[12]. Refractoriness of the elderly population to the anxiolytic effects of melatonin is well documented [12,19]. Though a higher dose (0.5 mg/kg) of melatonin was used, the current study did not find significant anxiolytic effects. Because cancer patients are more susceptible to extreme anxiety, the anxiolytic impact of melatonin may have been reduced in elderly population in the current study. There is no other published study that used oral melatonin for cancer patients in India. More research is required to explore the optimal and safe dose of oral melatonin as premedicant for its anxiolytic effects in cancer patients.

Similar to other studies, the current study reported an increased sedation score for melatonin as compared with the placebo group [11,12,24,25]. However, studies by Isik B et al., Sury MRJ and Fairweather K, did not find any significant sedative effect of melatonin [23,26]. This could be due to heterogeneous sample of children undergoing Magnetic Resonance Imaging (MRI) with resistance to easy sedation included in these studies. A study conducted by Dollins AB et al., concluded that melatonin improved sleepiness [27]. Similar to this study, sleepiness was better with the melatonin group than the placebo group in this study. The sedation and sleepiness score in melatonin groups was not deleterious as the patients were calm and easily arousable from their sedation state (mild sedation). They did not have any difficulty in intubation as they all had normal airway assessment preoperatively. In fact, the low sedation and sleepiness in the placebo group could have had disadvantage in terms of increased haemodynamic parameters. In contrast to this study, Jockovich M et al., concluded no beneficial effects of a 1 mg melatonin dose on sleep [28]. In the current study, higher doses of melatonin was used and the melatonin group showed better sleepiness when compared to placebo. Further, the present study also documented the sedative properties of melatonin in a dose-dependent manner. However, unlike previous studies, the present study did not compare melatonin with midazolam [12,24]. These studies that used midazolam had the highest degree of sedation for midazolam compared to melatonin and placebo. This highlights less precise monitoring for patients on oral melatonin (mild sedation) when compared to patients who receive midazolam (deep sedation) [24].

Gupta P et al., observed oral melatonin to produce stable haemodynamics at 60-120 minutes after premedication [29]. Similar to this study, the study found that increase in blood pressure in response to endotracheal intubation was lesser in melatonin group when compared to the placebo group [29].The haemodynamic response during endotracheal intubation after melatonin premedication was studied by Mohamed AA et al., [30]. They concluded that preoperative administration of melatonin provided a significant decrease in haemodynamic response of direct laryngoscopy and tracheal intubation. Concordance to that study, the present study found that blood pressure decrease was better in melatonin group when compared to the placebo group. Comparable to Gupta P et al., study, in this study, HR response to endotracheal intubation was better attenuated in melatonin groups when compared to the placebo group [29]. However, Mohamed AA et al., did not find significant difference in HR for Group II (melatonin 6 mg tablet group) and Group III (melatonin 9 mg tablet group) as compared to the control group [30]. In contrast

to this study, the present sudy used higher doses of melatonin, and showed significant reduction in HR at 0, 5, 10 and 15 minutes after intubation. The present study was the first study to document the dose-dependent effect of melatonin in cancer patients to the best of our knowledge. The present study used 0.5 mg/kg and 0.3 mg/kg of oral melatonin in adult cancer patients with minimal side effects compared to either smaller doses or sublingual routes used in previous studies [21,31].

Limitation(s)

One of the study's limitations was that it did not assess the anxiolytic and sedation properties postoperatively, which could have provided better insights on the usefulness of melatonin in postoperative care for ambulatory or day care surgeries. Further, the study was not double-blinded and was not designed for cost analysis. As the study was conducted in an oncology centre, the study was limited in knowing the dose-dependent effects of melatonin in general non oncological populations. The interaction of oral melatonin with endogenous melatonin could not be assessed as the plasma levels of melatonin was not measured.

CONCLUSION(S)

When compared to placebo, oral melatonin offers more sedation and sleepiness with greater haemodynamic stability during endotracheal intubation. When compared to melatonin at 0.3 mg/kg, melatonin at a dose of 0.5 mg/kg had a greater benefit in terms of sedation and sleepiness with less side effects. Melatonin is comparable to placebo when used alone for anxiolysis. More research is needed to determine the safe dose of oral melatonin for cancer patients' anxiolytic effect.

REFERENCES

[1] Stark DP, House A. Anxiety in cancer patients. Br J Cancer. 2000;83(10):1261-67.
[2] Kim WS, Byeon GJ, Song BJ, Lee HJ. Availability of preoperative anxiety scale as a predictive factor for haemodynamic changes during induction of anesthesia. Korean J Anesthesiol. 2010;58(4):328-33.
[3] Hata TM, Hata JS. Preoperative Patient Assessment and Management. In: Barash PG, Cullen BF, Stoelting RK, Cahalan M, Stock MC, Ortega R, editors Clinical Anesthesia. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. Pp. 603-07.
[4] Moppett IK, Aitkenhead AR. Preoperative Assessment and Premedication. In: Aitkenhead A, Thompson J, Rowbotham J, Moppett I, editors Smith and Aitkenhead's textbook of Anaesthesia. 6th ed. London: Churchill Livingstone; 2013. Pp. 373-75.
[5] Madsen BK, Zetner D, Møller AM, Rosenberg J. Melatonin for preoperative and postoperative anxiety in adults. Cochrane Database Syst Rev. 2020;12:CD009861.
[6] Coloma FM, Niles LP. Melatonin enhancement of [3H]-gamma-aminobutyric acid and [3H] muscimol binding in rat brain. Biochem Pharmacol. 1988;37(7):1271-74.
[7] Naguib M, Samarkandi AH. The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: A double-blinded, placebo-controlled study. Anesth Analg. 2000;91(2):473-79.
[8] Cao X, Yumul R, ElvirLazo OL, Friedman J, Durra O, Zhang X, et al. A novel visual facial anxiety scale for assessing preoperative anxiety. PLoS One. 2017;12(2):e0171233.
[9] Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2(5920):656-59.
[10] MacLean AW, Fekken GC, Saskin P, Knowles JB. Psychometric evaluation of the Stanford Sleepiness Scale. J Sleep Res. 1992;1(1):35-39.
[11] Khare A, Thada B, Jain N, Singh D, Singh M, Sethi SK. Comparison of effects of oral melatonin with oral alprazolam used as a premedicant in adult patients undergoing various surgical procedures under general anesthesia: A prospective randomized placebo-controlled study. Anesth Essays Res. 2018;12(3):657.
[12] Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. J Anaesthesiol Clin Pharmacol. 2015;31(1):37-43.
[13] Amudhan S, Mani K, Rai SK, Pandav CS, Krishnan A. Effectiveness of demand and supply side interventions in promoting institutional deliveries-a quasi-experimental trial from rural north India. Int J Epidemiol. 2013;42(3):769-80.
[14] Bansal T, Joon A. Preoperative anxiety-an important but neglected issue: A narrative review. Indian Anaesth Forum. 2016;17(2):37-42.
[15] Sigdel S. Perioperative anxiety: A short review. Glob AnesthPerioper Med. 2015;1(4):107-08.
[16] Butterworth IV JF, Mackey DC, Wasnick JD. Preoperative Assessment, Premedication, & Perioperative Documentation. In: Morgan & Mikhail's Clinical Anesthesiology. 6th ed. New York, NY: McGraw-Hill Education; 2018. Pp. 300-01.
[17] Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. BMJ. 2018;361:k1415.
[18] Maitra S, Baidya DK, Khanna P. Melatonin in perioperative medicine: Current perspective. Saudi J Anaesth. 2013;7(3):315-21.
[19] Kurdi MS, Patel T. The role of melatonin in anaesthesia and critical care. Indian J Anaesth. 2013;57(2):137-44.
[20] Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth Analg. 2009;108(4):1146-51.
[21] Ionescu D, Bădescu C, Ilie A, Miclutia I, Iancu C, Ion D, et al. Melatonin as premedication for laparoscopic cholecystectomy: A double-blind, placebo-controlled study. South Afr J Anaesth Analg. 2008;14(4):08-11.
[22] Capuzzo M, Zanardi B, Schiffino E, Buccoliero C, Gragnaniello D, Bianchi S, et al. Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesth Analg. 2006;103(1):121-23.
[23] Isik B, Baygin O, Bodur H. Premedication with melatonin vs midazolam in anxious children. Paediatr Anaesth. 2008;18(7):635-41.
[24] Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. Eur J Anaesthesiol. 2004;21(7):553-57.
[25] Pokharel K, Tripathi M, Gupta PK, Bhattarai B, Khatiwada S, Subedi A. Premedication with oral alprazolam and melatonin combination: A comparison with either alone- A randomized controlled factorial trial. Biomed Res Int. 2014;2014:356964.
[26] Sury MRJ, Fairweather K. The effect of melatonin on sedation of children undergoing magnetic resonance imaging. Br J Anaesth. 2006;97(2):220-25.
[27] Dollins AB, Lynch HJ, Wurtman RJ, Deng MH, Kischka KU, Gleason RE, et al. Effect of pharmacological daytime doses of melatonin on human mood and performance. Psychopharmacology. 1993;112(4):490-96.
[28] Jockovich M, Cosentino D, Cosentino L, Wears RL, Seaberg DC. Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts. Acad Emerg Med. 2000;7(8):955-58.
[29] Gupta P, Jethava D, Choudhary R, Jethava DD. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. Indian J Anaesth. 2016;60(10):712-18.
[30] Mohamed AA, Atef HM, El Kassaby AM, Ismail SA, Helmy AM. Effects of melatonin premedication on the hemodynamic responses and perfusion index during laryngoscopy and endotracheal intubation. Med J Cairo Univ. 2013;81(1):859-67.
[31] Mowafi HA, Ismail SA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. Anesth Analg. 2008;107(4):1422-26.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 26, 2021
- Manual Googling: Oct 30, 2021
- iThenticate Software: Nov 18, 2021 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 23, 2021**
Date of Peer Review: **Nov 13, 2021**
Date of Acceptance: **Nov 19, 2021**
Date of Publishing: **Dec 01, 2021**