Original Article

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Attenuation of Hemodynamic Pressor Response during Laryngoscopy and Intubation: A Clinical Study of Premedication with Different Doses of Oral Melatonin

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Abstract

Objectives: To assess the effect of two different doses of oral melatonin premedication on the hemodynamic parameters. **Subjects and Methods:** Ninety patients aged between 20 to 45 years of either sex belonging to ASA grade I and II were randomly divided into three groups. This randomized prospective study was conducted on patients undergoing elective surgeries on general anesthesia. In Group-C oral Placebo was given 120 minutes before surgery, in Group M6- Tab. Melatonin 6mg and in Group M9- Tab. Melatonin 9mg was given 120 minutes before surgery. Patients were assessed for intraoperative and post-operative hemodynamic parameters at different time intervals. **Results :** The mean heart rate in Group M6 and group M9 was significantly decreased from baseline (83.63±6.7) to (81.96±6.1) and from (82.82±.09) to (77.4±5.25) respectively, (P<0.001) while in Group C it was increased from baseline (81.2±5.33) to (92.0±4.64). Systolic blood pressure (SBP) was increased from baseline (123.56±3.25) to (132.76±3.77) in Group C, while in Group M6 and M9 it was significantly decreased from (121.13±3.82) to (118.13±31.3) and from (122.79±3.33) to (115.96±3.44) respectively. (P<0.001) Diastolic blood pressure (DBP) in Group C was increased from baseline (80.23±2.11) to (87.70±3.48). In Group M6 and M9, it was significantly decreased from baseline (78.03±5.15) to (73.56±3.77) and from (77.51±3.87) to (71.55±3.14) respectively. (P<0.001). **Conclusion:** Oral melatonin in a dose of 6mg and 9mg was more effective compared to placebo but 9mg attenuated the hemodynamic response asoociated with laryngoscopy and endotracheal intubation better as compared to 6mg melatonin.

Keywords: Melatonin, Laryngoscopy, Intubation, Hemodynamic Attenuation

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Introduction:

Both the laryngoscopy procedure and endotracheal intubation provokes reflex hemodynamic responses leading to a marked increase in heart rate and blood pressure. [1] The mechanisms of these hemodynamic alterations are somatovisceral reflexes due to sympathetic stimulation. During tracheal intubation, the laryngeal and tracheal sensory receptors are stimulated which results in the release of endogenous catecholamine resulting in tachycardia and hypertension. [2]

Since the invention of laryngoscopy and endotracheal intubation, various drugs like clonidine and dexmedetomidine and techniques have been used from time to time to attenuate the stress responses. [3] However, from each previously used drug; hypotension, decrease heart rate (bradycardia), increase heart rate (tachycardia), rebound hypertension, respiratory depression or allergic reactions have been found. Hence, there has always been a need for a better or newer drug.

The pineal gland secretes an endogenous sleep-regulating hormone which is known as Melatonin (N-acetyl-5-methoxytryptamine). It has been reported that this hormone facilitates the onset of sleep and also helps in improving sleep quality when given from outside. [4] It induces the natural sleep pattern without impairing the cognitive functions unlike benzodiazepines and their derivatives. It has been mainly evaluated in sedation in ICU, preoperative anxiolytic agents and also in pre-operative cognitive and psychomotor functions. [5]

In the literature search, very few studies were conducted to explore different doses of melatonin to attenuate the hemodynamic responses. This present prospective study was planned to know the effect of two different doses of melatonin administration as premedication on the pressor response during laryngoscopy procedure and endotracheal intubation.

Subjects and Methods

This prospective study was conducted only after approval from the Institutional Research Board in the Anaesthesia department of a tertiary care teaching hospital of Bikaner, Rajasthan. The study was conducted on 90 patients; all these enrolled patients in the study were randomly divided into three groups. Group M6-Oral melatonin 6mg, Group M9-Oral melatonin 9mg and Group C-Oral placebo (Tab. B complex) were given 120 minutes before induction.

All the patients of American Society of Anesthesiologists (ASA) Grade I or II, age 20 to 45 years of both sex and surgery requiring general anaesthesia for duration longer than 30 min were included in the study. The patients having hypertension, diabetes, psychiatric illness, and patients on antipsychotics, sedatives, anxiolytics and antiepileptic drugs; sleep disorders, obesity and drug allergy were excluded out from the study. All eligible patients were interviewed about their demographic details, laboratory investigation and post-operative assessment were done by using intra-operative hemodynamic parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and SPO_2.

A Pre-anesthesia checkup was carried out the day before surgery. The procedure of oral administration of tab. melatonin was first explained to each patient and written informed consent was taken from each patient and his relatives in the presence of an independent witness. All patients were kept nil by mouth on the night before surgery. Routine laboratory investigations like hemogram, sugar, serum creatinine, serum urea, coagulation profile, chest X-ray, ECG was done. Standard monitoring was done including non-invasive blood pressure, pulse rate, SpO_2.

Routine monitoring was done in operation theatre in each patient which includes HR, SPO_2, non-invasive blood pressure (NIBP), end-tidal carbon dioxide ($ETCO_2$), ECG and all the patients were anaesthetized by standard anesthetic technique.

Two puffs of 10% lignocaine were sprayed on his larynx. Pre-oxygenate the patient 100% oxygen for 3minute before induction. Glycopyrrolate 0.004mg/kg and fentanyl 1 mcg/kg was administered intravenously. Induction was attained with intravenous thiopentone 3-5 mg/kg I.V.

Succinycholine 2mg/kg was given intravenously to facilitate endotracheal intubation with a well-lubricated endotracheal tube of appropriate size.

Maintenance of anesthesia was attained with inhalation of sevoflurane with 2 minimum alveolar concentrations (MAC), nitrous oxide: oxygen in a ratio of 40:60. Vecuronium bromide of 0.06-0.08mg/kg I.V. as a loading dose and one-fourth of the initial dose as maintenance dose was given to attain muscle relaxation.

During surgery and after completion of surgery to maintain normocapnia, mechanical ventilation was adjusted. Neostigmine 50mcg/kg and glycopyrrolate 10mcg/kg i.v was administered to reverse the residual neuromuscular blockade.

SBP, DBP, MAP and HR were recorded before administration of a drug (baseline), 120 min after administration of study drug (just before induction), immediately after induction, at the time of laryngoscopy and intubation, just after laryngoscopy and intubation and at 1,3,5 and 10 min afterward.

In the post-anesthesia care, all the patients were received standard postoperative care. Any side effects like nausea, vomiting, dizziness, headache, respiratory depression, arrhythmias, bradycardia, hypotension and restlessness till 24 hours postoperatively were observed.

Statistical analysis

The obtained data were entered in an excel sheet and the data was tabulated in percentages or Mean and SD. The data of all three groups were analyzed using the ANOVA (one-way analysis of variance) test. P-value < 0.05 was considered significant at 95% confidence interval.

Results

All three study groups were similar demographically and the duration of surgery was also similar in all groups. The age of patients ranged from 20 to 45 years in the present study. The mean age was 36.13±11.23 years in Group C, 36.20±9.20 year in Group M6 and 33.20±9.23 year in Group M9 which was found were comparable and non-significant. Mean weight in Group C, M6 and M9 were 68.10±7.02, 69.93±7.22, 69.10±5.79 kg respectively. ($p>0.05$) In Group C, M6 and M9 the female was 56.66%, 53.33% and 53.33% respectively. [Table 1]

In Group C Heart rate was increased from the baseline (81.2±5.33) to (92.0±4.64). In Group M6 heart rate was stable at all the time intervals. In the group, M9 Heart rate was decreased from baseline (82.82±09) to (77.4±5.25) respectively. The intergroup comparison revealed that an increase in the mean heart rate in Group C was significantly more as compared to Group M6 and Group M9. ($p<0.001$) Moreover, a decrease in HR recorded in Group M6 and M9 just

Table 1: Patients' characteristics in all the three groups

Parameters	Group C	Group M6	Group M9	P-value
Age (Yrs)	36.13±11.23	36.20±9.20	33.20±9.23	p >0.05
Sex (Male/female)	11/19	7/23	11/19	p >0.05
Weight (Kg)	68.10±7.02	69.93±7.22	69.10±5.79	p >0.05
ASA grade I/II	25/5	25/5	25/5	p >0.05

after laryngoscopy and intubation. No significant difference was found between Group M6 and Group M9. (p>0.05) [Figure 1].

SBP was increased from baseline (123.56±3.25) to (132.76±3.77) in Group C, while in Group M6 and M9 SBP decreased from baseline (121.13±3.82) to (118.13±31.3) and from (122.79±3.33) to (115.96±3.44) respectively. The inter-group comparison revealed that the increase in SBP in Group C was significantly more (<0.001) in comparison to Group M6 and Group M9. There was no significant difference found in group M6 & M9. [Figure 2]

Diastolic blood pressure in Group I was increased from baseline (80.23±2.112) to (87.70±3.48). In Group M6 and M9, it was decreased from baseline (78.03±5.15) to (73.56±3.77) and from (77.51±3.87) to (71.55±3.14) respectively. (P <0.001) The intergroup comparison revealed that the increase in DBP in Group C was significantly more as compared to Group M6 and Group M9. [Figure 3]

Mean arterial pressure (MAP) in Group C was increased from baseline (94.66±1.91) to (102±3.19), while in group M6 and M9 it was decreased from its baseline from (91.83±4.5) to (87.46±3.38) and from (92.68±2.89) to (86.34±2.55) respectively. (P<0.001) The intergroup comparison also revealed that the increase in MAP in Group C was significantly more in comparison to Group M6 and Group M9 at different time intervals after 120 minutes of melatonin administration, during induction, during laryngoscopy and intubation, after 1, 3, 5, 10 min of intubation. [Figure 4]

The peripheral oxygen saturation was comparable between all the groups. A comparison of the fall of saturation was statistically insignificant between all three groups. In our study, hemodynamic variables were comparable before the procedure. When the procedure progressed with time, pulse rate and blood pressure were more stable in Group M9 patients as compared to Group M6 and Group M9 patients. The difference in variables between Group M6 and Group M9 was insignificant during the entire procedure.

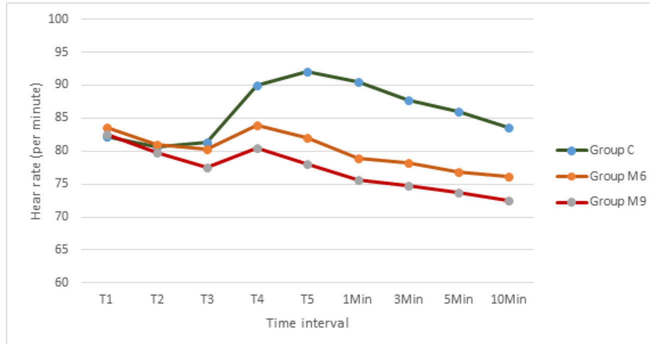

Figure 1: Heart rate (HR) at different time intervals in all the three groups

Figure 2: Systolic Blood Pressure (SBP) at different time intervals in all the three groups

Discussion:

Various studies conducted to evaluate the hemodynamic response concomitant to both laryngoscopy procedure and endotracheal intubation have reported that it varies from minimal cardiovascular response to a significant rise in HR and BP. Various adjutants have been studied to attenuate these responses.[6,7] The present prospective study was conducted to see the role of oral melatonin premedication for attenuation of the hemodynamic response of both laryngoscopy procedure and tracheal intubation. Previously it has been shown that melatonin may decrease the MBP in a healthy population.[8] The additional advantage of melatonin is that it provides conscious sedation without impairing cognitive and psychomotor function and provide analgesia without respiratory depression leading to a cooperative patient. This may also

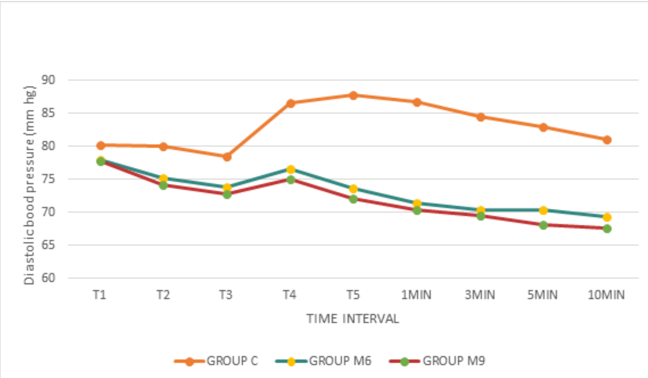

Figure 3: Diastolic Blood Pressure (DBP) at different time intervals in all the three groups

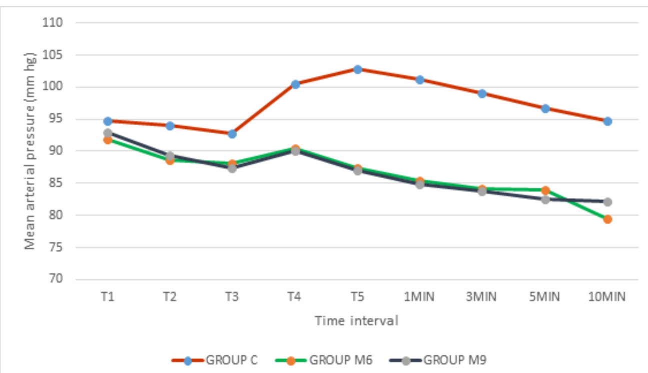

Figure 4: Mean arterial pressure (MAP) at different time intervals in all the three groups

help to mitigate hemodynamic response to both laryngoscopy procedures and intubation. [1]

In the present study, SBP was lower than baseline in both 6 and 9 mg melatonin group at all points of time untill 10 min after intubation as compared to the control group where a significant rise was observed. Similar results were found for DBP and MAP. Similarly Gupta et al also noted the hemodynamic stability during laryngoscopy procedure and intubation when melatonin was given 120 min before the procedure. They observed that the patients were stable at all points of time as compared to the control group in terms of SBP, DBP, and MAP. [1] They concluded that pretreatment with 6 mg melatonin administered 120 min before induction of anesthesia is effective in attenuating hemodynamic responses to both laryngoscopy procedure and intubation.[1] Mohammed et al found similar observations that the role of oral melatonin 6 mg and 9 mg with placebo administered 60 in before surgery in attenuating hemodynamic response of laryngoscopy and intubation. [9] They observed that there was a reduction of blood pressure about SBP, DBP MAP; and perfusion index in both the melatonin groups as compared to the placebo group. Sewerynek et al found a similar observation to our study that oral Melatonin in 1 mg dose reduces BP and also decreases catecholamine level after 90 min in humans. [10] It may reduce BP via the following actions: 1) by a direct effect on the hypothalamus; 2) by a reduction in the level of catecholamine; 3) by acting as an antioxidant which lowers blood pressure; 4) by smooth muscle relaxation in the aorta wall. This may also be due to its inhibitory actions on the central nervous system responsible for attenuating hemodynamic responses to laryngoscopy as well as in intubation. Rosenberg et al. in their study have also shown that melatonin has sympatholytic activity. [1,11]

Because of anxiolytic properties, pharmacokinetic properties, hypnotic effect, and hemodynamic effects of propofol during total intravenous anesthesia; Bienert et alin 2014 have compared melatonin with clonidine. [12] Maitra et alin 2013 has discussed that Melatonin's unique properties can be highly useful in the peri-operative care of patients. [13]

In the present study, there were no significant side effects such as bradycardia, arrhythmias, respiratory depression, restlessness, nausea in both the melatonin groups as compared to the placebo control group. Similar results were also found in other studies. [1] It has been reported melatonin is used for a short period is devoid of significant side effects. [14]

Conclusion:

Melatonin in a dose of 6mg and 9mg was more effective compared to the placebo drug in the hemodynamic stress response attenuation to both the laryngoscopy procedure and endotracheal intubation. Oral melatonin 9mg attenuates the hemodynamic response to both the laryngoscopy procedure and endotracheal intubation completely as compared to 6mg. Both doses of either 6 mg or 9mg melatonin were not having any significant side effects.

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