ORIGINAL RESEARCH PAPER

Anaesthesiology

EFFECT OF DIFFERENT DOSES OF ORAL MELATONIN AS A PREMEDICATION FOR ATTENUATION OF INTUBATION RESPONSE

KEY WORDS: Laryngoscopy, melatonin, premedication, intubation response, haemodynamics.

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ABSTRACT

Background And Aims: Airway manipulation during laryngoscopy and tracheal intubation acts as a powerful noxious stimuli leading to adverse cardiovascular responses, especially in patients with hypertension, coronary artery diseases etc. Melatonin is an endogenous sleep-regulating hormone exhibiting inhibitory actions on central nervous system, may also have role in attenuating hemodynamic responses to laryngoscopy and intubation. We hypothesized that, melatonin 9 mg is better than 6 mg in attenuating intubation response to laryngoscopy and endotracheal intubation. **Material And Methods:** The randomized control study was conducted on 80 patients scheduled to undergo elective surgeries under general anesthesia with endotracheal intubation. Group A received oral melatonin 6 mg and group B received 9 mg melatonin, 120 minutes before surgery. Hemodynamic parameters were recorded at baseline, 30, 60, 120 minutes after drug administration, pre-induction, post induction and every minute after intubation till 5 minutes then at 10th minute. Sedation scores were assessed using Ramsay sedation scores. **Results:** In group A, baseline mean HR was 84.78 ± 9.59 beats per minute (95% CI: 65.6 - 103.96) and postintubation at 1minute it was 88.25 ± 13.68 bpm (95% CI: 60.89 -115.61). In group B, baseline mean HR was 83.27 ± 14.84bpm (95% CI: 59.81-108.09) and postintubation at 1minute it was 83.28 ± 14.84 bpm (95% CI: 53.6 - 112.96). In group A, baseline mean MAP was 95.07 ± 9.05 mmHg (95% CI: 76.98 - 113.18) and postintubation at 1minute it was 87.88 ± 14.89mmHg (95% CI: 58.1 - 117.66). In group B, baseline mean MAP was 95.15 ± 10.54 mmHg (95% CI: 74.07 - 116.23) and postintubation at 1minute it was 88.35 ± 15.67 mmHg (95% CI: 57.01 - 119.69). Pressor response to tracheal intubation was attenuated in both groups and no statistical significance was noted between two groups. Both groups had sedation scores of 2-3. **Conclusion:** Both oral melatonin 6 mg and 9 mg when administered 120 minutes before induction of anaesthesia were effective in attenuating the hemodynamic responses to laryngoscopy and intubation.

INTRODUCTION:

Laryngoscopy and endotracheal intubation are an integral part of general anaesthesia for surgical procedures but these are considered potent noxious stimuli. The laryngeal and tracheal sensory receptors are stimulated during laryngoscopy which results in the release of endogenous catecholamines leading to marked increase in heart rate and blood pressure.[1,2] Such haemodynamic changes occurring during intubation may alter the delicate balance between myocardial oxygen demand and supply and precipitate myocardial ischemia in patients with coronary artery disease.[1] Failure to blunt these responses may lead to disastrous complications in patients with hypertension, coronary artery disease, aneurysmal vascular disease, raised intracranial pressure etc.[3]

Various medications like lignocaine, esmolol, clonidine, dexmedetomidine, opioids like fentanyl, calcium channel blockers, nitroglycerin are commonly adopted methods in attenuating haemodynamic stress response. Oral melatonin is one such drug used.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous sleep-regulating hormone secreted by pineal gland. It also regulates various physiological functions like circadian rhythm, reproduction, mood and immune function.[4] Exogenous administration of melatonin facilitates onset of sleep and improves sleep quality and has anxiolytic, anti-inflammatory and oxidative effects.[4,5] It produces natural sleep pattern and does not lead to impairment of cognitive functions.[6] Melatonin also has sympatholytic activity.[7] Such actions on central nervous system may have a role in attenuating haemodynamic responses to laryngoscopy and intubation.[8] It also causes significant dose-dependent increase in GABA concentrations. The sedative effect is mainly due to binding at GABA-A receptor and exertion of its anaesthetic effect.[9]

The present study aims at assessing the role of different doses of melatonin in attenuating haemodynamic responses like heart rate and blood pressure to laryngoscopy and endotracheal intubation. We hypothesized that oral melatonin 9mg is better than 6mg in attenuating the haemodynamic responses to laryngoscopy and intubation along with responses to tracheal extubation and provides better preoperative sedation scores. Our primary objective was to measure blood pressure (BP) and heart rate (HR) response to laryngoscopy and endotracheal intubation. Secondary objectives were to assess the level of preoperative sedation before induction of anaesthesia, to assess haemodynamic response to tracheal extubation and to observe for any side effects in the postoperative period.

METHODS:
After obtaining the institutional ethical committee approval (Ref No: EC142), the study was registered in the clinical trial registry of India (CTRI REF/2021/02/041350). A prospective, randomized, double blind study was conducted at our tertiary care hospital from February 2021 to July 2021.

Eighty patients belonging to American Society of Anesthesiologist's physical status (ASA PS) I & II in the age group 18 - 65 years of either gender, scheduled to undergo elective surgeries under general anaesthesia (GA) were recruited for the study based on inclusion criteria after obtaining written informed consent. Patients with anticipated difficult intubation as assessed by modified Mallampati (MPT) class 3 and 4, hypertension, cardiac disease, pregnancy and lactation and patients on hypnotics, sedatives, anxiolytics, anti-epileptics were excluded from the study. Any laryngoscopy and intubation lasting more than 15 seconds were also excluded from the study. Patients were randomly allocated into two groups based on computer generated randomization, where patients in Group A received 6 mg of oral melatonin and Group B received 9 mg of oral melatonin 120 minutes before surgery.

All patients were subjected to routine pre-anaesthetic evaluation. Routine investigations as appropriate for the surgeries were obtained and optimized. All patients were kept nil per oral as per standard ISA fasting & feeding guidelines and received tablet ranitidine 150 mg and tablet ondansetron 8 mg the night before surgery. After confirming nil per oral status, in the preoperative holding area, an intravenous line was secured with 18G cannula and ringer lactate fluid was started. Standard ASA monitoring like heart rate (HR), non-invasive blood pressure (NIBP) and oxygen saturation [SPO2] were connected and patients received oral melatonin with sips of water 120 minutes before induction of anaesthesia based on the group allotted. The preoperative sedation levels were assessed using Ramsay sedation score [10] at 0 [baseline], 30, 60, 90 and 120 minutes after drug administration. Both the anaesthesiologist and patient were kept blinded and unaware about group allocation. Allocation concealment was done using closed envelope technique.

Two hours post drug administration patients were wheeled into operation theatre and standard ASA monitors were connected. Patients were pre-oxygenated with 100% oxygen, intravenous (IV) fentanyl 2 mcg/kg was given for pre-emptive analgesia. Anaesthesia was induced with IV propofol 20 mg boluses given every 15 seconds until loss of verbal contact, and muscle relaxation was achieved with IV vecuronium 0.1 mg/kg to facilitate endotracheal intubation. All patients were ventilated for 3 minutes and later laryngoscopy and tracheal intubation was conducted by an anaesthesiologist with at least 5 years of experience. Total propofol dose required for induction and the time taken for laryngoscopy and intubation were noted. The time from insertion of laryngoscope blade into mouth until inflation of endotracheal cuff was considered as time taken for laryngoscopy and intubation. Hemodynamic parameters like heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP] and mean arterial pressure [MAP] were recorded at pre-induction, post-induction, after intubation [0 min] and every minute for first 5 minutes, then at 10^{th} minute and throughout the procedure at 5 minute interval. Anaesthesia was maintained with oxygen in nitrous oxide [40:60], with isoflurane to maintain 1 minimum alveolar concentration (MAC) and intermittent doses of vecuronium 0.02 mg/kg was administered to ensure muscle relaxation. Mechanical ventilation was adjusted to maintain normocapnia (EtCO2 35-45 mmHg). After completion of the surgery inhalational agent was stopped, 100% oxygen was provided and IV neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg was administered to reverse the residual neuromuscular blockade. The haemodynamic responses to extubation was also noted. All patients were observed in post anesthesia care unit for any side effects like nausea, vomiting, dizziness, headache, respiratory depression, bradycardia, hypotension, arrythmia, restlessness encountered postoperatively.

Sample Size:
As per published study [11], SBP immediately following intubation in melatonin 6mg group was 131.20 ± 8.32 mmHg and in melatonin 9mg group was 120.53 ± 9.93 mmHg. By keeping the power at 80% and confidence level at 95%, a sample of 36 will be required in each group. We have included 40 patients in each group, keeping in mind the possible dropouts and for better validity of study.

Statistical analysis:
Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software (IBM SPSS Statistics, Somers NY, USA). Chi-square test was used as test of significance for qualitative data. Normality of the continuous data, was tested by Kolmogorov–Smirnov test and the Shapiro–Wilk test. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. P value of < 0.05 was considered as statistically significant.

RESULTS:
A total of 100 patients were assessed for eligibility, 20 were excluded and 80 patients were included in the study and analyzed (figure 1).

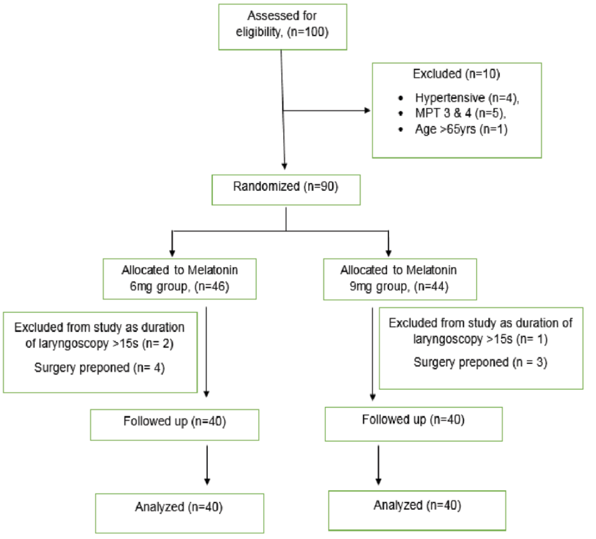

Figure 1: CONSORT diagram

Demographic characteristics including age, gender, weight, ASA- PS grade and duration of anaesthesia (DOA) were comparable in both the groups (table 1). Duration of laryngoscopy in group A was 13.25 ± 1.92 and in group B is 12.9 ± 2.37 with p value 0.47.

Table 1: Demographic characteristics of patients among both groups

	GROUP A	GROUP B	P value
Age (years) (Mean ± SD)	31.7 ± 9.43	37.95 ± 9.83	0.057
Gender (M: F)	18: 22	16: 24	0.651
ASA PS (1: 2)	14: 26	18: 22	0.361
Weight (kg) (Mean ± SD)	63.05 + 10.63	65.93 + 12.2	0.265
DOA (minutes) (Mean ± SD)	81.63 + 30.14	94.38 + 40.73	0.116

In group A, baseline mean HR per minute was 84.78 ± 9.59 bpm and post intubation at 1 minute it was 88 ± 13.68 bpm which was statistically insignificant. In group B, baseline mean HR was 83.95 ± 12.07 bpm and post intubation at 1 minute it was 83.28 ± 14.84 bpm which was statistically insignificant (table 2).

Table 2: Comparison of mean heart rate in both the groups

Mean HR (bpm)	BASELINE	POST INTUBATION						AT EX-TUBATION
		1 min	2 min	3 min	4 min	5 min	10 min	
Group A	84.78 ± 9.59	88.25 ± 13.68	86.77 ± 21.89	82.93 ± 12.61	81.05 ± 12.33	82.08 ± 13.09	79.83 ± 13.07	99.90 ± 14.40
Group B	83.95 ± 12.07	83.27 ± 14.15	81.75 ± 13.79	80.38 ± 13.27	78.23 ± 12.79	76.20 ± 14.71	73.60 ± 14.71	87.55 ± 13.35
p value	0.736	0.123	0.223	0.381	0.318	0.039 *	0.049 *	<0.001*

Baseline mean MAP in group A was 95.08 ± 9.05 mmHg and post intubation at 1 minute it was 87.88 ± 14.89 mmHg which was statistically significant. In group B, baseline mean MAP was 95.15 ± 10.54 mmHg and post intubation at 1 minute it was 88.35 ± 15.67 mmHg which was statistically insignificant (table 3).

Table 3: Comparison of mean arterial pressure in both the groups

Mean MAP (mmHg)	BASELINE	POST INTUBATION						AT EXTUBATION
		1 min	2 min	3 min	4 min	5 min	10 min	
Group A	95.07 ± 9.05	87.88 ± 14.89	82.00 ±11.4	77.82 ± 8.85	77.30 ± 8.85	79.15 ± 9.28	82.13 ± 10.35	104.07 ± 11.23
Group B	95.15 ±10.54	88.35 ± 15.67	82.60 ±14.71	78.12 ±9.86	76.62 ±13.08	76.60 ±12.66	76.42 ± 12.32	95.80 ± 15.32
P value	0.973	0.89	0.837	0.886	0.788	0.307	0.028 *	0.796

Baseline mean SBP in group A was 124.8 ± 8.54 (95%CI: 104.48 – 147.72) mmHg and post intubation at 1 minute it was 116 ± 17.87 (95%CI: 81.06 - 152.54) mmHg which was statistically significant. In group B, baseline mean SBP was 124 ± 16.86 (95%CI: 97.82 – 151.58) mmHg and post intubation at 1 minute, it was 119.2 ± 18.02 (95%CI: 83.16 - 155.24) mmHg which was statistically insignificant. In group A, baseline mean DBP was 81.08 ± 7.37 mmHg (95% CI: 66.34 – 95.82) and post intubation at 1 minute it was 71.65 ± 13.07mmHg (95% CI: 45.51 – 97.79) which was statistically significant. In group B, baseline mean DBP was 80.4 ± 10.37 mmHg (95% CI: 59.66 – 101.14) and post intubation at 1 minute, it was 72.13 ± 15.53 mmHg (95% CI: 41.07 – 103.19) which was statistically insignificant. At extubation, mean HR in group A was 99.90 ±14.40 bpm (p < 0.001) and in group B was 87.55 ± 13.35 bpm (p 0.107). Mean MAP in group A was 104.07 ± 11.3 mmHg (p<0.001) and in group B it was 95.80 ± 15.32 mmHg (p 0.796). Mean SBP in group A was noted to be 141.23 ± 11.50 mmHg (p < 0.001*) and in group B it was 128.40 ± 18.61 mmHg (p 0.253) and mean DBP in group A was 85.92 ± 11.38mmHg (p 0.019) and in group B it was 79.60 ± 13.71mmHg (p 0.028).

Ramsay sedation scores were between 2 and 3 in both groups. Mean propofol dose required for induction in group A was noted to be 88.25 ± 20.11 mg and in group B it was 81 ± 23.62 mg which was lesser than recommended doses of 126.1 ± 21.26 mg and 131.86 ± 24.4 mg in group A and B respectively. None of the patients had any side effects.

DISCUSSION:

Direct laryngoscopy and endotracheal intubation during general anaesthesia leads to stimulation of sympathetic nervous system thus releasing catecholamines. This hemodynamic stress response may be tolerated by healthy individuals, but it may have deleterious effects in patients with compromised cardiac function. This study was conducted to assess the efficacy of two different doses of oral melatonin on attenuation of hemodynamic responses like heart rate and blood pressure to laryngoscopy and endotracheal intubation when given 120 minutes before the procedure.

Our study results showed that SBP, DBP and MAP did not increase from the baseline after intubation in both the groups. But HR increased in Group A after intubation which returned to baseline values by 3 minutes whereas in Group B HR did not rise from the baseline values. At extubation, HR, SBP, DBP and MAP increased from the baseline values in both the groups but the rise was significant in Group A.

In a study conducted by Mohamed et al., SBP, DBP and MAP were attenuated in both 6mg and 9mg melatonin groups following intubation when compared to placebo group, but there was no significant difference in HR among the 3 groups. [11] Others have observed that oral melatonin in a dose of 6 mg and 9 mg was more effective in attenuating hemodynamic response to intubation when compared to placebo, but 9mg attenuated the hemodynamic response better as compared to 6mg melatonin. [12]

In other studies, when melatonin 6 mg was compared with placebo, it was noticed that melatonin group had significant attenuation of SBP, DBP and MAP following laryngoscopy and tracheal intubation [8, 13] but HR increased during intubation, which returned to baseline values by 1 minute [8]. In another study, it was noticed that, during extubation both the blood pressure (SBP, DBP, MAP) and HR were attenuated in melatonin 6 mg group when compared to the placebo group. [13]

Others have observed that there was a 10.59% and 37.08% rise in HR at 1 minute respectively in 6 mg melatonin group compared to placebo group. Maximum percentage increase in SBP, DBP, and 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 minute post intubation. [14] In a study comparing melatonin 6 mg and clonidine 0.2 mg [15] or 0.1mg [16] it was observed that oral melatonin is superior to oral clonidine in attenuating hemodynamic response to laryngoscopy and tracheal intubation. When melatonin 6 mg was compared with pregabalin 150 mg and placebo, it was observed that melatonin 6mg was more effective in attenuating hemodynamic responses than that of the pregabalin 150 mg and placebo. [17]

We have also observed in our study that Ramsay sedation scores were between 2 and 3 in both the groups at all time intervals and it was comparable between the groups which was also seen in other studies [15].

CONCLUSION:

Although both the doses of oral melatonin 6 mg and 9 mg administered 120 minutes before induction of general anaesthesia were effective in attenuating the haemodynamic responses to laryngoscopy and intubation; oral melatonin 6 mg was observed to be adequate since it produces clinically relevant attenuation and acceptable levels of sedation.

REFERENCES:

1. Kanchi M, Nair HC, Banakal S, Murthy K, Murugun C. Haemodynamic response to endotracheal intubation in coronary artery disease: Direct versus video laryngoscopy. Indian J Anaesth. 2011; 55:260–65.
2. Russell WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth. 1981; 53(8): 8379.
3. Koti VR, Cheuri SB, Pulla S, Varunchander G. Attenuation of haemodynamic response to intubation with oral clonidine and oral atenolol. Indian J Clin Anaesth. 2016; 3:251–56.

4. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S: Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: A randomized clinical trial. J Anesth. 2010; 24:155–60.
5. Bourne RS, Mills GH, Minelli C: Melatonin therapy to improve nocturnal sleep in critically ill patients: Encouraging results from a small randomized controlled trial. Critical Care. 2008; 12:R52.
6. Baandrup L, Fagerlund B, Jennum P, Lublin H, Hansen JL, Winkel P, et al. Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia: A randomized clinical trial – The SMART trial protocol. BMC Psychiatry. 2011; 11:160.
7. Rosenberg J, Gögenur I, Lykkesfeldt J. Modification of surgical stress response by perioperative melatonin administration. Dan Med Bull. 2010; 57:4144.
8. Gupta P, Jethava D, Choudhary R, Jethava DD. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. Indian J Anaesth. 2016; 60:712-18.
9. Wan Q, Man HY, Liu F, Braunton J, Niznik HB, Pang SF, Brown GM, Wang YT. Differential modulation of GABAA receptor function by Mel1a and Mel1b receptors. Nat Neurosci. 1999; 2(5):401-3.
10. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974 Jun 22; 2(5920):656-9.
11. Mohamed, Ahmed & Atef, Hosam & El-Din, Alaa & Kassaby, M & Ismail, A & Helmy, Amr. Effects of Melatonin Premedication on the Hemodynamic Responses and Perfusion Index During Laryngoscopy and Endotracheal Intubation. Med J Cairo Univ. 2014; 81:859-867.
12. Devtara A, Gandhi A, Damor M, JainS, Sharma A, Verma A. Attenuation of Hemodynamic Pressor Response during Laryngoscopy and Intubation: A Clinical Study of Premedication with Different Doses of Oral Melatonin. Acad. Anesthesiol. Int. 2020; 5(2):75-79.
13. Adithi Devi E, Bhawathi M, Kalyanam P, Shiva PV. Laryngoscopy intubation and extubation are affected by melatonin : A prospective study. *European Journal of Molecular & Clinical Medicine.* 2022; 9(4):3209-3216.
14. Kumar R, Kumari K, Janweja S, Kumar R, Verma M, Sharma A, Paliwal B, Kishan R. Role of melatonin in attenuation of hemodynamic response to intubation and anesthetic requirements: a randomized, controlled, double-blind study. Braz J Anesthesiol. 2021 Sep 21:S0104-0014(21)00339-0.
15. Choudhary S, Sharma S, Kumari I, Kalluraya S, Meena K, Dave T: Attenuation of haemodynamic response to laryngoscopy and tracheal intubation with oral melatonin and oral clonidine. Indian J Anaesth. 2020; 64(8):696-703.
16. Banerjee SG, Sanyal P, Bandyopadhyay U. Study to Compare the Efficacy of Orally Administered Melatonin and Clonidine for Attenuation of Hemodynamic Response During Laryngoscopy and Endotracheal Intubation in Gastrointestinal Surgeries. Int J Cur Res Rev. 2021; 13(07):156.
17. Sayed Faheem Maqbool. Comparative Clinical Evaluation of Preoperative Oral Pregabalin and Melatonin for Attenuation of Haemodynamic Responses to Laryngoscopy and Intubation. IOSR Journal of Dental and Medical Sciences. 2019; 18(4):35-40.