

## ORIGINAL INVESTIGATION

## Role of melatonin in attenuation of hemodynamic response to intubation and anesthetic requirements: a randomized, controlled, double-blind study



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### KEYWORDS

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Propofol

### Abstract

**Background:** Melatonin has been studied to have anxiolytic, sedative, and analgesic effects. However, there is limited data on the effect of melatonin in the attenuation of hemodynamic response to intubation. We aimed to study whether preanesthetic oral melatonin attenuates hemodynamic responses to intubation and anesthetic requirements.

**Methods:** Sixty-four patients scheduled for laparoscopic cholecystectomy were randomized into melatonin or placebo group (n = 32 each). Melatonin group received two tablets (3 mg each) of melatonin, and the placebo group received two tablets of vitamin D3 120 min before induction. Hemodynamic parameters were recorded during induction and postintubation for 15 minutes. Total induction dose of propofol, total intraoperative fentanyl consumption, and adverse effects of melatonin were also noted.

**Results:** Postintubation rise in heart rate (HR) was less in the melatonin group compared to the placebo group (10.59% vs. 37.08% at 1 min, respectively) ( $p < 0.0001$ ). Maximum percentage increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) was lesser in melatonin group than placebo group (SBP 9.25% vs. 37.73%, DBP 10.58% vs. 35.51%, MBP 9.99% vs. 36.45% at 1 min postintubation, respectively) ( $p < 0.0001$ ). Induction dose of propofol ( $1.42 \text{ mg} \cdot \text{kg}^{-1}$  vs.  $2.01 \text{ mg} \cdot \text{kg}^{-1}$ ) and the number of patients requiring additional fentanyl intraoperatively (3 vs. 11) were also significantly reduced in the melatonin group.

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**Conclusion:** Premedication with 6 mg of oral melatonin resulted in significant attenuation of postintubation rise in HR, SBP, DBP, and MBP. It also reduced the induction dose of propofol, total intraoperative fentanyl consumption without any adverse effects.

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## Introduction

Laryngoscopy and endotracheal intubation are some of the most noxious stimuli in anesthesia, which trigger reflex responses resulting in a marked increase in heart rate and blood pressure.<sup>1</sup> Such response is well tolerated by healthy individuals, but is associated with increased morbidity and mortality in patients with underlying coronary artery disease or cerebrovascular pathology. Various techniques and drugs have been used to attenuate these stress responses but each agent or technique has some limitation and therefore, there has always been a search for a new therapeutic option.<sup>2–4</sup>

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally-occurring hormone in the human body secreted by the pineal gland. Various studies have evaluated its hypnotic, sedative, analgesic, anxiolytic, anti-inflammatory, and antioxidative effects.<sup>5</sup> Melatonin has also been studied to decrease blood pressure along with the reduction of norepinephrine concentration.<sup>6</sup> Considering the above effects of melatonin and very limited study on the effect of melatonin on the attenuation of hemodynamic response to intubation as well as anesthetic requirements, we aimed to study whether preanesthetic oral melatonin attenuates hemodynamic responses to intubation and anesthetic requirements. Our hypothesis was that oral melatonin premedication will attenuate hemodynamic response to intubation and will decrease the induction dose of propofol and intraoperative fentanyl consumption. The primary objective of the present study was to observe the changes in hemodynamics during laryngoscopy and intubation.

## Methods

This prospective, randomized, double-blinded study was conducted after obtaining approval from Institutional Ethics Committee (Reference no. F. 1/Acad/MC/JU/17/17558), and registered under the clinical trial registry of India (CTRI/2018/12/016498). After written informed consent, 64 patients of either sex, aged 18 to 60 years, American Society of Anesthesiologists (ASA) physical status I/II, who were scheduled to undergo elective laparoscopic cholecystectomy surgery under general anesthesia requiring tracheal intubation were included in the study. The exclusion criteria were anticipated difficult airway, body mass index (BMI) > 30 kg.m<sup>-2</sup>, patients taking anxiolytics, sedatives, antipsychotic, or antiepileptic drugs, patients having a sleep disorder, hiatus hernia, gastroesophageal reflux, known allergy to melatonin, and a known case of coronary artery disease.

Using computer-generated random number table, 64 consecutive eligible patients were randomly allocated to either

the melatonin group (n=32) or placebo group (n=32), and allocation concealment was done using sealed opaque envelopes. Melatonin group patients received two tablets (3 mg each) of melatonin and placebo group patients received two tablets of vitamin D3, 120 minutes before induction. The study drugs of both groups were the same in size and color, given by the nursing staff in the pre-operative ward. The contents of tablets were unknown to the anesthesiologist involved in providing general anesthesia and recording observations.

One day before surgery, all patients underwent a detailed preoperative anesthesia evaluation and were kept fasting as per standard ASA protocol. All patients received oral alprazolam 0.25 mg and pantoprazole 40 mg the night before the surgery. On arrival to the operation theater, standard monitoring – pulse oximetry, noninvasive arterial blood pressure, electrocardiography, and capnography (S/5™ DatexOhmeda USA) – was applied, and baseline parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and arterial oxygen saturation (SpO<sub>2</sub>) were recorded.

After recording baseline parameters, all patients received injection of fentanyl 2 µg.kg<sup>-1</sup>. After preoxygenation with 100% oxygen for 3 minutes, anesthesia was induced with propofol 1% injection mixed with preservative-free lignocaine hydrochloride (20 mg in 10 ml propofol) administered by slow manual bolus till the loss of verbal response. Vecuronium bromide 0.1 mg.kg<sup>-1</sup> injection was administered to facilitate tracheal intubation, and the patient's lungs were manually ventilated for 3 minutes with 100% oxygen. Direct laryngoscopy was performed with Macintosh laryngoscope, and the trachea was intubated with an appropriate size cuffed endotracheal tube by the same person each time. The lungs were ventilated with a tidal volume of 6–8 mL.kg<sup>-1</sup> using volume-controlled ventilation with 5 cmH<sub>2</sub>O positive end-expiratory pressure (PEEP). The respiratory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure (EtCO<sub>2</sub>) 30–35 mmHg with an inspiratory/expiratory ratio of 1:2. Anesthesia was maintained with air (50%), oxygen (50%), isoflurane with a minimum alveolar concentration (MAC) of 1.0. Intraoperatively, supplemental analgesia was provided with fentanyl (0.5 µg.kg<sup>-1</sup>) injection bolus if HR or mean blood pressure (MBP) exceeded 30% of the preoperative values after excluding other causes like a light plane of anesthesia or creation of pneumoperitoneum. At the end of the surgery, all the patients received ondansetron 0.1 mg.kg<sup>-1</sup> and diclofenac sodium 1 mg.kg<sup>-1</sup> injection for postoperative emesis and analgesia, respectively. After completion of the surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 mg.kg<sup>-1</sup> and glycopyrrolate 0.01 mg.kg<sup>-1</sup>. Once awake and responsive, the patient was extubated and shifted to the postanesthesia care unit (PACU).

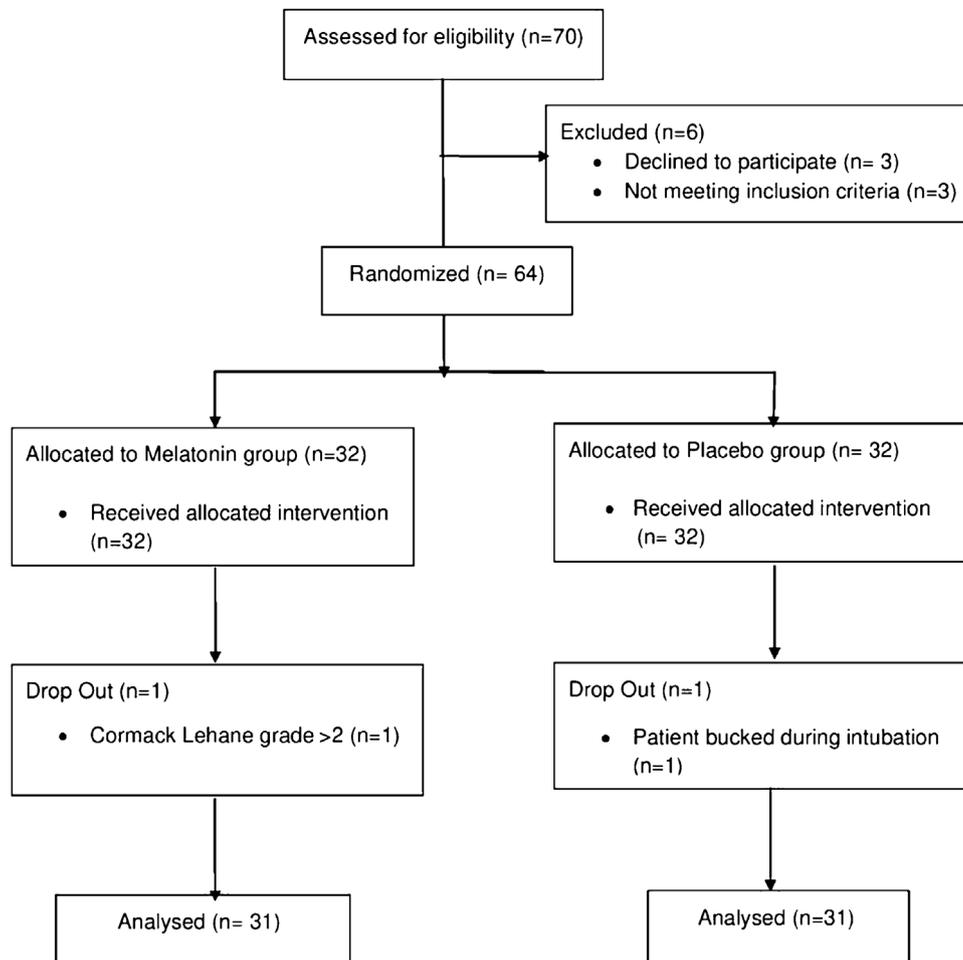


Figure 1 CONSORT flow diagram.

The primary objective of the present study was to observe the changes in hemodynamics during laryngoscopy and intubation for which HR, SBP, DBP, MBP, SpO<sub>2</sub>, EtCO<sub>2</sub> were continuously monitored and recorded at baseline (T0), 120 minutes after administration of study drug on arrival to operation theater (T1), after induction (T2), just before laryngoscopy and intubation (T3), after intubation at 1-min (T4), 3-min (T5), 5-min (T6), 10-min (T7) and 15-min (T8) intervals. During the study, the total dose of propofol required for induction and the number of patients requiring additional fentanyl intraoperatively were also recorded, which were the secondary objectives of study. Side effects of the study drugs like bradycardia, hypotension, nausea, vomiting, dizziness, headache, and respiratory depression were also observed till 24 hours postoperatively. The case was dropped from the study if the patient moved or bucked during laryngoscopy or intubation, Cormack Lehane grade<sup>7</sup> more than 2, or more than one attempt required for intubation.

The sample size was calculated for the primary objective to detect a minimum significant difference in heart rate at 1-min postintubation based on results of the pilot study conducted on 10 patients in each group. Based on the results of the pilot study, to detect a minimum of  $19 \pm 22$  beats/min difference in HR between the two groups 1-min postintuba-

tion a sample size of a minimum of 28 in each group was required with a power of 90% and alpha error of 0.05. Considering 10% attrition, the sample size was further enhanced and rounded to 31 in each group.

Statistical analysis was done using SPSS software version 20 (trial version) (SPSS Inc., Chicago, IL, USA). All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). The normality of data was checked by measures of skewness and Kolmogorov-Smirnov tests of normality. Demographic data were analyzed by Student's t-test and Chi-square test. ANOVA was used to analyze changes over time. Intergroup comparisons for hemodynamic parameters were made with unpaired t-test.

## Results

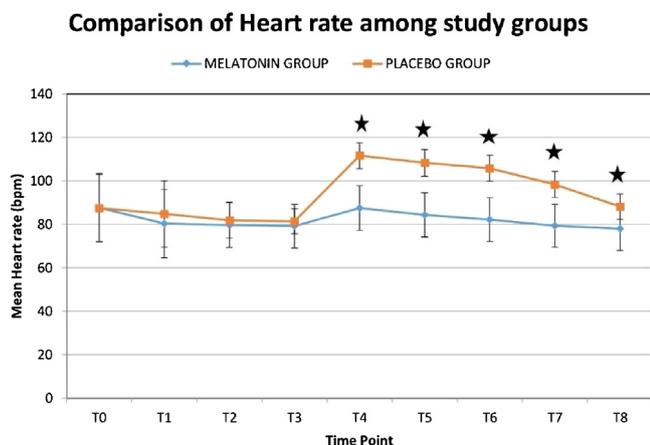
A total of 70 patients were assessed for eligibility, 6 patients were excluded, and 64 patients were included in the study and of which 2 were dropped out and finally, the results of 62 patients were analyzed (Fig. 1). The demographic characteristics of the patients, ASA physical status, patients on beta-blockers as antihypertensives, and duration of surgery were comparable between both groups (Table 1). Baseline

**Table 1** Demographic characteristics.

	Melatonin Group (n = 31)	Placebo Group (n = 31)	p
Age (years) (mean ± SD)	41.13 ± 10.43	40.13 ± 11.00	0.720
Weight (kg) (mean ± SD)	52.66 ± 5.03	52.26 ± 2.85	0.706
Sex (M/F) (numbers)	20/11	18/13	0.789
ASA (I/II) (numbers)	23/8	25/6	0.731
Patients on beta-blockers (n)	3	3	1
Duration of surgery (mean ± SD)	47.90 ± 8.08	49.30 ± 6.22	0.414

ASA, American Society of Anesthesiologists physical status.

Unpaired t-test used for comparing age, weight, and duration of surgery. Chi-Square test used for comparing sex, ASA physical status, and patients on beta-blockers.



**Figure 2** Comparison of heart rate among the study groups. T0, baseline; T1, 120 min after administration of study drug on arrival to operation theater; T2, after induction; T3, just before laryngoscopy and intubation; T4, 1 min after intubation; T5, 3 min after intubation; T6, 5 min after intubation; T7, 10 min after intubation; T8, 15 min after intubation.  $p$ -value < 0.0001.

ANOVA used to analyze changes over time. Unpaired  $t$ -test used for intergroup comparisons.

hemodynamic parameters were comparable between the two groups.

Figure 2 depicts the trend of HR in the melatonin and placebo groups. Two hours after administration of the study drug, a fall in HR was observed in the melatonin group as compared to baseline value and was also lower than that of the placebo group at all time intervals. After laryngoscopy and intubation an increase in HR was seen in both groups compared to preintubation value but the rise in HR was significantly less in the melatonin group compared to the placebo group (10.59% vs. 37.08% at 1 min and 6.60% vs. 33.08% at 3 min, respectively) which stabilized after 5 minutes in melatonin group, but the increased HR persisted even till 15 minutes postintubation in the placebo group. A significant difference in HR was observed between the two groups at all time points postintubation ( $p < 0.001$ ) (Fig. 2).

After oral intake of the study drug, significantly lower SBP, DBP, and MBP were seen in the melatonin group compared to baseline and was also lower than that of the placebo group, at almost all time intervals (Fig. 3A-C). After laryngoscopy and tracheal intubation, compared to preintubation

value, the increase in SBP, DBP, and MBP were significantly lower in the melatonin group than in the placebo group (SBP 9.25% vs. 37.73%, DBP 10.58% vs. 35.51%, MBP 9.99% vs. 36.45% at 1 min postintubation, respectively). Postintubation at all time points, a significant difference in SBP, DBP, and MBP was observed between the two groups ( $p < 0.001$ ) (Fig. 3A-C).

The mean total induction dose of propofol in the melatonin and placebo group was  $74.21 \pm 12.483$  mg and  $118.00 \pm 16.361$  mg, respectively, which was equivalent to  $1.42 \text{ mg} \cdot \text{kg}^{-1}$  and  $2.01 \text{ mg} \cdot \text{kg}^{-1}$  respectively, and the difference was statistically significant ( $p < 0.001$ ). In addition to an induction dose of fentanyl ( $2 \mu\text{g} \cdot \text{kg}^{-1}$ ), 11 patients in the placebo group and 3 patients in the melatonin group needed additional fentanyl boluses ( $0.5 \mu\text{g} \cdot \text{kg}^{-1}$ ) intraoperatively ( $p = 0.031$ ) (Table 2).

None of the patients in either group had any adverse events such as bradycardia, hypotension, nausea, vomiting, dizziness, headache, or respiratory depression.

## Discussion

The results of the present study show that 6 mg melatonin administered 120 minutes before induction of anesthesia resulted in significant attenuation of hemodynamic responses to laryngoscopy and tracheal intubation, and also reduced dose of propofol required for induction and total intraoperative fentanyl consumption. Melatonin has several advantages over other drugs such as opioids, alpha agonists, beta-blockers used for attenuation of hemodynamic responses to laryngoscopy and intubation. Melatonin is easily available and is easy to administer, is effective in attenuating the rise in both heart rate and blood pressure with no risk of bradycardia and hypotension. Exogenous melatonin has its peak effect ranging from 60 to 150 minutes. So, in the present study melatonin was administered 120 minutes before induction of anesthesia, and a dose of 6 mg was used based on our pilot study where desired effects were obtained with 6 mg, without any adverse effects.

The heart rate-lowering effect of melatonin as seen in the present study may be because of its anxiolytic action due to the synergy between melatonergic and GABAergic systems. Melatonin reduces mean blood pressure in healthy volunteers as shown in the present and previous studies, through a complex mechanism of action on the circulatory system by binding to specific melatonin receptors present in the blood vessels and interfering with the vascular response

**Table 2** Comparison of propofol and fentanyl requirements.

	Melatonin Group (n = 31)	Placebo Group (n = 31)	p
Induction dose of propofol (mg. kg <sup>-1</sup> ) (mean ± SD)	1.42 ± 0.31	2.01 ± 0.37	<0.001
N <sup>o</sup> of patients requiring additional fentanyl boluses (0.5 µg.kg <sup>-1</sup> ) intraoperatively (n)	3	11	0.031

Unpaired t-test used for comparing induction-dose of propofol. Chi-Square test used for comparing patients requiring additional fentanyl boluses.

to catecholamine,<sup>8</sup> and also by smooth muscle relaxation of the arterial walls by increasing nitric oxide availability.<sup>9</sup> In the present study, after administration of melatonin, both HR and blood pressure were lower than baseline values at all time points. After laryngoscopy and tracheal intubation, rise in the HR and blood pressure was significantly less compared to the placebo group. Hemodynamic response to tracheal intubation is attributed to a rise in a plasma catecholamine, and we observed significant attenuation of this response with oral melatonin, which is known to cause a reduction in adrenergic outflow and catecholamines levels by interfering with the peripheral and central autonomic system.<sup>10</sup> Our results were in agreement to the study by Gupta et al.<sup>11</sup> and Choudhary et al.<sup>12</sup> where 6 mg of orally administered melatonin resulted in attenuation of the rise in both HR and blood pressure after intubation, however in the above studies, the requirement of anesthetic agents like propofol and fentanyl were not compared, and were also compared and found to be decreased in the melatonin group of our study. In another study by Mohammed et al., oral melatonin 6 mg and 9 mg were compared with placebo for attenuation of hemodynamic response to intubation and significant reduction of blood pressure was observed in both melatonin groups compared to the placebo group. However, no difference was observed in the changes in HR in the melatonin and placebo group postintubation.<sup>13</sup>

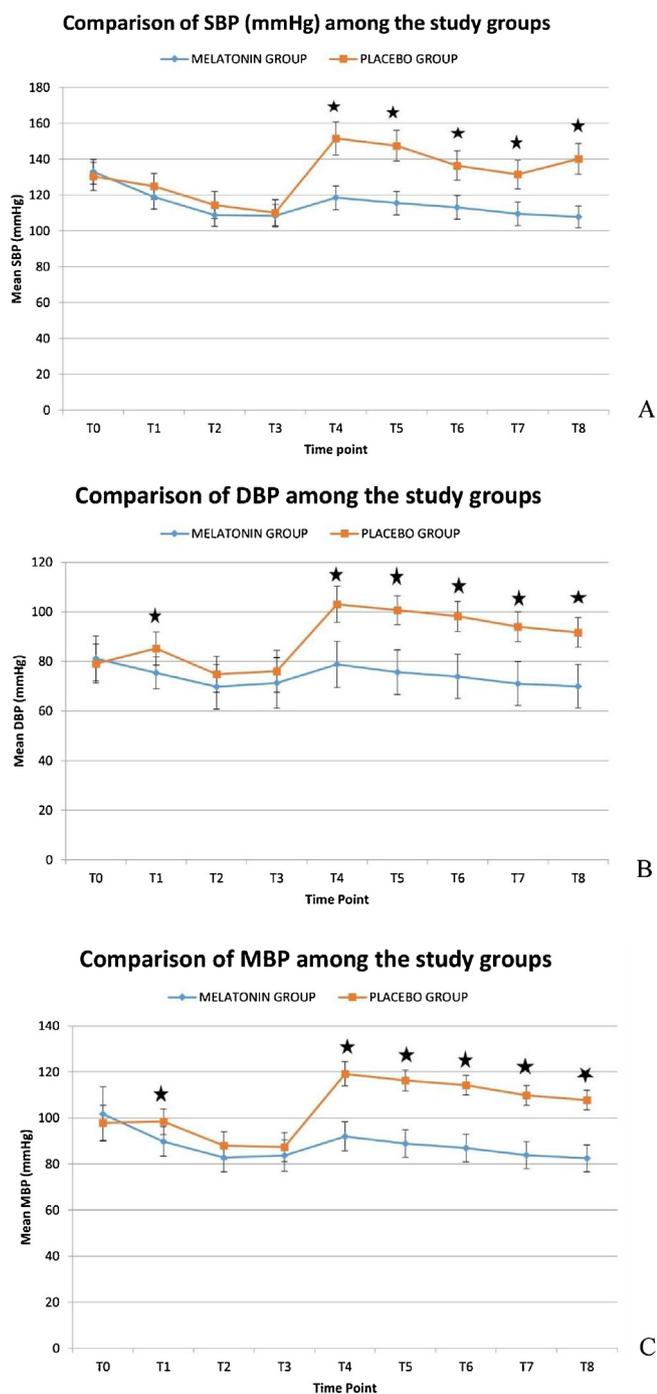
The hemodynamic stability seen after melatonin administration may also be due to its anxiolytic and analgesic effect, as seen in the present study and also reported in a few previous studies.<sup>14</sup> The precise mechanism and site of action for the analgesic action of melatonin are not clear. The analgesic effect may be due to G(i)-coupled melatonin receptors, or G(i)-coupled opioid  $\mu$ -receptors or GABA-B receptors resulting in unknown downstream changes leading to decreased anxiety and pain.<sup>15</sup> In the present study, the melatonin analgesic effect was clinically evident by the lesser number of patients who needed additional intraoperative fentanyl boluses with a reduction in the intraoperative fentanyl consumption. But postoperative pain scores were not assessed in our study, which is one of the limitations of the study. Our results are similar to a study by Ismail et al. in which perioperative verbal pain scores were significantly lower in the melatonin group with less intraoperative fentanyl requirement compared with the control group in patients undergoing cataract surgery with topical anesthesia.<sup>16</sup> In another clinical study by Caumo et al.<sup>17</sup> on female patients undergoing abdominal hysterectomy under epidural anesthesia, it was seen that melatonin premedication enhanced postoperative analgesia. Melatonin has also

been studied to improve tourniquet tolerance and enhance postoperative analgesia in patients receiving intravenous regional anesthesia.<sup>18</sup> The present study also showed that melatonin resulted in a significant reduction in the induction dose of propofol. Our results were similar to the previous studies, where oral melatonin premedication in a dose of either 3 or 5 mg reduced the dose of propofol to achieve a Bispectral Index score of 45.<sup>19</sup> Also, Naguib et al.<sup>20</sup> studied that oral melatonin premedication decreased the doses of both propofol and thiopental required to induce anesthesia when used in a dose of 0.2 mg.kg<sup>-1</sup>.

In our study, 6 mg of oral melatonin was well tolerated, and no adverse effects like bradycardia, hypotension, headache, nausea, vomiting, dizziness, or respiratory depression were noticed in any patient. Our results are in agreement with the results of Kain et al. where 0.4 mg.kg<sup>-1</sup> oral melatonin was safely used in children without any adverse effects.<sup>21</sup> However, Rosenberg et al. reported that hypotension and bradycardia occurred more frequently after melatonin administration.<sup>22</sup> This difference in results may be due to the high dose (9 mg) of melatonin used by Rosenberg et al. resulting in a higher incidence of hypotension and bradycardia. In a few past studies, using very high doses of melatonin for its anxiolytic action dizziness, irritability and headache were seen in some patients.<sup>23</sup>

The strength of the present study includes its randomized controlled double-blind design and the homogeneous nature of the study population. Moreover, through a single study, we have highlighted multiple roles of melatonin, useful for attenuating hemodynamic response to intubation as well as reducing the requirement of anesthetic agents like propofol and fentanyl. However, the present study has few limitations. One is that we did not measure melatonin plasma levels after melatonin premedication, and also we did not measure plasma catecholamine levels, which is more objective means for evaluating hemodynamic response. Moreover, intraoperative bispectral index (BIS) monitoring and measurement of the effect-site concentration of propofol would have been a more objective method in deciding the depth of anesthesia and the requirement of an induction dose of propofol, which was not used in our study. In the present study, though reduced requirement of anesthetic agents like propofol and fentanyl was seen with use of melatonin, it was not designed or powered to study the effect of melatonin on anesthetic requirements, which is another limitation.

In conclusion, 6 mg melatonin administered orally 120 minutes before induction of anesthesia significantly attenuated the hemodynamic responses to laryngoscopy and intubation. It also reduced the dose of propofol required



**Figure 3** A, comparison of systolic blood pressure (SBP) among the study groups; B, comparison of diastolic blood pressure (DBP) among the study groups; C, comparison of mean blood pressure (MBP) among the study groups.

T0, baseline; T1, 120 min after administration of study drug on arrival to operation theater; T2, after induction; T3, just before laryngoscopy and intubation; T4, 1 min after intubation; T5, 3 min after intubation; T6, 5 min after intubation; T7, 10 min after intubation; T8, 15 min after intubation.

$p$ -value < 0.0001.

ANOVA used to analyze changes over time. Unpaired  $t$ -test used for intergroup comparisons.

for induction and total intraoperative fentanyl consumption, and was not associated with any adverse effects.

## Conflicts of interest

The authors declare no conflicts of interest.

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