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Original article

A COMPARATIVE STUDY OF MELATONIN WITH PLACEBO IN ATTENUATION OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

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Abstract: **Introduction:** An increase in blood pressure and heart rate is observed during laryngoscopy and insertion of the endotracheal tube. Melatonin is used for sedation in the Intensive Care Unit. Our study was based on the hypothesis that administrating 3 mg and 6 mg of melatonin 90 minutes before induction attenuates hemodynamic responses encountered during laryngoscopy and intubation.

Materials and Methods: Seventy-five adult patients scheduled for elective surgical procedures, ASA I and II, were assigned into 3 groups (25 patients in each group) to receive oral placebo, melatonin 3 mg, or melatonin 6 mg 90 minutes prior to induction of anesthesia. Hemodynamic variables were recorded at baseline, before induction, and at 3, 6, 9, 12, 15, and 30 minutes after induction. Analysis of variance (ANOVA) was used for intergroup analysis of data. Categorical variables were compared using non-parametric tests like the Chi-square test or Fisher's exact test. Bonferroni correction was applied for intergroup analysis. Statistical significance was considered when $p < 0.05$.

Results: An increase in heart rate and blood pressure at 3, 6, and 9 minutes after induction of general anesthesia was observed in the control group compared to the melatonin 3 mg and 6 mg groups administered 90 minutes prior to induction. Oral administration of 6 mg of melatonin was found to provide greater attenuation than 3 mg of melatonin.

Conclusion: Oral administration of 3 mg and 6 mg melatonin effectively attenuates the hemodynamic pressor changes observed during laryngoscopy and tracheal intubation.

Keywords: Laryngoscopy, pressor response, melatonin, pre-operative anxiety, hemodynamic changes.

INTRODUCTION

Laryngoscopy and endotracheal intubation elicit profound hemodynamic changes characterized by increased heart rate and blood pressure. These responses can be particularly detrimental in individuals with limited cardiorespiratory reserve (1), highlighting the importance of attenuating sympathetic stimulation (2).

Various pharmacological approaches, including beta-adrenergic blockers, hypotensive agents, calcium channel blockers, and opioids, have been assessed for their ability to mitigate the hemodynamic pressor response during premedication or induction. However, these interventions may carry risks such as bradycardia, hypotension, and postoperative respiratory depression (3).

Preoperative anxiety, arising from concerns about the disease, anesthesia, and surgery, can lead to altered analgesic responses and may benefit from pharmacological intervention (4, 5).

Melatonin influences the sleep cycle by impacting the sleep-wake cycle and facilitating sleep induction (6). Upon oral administration, melatonin modulates gamma-aminobutyric acid ($GABA_A$) receptors, leading to sedation (7, 8). This sedative and hypnotic action of melatonin may help decrease heart rate and

blood pressure during laryngoscopy and intubation (9, 10).

Our research question was based on the hypothesis that the oral administration of 6 mg of melatonin 90 minutes before anesthesia induction may attenuate noxious stimuli (hypertension and tachycardia) more effectively than oral premedication with 3 mg of melatonin during laryngoscopy and intubation. In our study, the primary objective was to compare the impact of oral melatonin 6 mg and oral melatonin 3 mg versus placebo on blood pressure variation during laryngoscopy and intubation. The secondary objectives included comparing heart rate, anxiety scores, and analgesia between the two melatonin dosage regimens and placebo.

MATERIALS AND METHODS

Approval from the institutional ethical committee (IEC/SKIMS Protocol # RP 20/2019 dated 9 July 2019) was obtained, and the study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki, following informed written consent from the patients. Seventy-five patients were allocated to one of three study groups, with each group comprising 25 patients at the discretion of the attending anesthesiologist.

Group M3 (n = 25): Received oral melatonin 3 mg, 90 minutes prior to anesthesia administration with a sip of water.

Group M6 (n = 25): Received oral melatonin 6 mg, 90 minutes before induction of anesthesia with a sip of water.

Group P (n = 25): Received a placebo tablet (sugar-free tablet consisting of lactose, aspartame, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and polyvinyl pyrrolidone), 90minutes before induction of anesthesia with a sip of water.

All patients classified as American Society of Anesthesiologists (ASA) physical status I and II, aged between 18 and 65 years, of either sex, undergoing elective surgeries for supratentorial tumors requiring general anesthesia were included in the study.

Exclusion criteria included patients with any psychiatric disorders, history of allergies, use of antiepileptic or sedative agents, pregnancy, lactation, or coagulopathy, as well as patients with anticipated difficult airways, requiring more than one attempt at laryngoscopy, or where laryngoscopy time exceeded 20 seconds, and those with artificial airways in situ or accompanying spinal cord lesions. All enrolled patients underwent a pre-operative evaluation including relevant history, physical examination, and airway assessment. Routine pre-operative investigations and procedure-specific investigations were conducted according to institutional protocol. Patients followed nil per oral instructions for 6 hours prior to surgery.

Before administration of melatonin or placebo, baseline values of heart rate, mean, systolic, and diastolic blood pressures were noted. On the morning of surgery, after recording baseline vitals and assessing anxiety levels, melatonin or placebo was administered with sips of water approximately 90 minutes before anesthesia induction. An 18-gauge intravenous cannula was established, and a 0.9% NaCl solution was infused at 100-150 ml/h. In the operation theatre, essential monitors were applied, and vitals were recorded. General anesthesia was induced with fentanyl 2 μg/kg, preservative-free lidocaine hydrochloride (1.5 mg/kg), and propofol administered incrementally (20 mg increments) until loss of verbal response. Endotracheal intubation was performed after administration of atracurium 0.5 mg/kg. Maintenance anesthesia comprised a mixture of oxygen, nitrous oxide, and isoflurane. Heart rate, noninvasive blood pressure, and arterial oxygen saturation were recorded before induction and at 3, 6, 9, 12, 15, and 30 minutes after induction. Neostigmine (0.06 mg/kg) and glycopyrrolate (0.01 mg/kg) were administered at the end of surgery to reverse residual neuromuscular blockade. Tracheal extubation occurred after ensuring recovery of neuromuscular blockade. Patients were transferred to the recovery room where vitals were monitored, and appropriate interventions were initiated if necessary. Undesirable postoperative events such as blurred vision, nausea, vomiting, and persistent sedation were noted.

Anxiety levels were assessed using the Beck Anxiety Inventory (BAI)score before medication administration, at induction, and at intervals of 15 and 30 minutes, 3, 6, and 24 hours after extubation.

The BAI scores were classified as low anxiety (0-21), moderate anxiety (22-35), and severe anxiety (> 35) (11). While calculating BAI score 21 parameters related to anxiety were taken into consideration assigning a score of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). The behavioral rating scale for pain consisted of 5 factors for face, restlessness, muscle tone, vocalization and consolability with a scoring system of 0 for absent, 1 for moderate and 2 for severe symptoms (12).

Data collection was performed by an independent attending anesthetist. Sample size was calculated using OpenEpi software version 3.01(Centers for Disease Control and Prevention (CDC), Atlanta,Georgia, USA Atlanta, GA, USA) based on a previous study by Gupta et al.(9), aiming for a confidence interval of 95% and power of 90% to detect a clinically significant reduction in mean blood pressure with 6 mg

melatonin. Considering potential dropouts due to intraoperative complications, 25 patients were recruited in each group. Data was entered into a Microsoft Excel spread sheet (developed by Microsoft for Windows, Washington USA) and analyzed using SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as Mean ± SD, and categorical variables as percentages. Intra-group comparisons were made using analysis of variance (ANOVA), and categorical variables were compared using the Chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

All three groups exhibited comparable demographic characteristics, ASA grade, and Mallampati grading (MPG) (Table 1). At baseline and before induction, the mean heart rate among patients receiving placebo, 3 mg, and 6 mg melatonin was similar. However, at 3, 6, and 9 minutes after induction, the observed mean heart rate differed significantly among patients receiving placebo, 3 mg, and 6 mg of melatonin. As the duration of anesthesia progressed, from 12 to 30 minutes, there were no significant differences in heart rate ($p \geq 0.05$) (Figure 1). Intergroup comparison following Bonferroni correction demonstrated significantly lower heart rates at 3, 6, and 9 minutes after induction among patients administered 6 mg melatonin compared to placebo (Table 2, Figure 1).

The mean systolic blood pressure (BP) baseline values and values before induction among the three groups were comparable. However, at 3, 6, 9, and 12

Table 1. *Demographics*

Variable	Group M3 (n = 25)	Group M6 (n = 25)	Group P (n = 25)	p value
Age (in years), mean ± S.D	37.6 ± 12.39	40 ± 2.46	42.6 ± 14.49	0.403
Sex (male/female) (n = 25)	13/12	10/15	11/14	0.771
ASA grade (I/II) (n = 25)	18/7	17/8	16/9	0.951
MPG (I/II/III/IV) (n = 25)	7/15/2/1	7/13/5/0	6/12/6/1	0.754
Comorbidities				
Smoker n (%)	4 (16)	8 (32)	6 (24)	0.416
Hypertension n (%)	7 (28)	4 (16)	8 (32)	0.401
Diabetes n (%)	1 (4)	2 (8)	3 (12)	0.581
Hypothyroid n (%)	2 (8)	3 (12)	5 (20)	0.446

n = number of patients, % = percentage; M3 = Melatonin 3mg, M6 = Melatonin 6 mg, P = Placebo, MPG = Mallampati grading

Table 2. *Intergroup comparison of hemodynamic parameters between the three groups at different intervals (p values with Bonferroni correction)*

Time interval	M3 vs M6	M3 vs P	M6 vs P
1	2	3	4
Baseline HR	1.000	1.000	1.000
Baseline SBP	1.000	1.000	1.000
Baseline DBP	1.000	1.000	1.000
Baseline MAP	1.000	1.000	1.000
Before Induction HR	1.000	1.000	1.000
Before Induction SBP	1.000	1.000	1.000
Before Induction DBP	1.000	1.000	1.000
Before Induction MAP	1.000	1.000	1.000
3 Minutes after induction HR	0.486	0.708	0.033*
3 Minutes after induction SBP	0.517	0.776	0.042*
3 Minutes after induction DBP	1.000	1.000	0.942
3 Minutes after induction MAP	1.000	0.996	0.304
6 Minutes after induction HR	0.466	0.563	0.022*
6 Minutes after induction SBP	0.009*	1.000	0.004*

1	2	3	4
6 Minutes after induction DBP	0.394	1.000	0.049*
6 Minutes after induction MAP	0.090	1.000	0.021*
9 Minutes after induction HR	0.818	0.169	0.010*
9 Minutes after induction SBP	0.098	1.000	0.012*
9 Minutes after induction DBP	0.610	0.492	0.027*
9 Minutes after induction MAP	0.265	0.610	0.011*
12 Minutes after induction HR	1.000	0.408	0.202
12 Minutes after induction SBP	0.474	0.191	0.004*
12 Minutes after induction DBP	1.000	0.027*	0.013*
12 Minutes after induction MAP	1.000	0.038*	0.033*
15 Minutes after induction HR	1.000	0.413	0.626
15 Minutes after induction SBP	1.000	0.323	0.131
15 Minutes after induction DBP	0.888	0.083	0.707
15 Minutes after induction MAP	1.000	0.094	0.311
30 Minutes after induction HR	1.000	1.000	1.000
30 Minutes after induction SBP	1.000	1.000	0.622
30 Minutes after induction DBP	0.697	0.524	1.000
30 Minutes after induction MAP	1.000	0.582	1.000

Legends: *Statistically Significant Difference; P-value by Bonferroni correction; M3 = Melatonin 3 mg, M6 = Melatonin 6 mg, P = Placebo, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure.

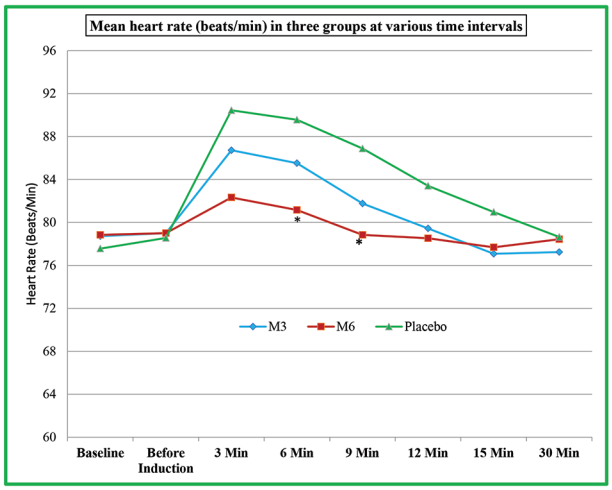

Figure 1. *Line diagram showing mean heart rate (beats/minute) M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

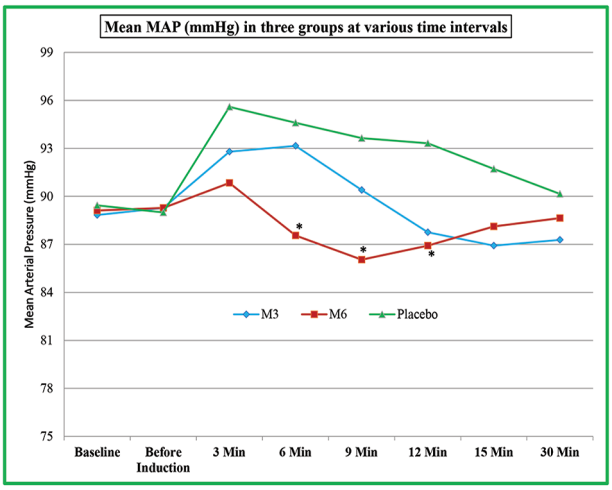

Figure 2. *Line diagram showing mean arterial pressure (mmHg) M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

minutes after induction, there were significant differences in mean systolic BP among the three groups. As the duration of anesthesia progressed to 15 and 30 minutes, there were no significant differences in mean systolic blood pressure values ($p \geq 0.05$). Intergroup comparison revealed that mean systolic blood pressure was significantly lower at 3, 6, and 9 minutes after induction in patients administered 6 mg melatonin compared to placebo (Figure 2). Similarly, systolic blood pressure was significantly lower at 6 and 9 minutes after induction between patients administered 3 mg and 6 mg melatonin.

At baseline, before induction, and 3 minutes after induction, there were no differences in mean diastolic BP between the three groups. However, at 6, 9, and 12 minutes after induction, the difference in mean diastolic BP among the three groups was statistically significant. As the duration of anesthesia progressed, at 15 and 30 minutes, the differences in mean diastolic BP values became comparable ($p < 0.05$). A similar trend was observed in mean arterial pressure ($p < 0.05$). Intergroup comparison showed that mean diastolic blood pressure was significantly lower at 6, 9, and 12 minutes after induction in patients administered 6 mg

Table 3. *Intergroup comparison based on interoperative BAI score among three groups at various time intervals*

Time Interval	P-value		
	M3 vs M6	**M3 vs Placebo**	**M6 vs Placebo**
Before giving premedication	1.000	1.000	1.000
At time of induction	0.047*	0.923	0.006*
15 minutes after extubation	0.001*	1.000	< 0.001*
30 minutes after extubation	0.162	0.162	0.001*
3 hours	0.544	0.851	0.053
Intergroup comparison based on perioperative pain score among three groups at various time intervals			
Before giving premedication	1.000	1.000	1.000
At time of induction	1.000	1.000	1.000
15 minutes after extubation	0.043*	< 0.001*	< 0.001*
30 minutes after extubation	0.009*	< 0.001*	< 0.001*
3 hours	0.760	< 0.001*	< 0.001*
6 hours	1.000	0.008*	0.008*
24 hours	1.000	0.297	0.297

**Statistically Significant Difference (P-value < 0.05); P-value by* Bonferroni correction. BAI = Beck Anxiety Inventory

melatonin compared to placebo. After Bonferroni correction in intergroup comparison, significantly lower mean arterial blood pressure was observed at 3, 6, and 9 minutes after induction in patients administered 6 mg melatonin compared with placebo (Table 2, Figure 2).

Before administering premedication with melatonin, the mean Beck Anxiety Inventory (BAI) scores among the three groups were comparable (Table 3). However, at the time of induction, and 15 minutes and 30 minutes after extubation, the differences in mean BAI scores among the three groups were statistically significant. As time progressed, the differences in mean BAI scores became comparable again 3 hours after extubation. No significant differences in mean BAI scores were observed at 6 hours and 24 hours after extubation (Figure 3).

Before premedication and at the time of induction, there were no differences in mean pain scores among the three groups. However, at 15 minutes, 30 minutes, 3 hours, and 6 hours after extubation, there were statistically significant differences in mean pain scores among patients receiving placebo, 3 mg, and 6 mg of melatonin (Table 3).

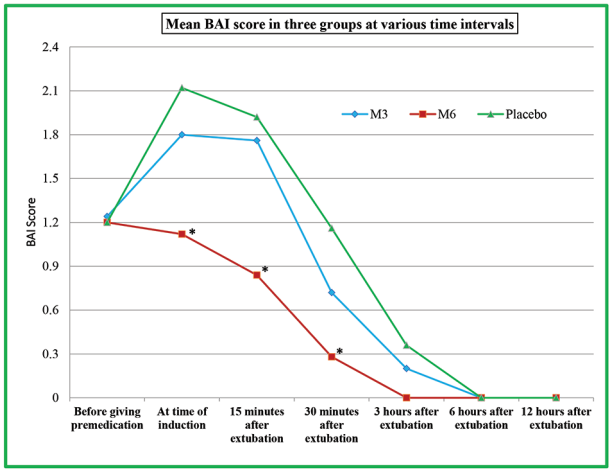

Figure 3. *Line diagram showing Beck Anxiety Inventory score M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

Additionally, lower mean anxiety scores at the time of induction and in the postoperative period, as well as lower mean pain scores in the postoperative period, were noted with melatonin administration compared to the control group.

DISCUSSION

In our study, we observed that administration of melatonin at doses of 6 mg and 3 mg (given 90 minutes prior to induction of general anesthesia) effectively attenuated hemodynamic responses up to 12 minutes after induction compared to the control group.

Effect on Hemodynamic Parameters

Our results align with findings from Gupta et al. **(9)** who reported an increase in heart rate during laryngoscopy, with the increase lasting up to 10 minutes in the control group. However, with oral melatonin administration, the heart rate increase was transient during laryngoscopy and returned to baseline within

1 minute. Kumar **et al.** (13) also observed a notable reduction in heart rate 1 minute following intubation with melatonin 3 mg compared to the control group.

In our study, we observed an increase in systolic, diastolic, and mean blood pressure at 3, 6, 9, and 12 minutes in the control group. However, with progression in the duration of anesthesia, at 15 and 30 minutes, there were no significant differences in the values of mean systolic blood pressure ($p \geq 0.05$). This finding is similar to that observed by Gupta et al. (9), who found higher systolic blood pressure during laryngoscopy and intubation compared to baseline values in the control group, whereas oral administration of 6 mg of melatonin attenuated this response.

Similar findings were reported by other studies. For example, oral melatonin at doses of 6 mg and 9 mg administered one hour before the preoperative period resulted in a significant decrease in blood pressure at 1, 2, 3, 5, and 10 minutes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) compared to the control group (11).

These studies collectively support the role of melatonin in mitigating hemodynamic responses during laryngoscopy and intubation, possibly through its sedative and anxiolytic effects.

Effects on Anxiety

Our study observed lower mean Beck Anxiety Inventory (BAI) scores with the administration of 6 mg of melatonin compared to the control group and 3 mg of melatonin. This finding is consistent with previous research. Abbasivash et al. (14) reported that melatonin administration decreased perioperative anxiety levels compared to control subjects, aligning with our results. Similarly, Rosas-Luna **et** al. (15) found that oral administration of melatonin at a dose of 5 mg was associated with anxiolysis compared to control groups. Brignardello-Petersen et al. (16) also demonstrated preoperative anxiolysis with melatonin administration compared to placebo, similar to our findings. Additionally, Yılmaz (17) reported that melatonin was associated with less postoperative anxiety compared to placebo. Etedali et al. (18) observed a 33% reduction in anxiety scores after administration of oral melatonin. Furthermore, Jouybar et al. (19), Shahrokhi et al. (20), and Saneet et al. (21) found that melatonin premedication effectively reduced perioperative anxiety in adults and improved patient comfort.

Effects on Analgesia

In our study, we observed statistically significant higher mean pain scores in patients receiving placebo compared to those receiving 3 mg and 6 mg of melatonin at 15 minutes, 30 minutes, 3 hours, and 6 hours after extubation. These findings are consistent with previous research. Kiabi et al. (22) reported that melatonin premedication (10 mg) reduced postoperative analgesic requirement in patients undergoing caesarean section, similar to our study. Javaherforooshzadeh et al. (23) demonstrated that pre-treatment with melatonin decreased anxiety and pain in lumbar surgery compared to placebo. Additionally, in patients receiving intravenous regional analgesia, melatonin was shown to have postoperative analgesic effects (24), aligning with our study findings.

Our study compared the effects of two doses of melatonin (6 mg and 3 mg) with a control group, whichis a unique contribution to the existing literature. However, limitations of our study include the lack of randomization of patients into different treatment arms, potentially introducing selection bias due to subjective considerations of the attending anesthesiologist during allocation. Furthermore, the size and location of supratentorial tumors could have influenced postoperative recovery characteristics.

Future studies should be conducted to further assess the efficacy of melatonin in reducing hemodynamic responses and providing adequate analgesia, and to establish dose-response relationships to achieve desired effects. Randomized controlled trials with larger sample sizes and standardized methodologies will contribute to a better understanding of the therapeutic potential of melatonin in perioperative care.

CONCLUSION

Premedication with oral melatonin at doses of 3 mg and 6 mg administered before induction of anesthesia in elective surgical procedures effectively reduces the pressor response to intubation and laryngoscopy. Additionally, melatonin provides analgesic and anxiolytic effects, with oral melatonin 6 mg showing greater effectiveness compared to 3 mg.

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Author contribution: All authors have contributed equally.

Sažetak

KOMPARATIVNO ISPITIVANJE MELATONINA SA PLACEBOM U SMANJENJU HEMODINAMIČKIH ODGOVORA NA LARINGOSKOPIJU I INTUBACIJU

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Uvod: Povećanje krvnog pritiska i srčane frekvencije primećuje se tokom laringoskopije i intubacije. Melatonin se koristi za sedaciju u jedinicama intenzivne nege. Naše istraživanje se baziralo na hipotezi da primena melatonina u dozama od 3 mg i 6 mg 90 minuta pre uvoda u anesteziju smanjuje hemodinamičke odgovore tokom laringoskopije i intubacije.

Materijal i Metode: 75 odraslih pacijenata zakazanih za elektivne hirurške procedure, ASA I i II, podeljeni su u 3 grupe (25 pacijenata u svakoj grupi) koje su primile, 90 minuta pre indukcije anestezije, oralni placebo, melatonin 3 mg i melatonin 6 mg, redom. Hemodinamički parametri su mereni pre anestezije, i nakon indukcije anestezije u intervalima od 3, 6, 9, 12, 15 i 30 minuta. Analiza varijanse (ANOVA) je korišćena za međugrupnu analizu podataka. Kategoričke varijable su upoređivane primenom neparametrijskih testova Chi-kvadrat ili Fisherovog egzaktnog testa. Bonferronijeva korekcija je korišćena za međugrupnu analizu. Statistička značajnost je uzeta u obzir kada je $p < 0,05$.

Rezultati: Primećeno je povećanje srčane frekvencije i krvnog pritiska u 3, 6 i 9 minuta nakon indukcije opšte anestezije u kontrolnoj grupi, u poređenju sa grupama koje su primile melatonin u dozama od 3 mg i 6 mg 90 minuta pre indukcije opšte anestezije. Melatonin u dozi od 6 mg oralno je izazvao veće smanjenje nego melatonin u dozi od 3 mg.

Zaključak: Oralna primena melatonina u dozama od 3 mg i 6 mg efikasno smanjuje hemodinamičke promene tokom laringoskopije i intubacije.

Ključne reči: Laringoskopija, odgovor na podražaj, melatonin, preoperativna anksioznost, hemodinamske promene.

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