Original Article

Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation

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ABSTRACT

Background and Aims: Laryngoscopy and endotracheal intubation are considered as potent stimuli which lead to an increase in heart rate and blood pressure. Melatonin (N-acetyl-5-methoxytryptamine) has been studied for pre-operative anxiolysis and sedation in Intensive Care Unit. We made a hypothesis that melatonin can provide haemodynamic stability during laryngoscopy and intubation when given 120 min before the procedure. **Methods:** Sixty American Society of Anesthesiologists physical status Grade I and II patients of either gender, 20–45 years old, 40–65 kg body weight, scheduled to undergo elective surgical procedures under general anaesthesia were assigned into two equal groups - Group C (control) and Group M (melatonin). They received oral placebo or melatonin tablets 6 mg, respectively, 120 min before surgery. The haemodynamic parameters were recorded preoperatively, during laryngoscopy and endotracheal intubation and thereafter at 1, 3, 5 and 10 min. Unpaired t-test was used for between-group comparison of ratio and interval scale data. For within-group comparison of ratio and interval scale data, repeated-measures ANOVA and post hoc Bonferroni t-tests were used. **Results:** It was observed that in the control group, there was a significant increase in heart rate and blood pressure at laryngoscopy and intubation and persisted till 10 min post-intubation. In melatonin group, there was an insignificant increase in heart rate at the time of laryngoscopy and intubation which however settled within 1 min post-intubation. **Conclusion:** Melatonin is an effective drug for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation.

Key words: Laryngoscopy, melatonin, premedication, pre-operative anxiety, pressor response

INTRODUCTION

Laryngoscopy and endotracheal intubation are considered potent noxious stimuli which provoke haemodynamic responses leading to a marked increase in heart rate and blood pressure.[1] This is probably of no consequence in healthy individuals. However, these events are especially detrimental in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmias, congestive heart failure, hypertension, cardiomyopathy and geriatric age group.[2] Hence, it is mandatory to take measures to attenuate these pressor responses. The mechanisms of these haemodynamic alterations are somatovisceral reflexes due to sympathetic stimulation. During intubation of trachea, the laryngeal and tracheal sensory receptors are stimulated which result in the release of endogenous catecholamines resulting in tachycardia and hypertension.[3]

Since the invention of laryngoscopy and endotracheal intubation, various drug regimens and techniques have been used from time to time to attenuate these stress responses. Some of such agents being

opioids (fentanyl, alfentanil), calcium channel blockers (verapamil, diltiazem), sympatholytics (clonidine, dexmedetomidine and methyldopa), beta blockers (esmolol, propranolol), benzodiazepines (midazolam, alprazolam), barbiturates, propofol, pregabalin and peripheral vasodilators (sodium nitroprusside, nitroglycerine).[4] However, each agent has some limitations such as respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension or allergic reactions. Hence, there has always been a need for a better agent.

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous sleep-regulating hormone secreted by pineal gland. Exogenous administration of melatonin facilitates sleep onset and improves the quality of sleep. It is different from benzodiazepines and their derivatives in that it produces natural sleep pattern and does not lead to impairment of cognitive functions.[5] Various researchers have used this drug in different dose patterns as premedication in both adults as well as children. It has been mainly studied in view of pre-operative anxiolysis, sedation in Intensive Care Unit, pre-operative cognitive and psychomotor functions.[6]

We assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have role in attenuating haemodynamic responses to laryngoscopy and intubation. Based on this, we made a hypothesis that melatonin can provide haemodynamic stability during laryngoscopy and intubation when given 120 min before the procedure. The primary objective was to study the changes in blood pressure during laryngoscopy and intubation.

METHODS

This prospective randomised double-blind study was conducted after obtaining permission from the Hospital Ethical Committee and informed patient consent. Sixty patients were randomly assigned to two equal groups (n = 30). Randomisation was done according to a computer-generated list. Group C (control group) received two placebo tablets 120 min before surgery. Group M (melatonin group) received oral melatonin tablets 6 mg (two tablets of 3 mg each), administered 120 min before surgery. Each patient received either drug based on the generated list in a thick opaque, similar looking envelope by the pre-operative nurse. Both patient and investigator were unaware of the type of drug. Vitamin D3 tablets were used as placebo

and looked similar to melatonin tablets. Moreover, the study drugs were administered by nurse in the pre-operative area, and she was unaware of the study.

Inclusion criteria were patients belonging to the American Society of Anesthesiologists (ASA) physical status Grade I and II, age 20–45 years of either gender and surgery requiring general anaesthesia for duration longer than 30 min. Exclusion criteria were diabetes, hypertension, psychiatric illness, intake of antipsychotics, sedatives, anxiolytics and antiepileptic drugs; sleep disorders, obesity and drug allergy. Likewise, patients with anticipated difficult intubation and those requiring more than one attempt or more than 20 s for laryngoscopy were excluded from the study. The pregnant and lactating females were also excluded from the study. In the pre-operative room, the study drugs were administered with a sip of water 120 min before surgery. Continuous monitoring of the pulse rate, respiratory rate, blood pressureand arterial oxygen saturation (SpO_2) was done in the pre-operative period at an interval of 5 min by the nurse posted in the pre operative room.

On receiving the patient in the operation theatre, routine monitoring was commenced which included heart rate, electrocardiogram, arterial SpO_2, non-invasive blood pressure (NIBP) and end-tidal carbon dioxide ($EtCO_2$). Two puffs of 10% lignocaine were sprayed on the larynx. All the patients were administered 100% oxygen for 3 min before induction. Glycopyrrolate 0.004 mg/kg and fentanyl 1 µg/kg were administered intravenously. Induction was attained with intravenous propofol 2 mg/kg intravenously mixed with preservative-free lignocaine hydrochloride. Succinylcholine was given intravenously 2 mg/kg to facilitate endotracheal intubation with proper sized well-lubricated cuffed endotracheal tube by the same person each time. Maintenance of anaesthesia was attained with inhalation of isoflurane 1 minimum alveolar concentration; nitrous oxide: oxygen 40:60. Muscle relaxation was attained with vecuronium bromide administered in the dose of 0.06–0.08 mg/kg intravenously as loading dose and one-fourth of the initial dose as maintenance doses. Mechanical ventilation was adjusted to maintain normocapnia ($EtCO_2$ values of 35–38 mmHg). Intravenous infusion of injection diclofenac sodium 75 mg was administered slowly 15 min before completion of surgery for post-operative analgesia. After completion of the surgery, neostigmine 50 µg/kg and injection glycopyrrolate 10 µg/kg were administered intravenously to reverse the residual neuromuscular blockade.

Haemodynamic parameters such as heart rate: systolic, diastolic and mean blood pressures were recorded before the administration of drug (baseline), 120 min after administration of study drug (just before induction), immediately after induction, at laryngoscopy and intubation, just after laryngoscopy and intubation and at 1, 3, 5 and 10 min thereafter.

In the post-anaesthesia care unit, the patients received the standard post-operative care including oxygen administration via face mask at 4–6 L/min and monitoring of heart rate, NIBP, respiratory rate and SpO_2. We observed for any episodes of nausea, vomiting, dizziness, headache, respiratory depression, arrhythmias, bradycardia, hypotension and restlessness till 24 h postoperatively.

The primary outcome was maintenance of systolic blood pressure within 10% of baseline values at laryngoscopy and intubation. The secondary outcomes were minimal respiratory depression ($SpO_2 < 90\%$, respiratory rate <12/min), bradycardia (heart rate <20% of baseline) and hypotension (systolic blood pressure <20% of baseline) in the post-operative period.

Ratio and interval scale data were summarised as a mean and standard deviation, whereas nominal scale data as ratio and proportions. Shapiro–Wilk test was used to assess normality of data. Nominal scale data were analysed using Fisher's exact test, whereas unpaired *t*-test was used for between-group comparison of ratio and interval scale data. For within-group comparison of ratio and interval scale data, repeated-measures ANOVA and *post hoc* Bonferroni *t*-tests were used. $P < 0.05$ was considered statistically significant. As the Bonferroni's test is very conservative *post hoc* test, the conventional $P < 0.05$ was selected even for multiple comparisons. MedCalc version 12.2.1.0 software (Ostend, Belgium) was used for statistical calculations.

Sample size was calculated at 80% study power and alpha error of 0.05 assuming a standard deviation of 6.5 mmHg in systolic blood pressure after 2 h of 6 mg melatonin per oral administration as per results of pilot study conducted before this study on ten patients. For difference of 5 mmHg to be detected in mean systolic blood pressures between the groups, 28 patients in each group were required as sample size. It was further enhanced and rounded off to thirty patients in each group as the final sample size for the present study.

RESULTS

Both the study groups were identical in terms of age, gender distribution, weight, ASA status and duration of surgery [Table 1].

Systolic blood pressure was higher from baseline values in control group during laryngoscopy and intubation. Thereafter, this increase persisted at all points of time until 10 min ($P < 0.0001$). In the melatonin group, there was no rise and the patients were stable at all points of time after the administration of the study drug ($P < 0.0001$) [Table 2]. Similar trends were observed for diastolic and mean blood pressure ($P < 0.0001$) [Tables 3 and 4].

In the control group, there was a rise in heart rate from baseline values at laryngoscopy which attained statistical significance at 1 min and persisted thereafter till 10 min. In the melatonin group, there was a rise in heart rate from baseline values at the time of laryngoscopy, but it was not statistically significant and returned to previous values within 1 min. Thereafter, it was maintained at lower values

Table 1: Demographics

Variable	Group C	Group M	P
ASA grade (I/II) (*n*=30)	17/13	14/16	0.606*
Gender (male/female) (*n*=30)	20/10	18/12	0.789*
Type of surgery (open/laparoscopic) (*n*=30)	19/11	22/8	0.580*
Duration of surgery (min), mean±SD	68.10±10.03	66.17±11.33	0.487#
Age (years), mean±SD	30.57±3.31	31.30±3.41	0.401#
Weight (kg), mean±SD	53.10±5.47	54.37±4.49	0.331#

*Fisher's exact test; #Unpaired *t*-test. *n* – Number of patients; SD – Standard deviation; ASA – American Society of Anesthesiologists

Table 2: Systolic blood pressure at various points of time (mmHg)

Point of time	Group C	Group M	P*
Baseline (mean±SD)	123.63±5.79	124.43±6.65	0.621
120 min after study drug (mean±SD)	124.80±6.30	119.10±8.36	0.004
Just after induction (mean±SD)	122.13±6.27	115.77±8.12	0.001
Laryngoscopy and intubation (mean±SD)	132.50±5.88	120.60±9.73	<0.0001
After intubation, min (mean±SD)			
1	140.10±11.54	112.83±7.52	<0.0001
2	137.57±9.73	107.30±9.13	<0.0001
3	132.23±6.85	104.93±9.56	<0.0001
5	129.70±6.86	104.23±8.63	<0.0001
10	127.07±5.92	105.47±8.39	<0.0001

*Unpaired *t*-test. SD – Standard deviation

Table 3: Diastolic blood pressure at various points of time (mmHg)			
Point of time	Group C	Group M	P*
Baseline (mean±SD)	80.87±4.52	79.17±6.34	0.237
120 min after study drug (mean±SD)	85.20±5.74	75.50±6.43	<0.0001
Just after induction (mean±SD)	82.53±5.32	74.67±5.73	<0.0001
Laryngoscopy and intubation (mean±SD)	90.10±4.69	79.43±6.75	<0.0001
After intubation, min (mean±SD)			
1n	95.53±6.00	73.00±7.35	<0.0001
2	92.00±3.40	68.80±7.12	<0.0001
3	88.27±3.78	66.03±6.14	<0.0001
5	85.53±3.41	65.43±6.25	<0.0001
10	84.87±3.43	65.67±5.76	<0.0001

*Unpaired *t*-test. SD – Standard deviation

Table 4: Mean blood pressure at various points of time (mmHg)			
Point of time	Group C	Group M	P*
Baseline (mean±SD)	95.10±4.71	94.27±5.58	0.534
120 min after study drug (mean±SD)	98.43±5.54	89.97±6.45	<0.0001
Just after induction (mean±SD)	95.73±5.04	88.40±6.02	<0.0001
Laryngoscopy and intubation (mean±SD)	104.27±4.49	93.10±6.65	<0.0001
After intubation, min (mean±SD)			
1	110.33±6.99	86.27±5.97	<0.0001
2	107.13±4.83	81.57±6.78	<0.0001
3	102.87±4.25	78.97±6.35	<0.0001
5	100.17±4.19	78.47±5.72	<0.0001
10	98.97±3.91	78.97±5.45	<0.0001

*Unpaired *t*-test. SD – Standard deviation

Table 5: Heart rate at various points of time (beats/min)			
Point of time	Group C	Group M	P*
Baseline (mean±SD)	82.00±5.76	82.43±9.26	0.829
120 min after study drug (mean±SD)	83.93±5.90	80.57±9.85	0.115
Just after induction (mean±SD)	81.37±5.73	79.13±9.97	0.293
Laryngoscopy and intubation (mean±SD)	87.40±8.89	83.90±10.61	0.171
After intubation, min (mean±SD)			
1	89.87±11.65	79.00±10.02	<0.0001
2	89.50±10.05	76.33±9.49	<0.0001
3	86.57±8.83	75.43±9.05	<0.0001
5	84.03±8.10	74.03±9.02	<0.0001
10	83.27±7.08	74.60±8.87	<0.0001

*Unpaired *t*-test. SD – Standard deviation

Table 6: Complications		
Variable	Group C (*n*=30)	Group M (*n*=30)
Bradycardia	0	0
Headache	0	0
Nausea/vomiting	1	1
Restlessness	2	0
Arrhythmias	0	0
Hypotension	0	0
Respiratory depression	0	0

at all points of time till 10 min after laryngoscopy and intubation ($P < 0.0001$) [Table 5].

In the control group, one patient had nausea and vomiting; two patients were agitated and restless in the immediate post-operative period. In the melatonin group, one patient had nausea and vomiting in the post-operative period. None of the patients had respiratory depression or hypotension [Table 6]. Totally thirty participants were included in each study group. Of these, none had to be dropped off.

DISCUSSION

The present study is aimed at assessing the role of melatonin in attenuating haemodynamic responses to laryngoscopy and intubation. Melatonin (*N*-acetyl-5-methoxytryptamine) is a pineal gland hormone which controls the circadian rhythm. It has been used for sleep disorders, jet lag, perioperative anxiolysis and sedation, cognitive and psychomotor functions.[7-10] We assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have a role in attenuating haemodynamic responses to laryngoscopy and intubation. Rosenberg *et al.* studied the role of perioperative melatonin in the modification of surgical stress response indicating that melatonin has sympatholytic activity.[11] This is in support of our assumption. The peak effect of exogenous melatonin ranges from 60 to 150 min.[12] Based on this, we made a hypothesis that melatonin can provide haemodynamic stability during laryngoscopy and intubation when given 120 min before the procedure. We performed a pilot study in which we did not observe the desired effects with 3 mg but with 6 mg oral melatonin and not at 90 min but after a period of 120 min and our patients were tranquil and haemodynamically stable. Hence, we administered 6 mg melatonin 120 min before induction of anaesthesia.

We observed that in melatonin group, systolic blood pressure was lower than baseline values at all points of time till 10 min after intubation as compared to the control group in which there was a significant rise. Similar trends were observed for diastolic and mean blood pressure. It has been studied that

melatonin reduces mean blood pressure in healthy volunteers.[13,14] A study on rats revealed that pinealectomy resulted in severe hypertension.[15] Mohammed *et al.* compared the role of oral melatonin 6 mg and 9 mg with placebo administered 1 h before surgery in attenuating pressor response to laryngoscopy and intubation. They observed that there was a reduction of blood pressure with regard to systolic, diastolic and mean blood pressure; and perfusion index in both melatonin groups as compared to the placebo group.[16]

The mechanism of effect of melatonin on circulation is complex. The blood pressure lowering effect may be attributed to the specific binding of melatonin to melatonin receptors in the blood vessels, interfering with the vascular response to catecholamines.[17] It may interfere with the peripheral as well as central autonomic system, causing a reduction in adrenergic outflow and resulting catecholamine levels.[18] Furthermore, it may induce relaxation of arterial wall smooth muscle by enhancing the availability of nitric oxide.[19] In addition, it may also act via specific receptors melatonin type 1 or melatonin type 2 located peripherally in the blood vessels and centrally in blood pressure regulating area of the brain.[20] It also has free radical scavenging effect leading to dilatation of blood vessels, and it may work via epigenetic mechanism at area postrema in the brain.[21] The blood pressure lowering effect could also be due to the sedative action of orally administered melatonin. The sedative effect is mainly due to binding at GABA-A receptor and exerting its anaesthetic effect.[17]

We observed that heart rate was also lower than baseline values at all points of time in melatonin group as compared to the control group. However, in a similar study, no difference was observed in the changes of heart rate in the melatonin groups as compared to the placebo group.[16] The heart rate lowering effect of melatonin may be attributed to its anxiolytic actions. The underlying mechanism is probably the synergy between melatonergic and GABAergic systems. It also has analgesic effects as observed by various investigators and this may also contribute to the haemodynamic stability.[22]
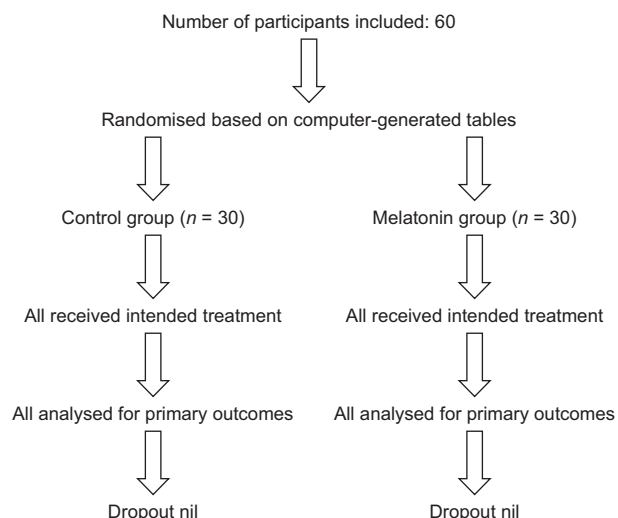
Moreover, the magnitude of the haemodynamic responses is directly proportional to the duration of laryngoscopy and to the force applied during laryngoscopy. Hence, those patients requiring more than one attempt and more than 20 s for laryngoscopy

were not to be included in the study. Since this study is regarding haemodynamic responses and antihypertensive agents desensitise the autonomic receptors, diabetic patients usually have some degree of autonomic neuropathy, as age progresses blood vessel wall gets atherosclerosis. All these may interfere with the results; hence, these patients were excluded from the study.

In our series of patients, there were no significant side effects such as bradycardia, arrhythmias, respiratory depression, restlessness, nausea and drug interactions. Various studies indicate that melatonin has an excellent safety profile. Very high doses up to 300 mg/day orally for 2 years have been administered safely.[23] Even in children doses up to 20 mg have been used without any significant side effects apart from sedation.[24] Kain *et al.* safely used 0.4 mg/kg oral melatonin in children.[25] There is no liability to cause dependence and addiction. It may cause fatigue (4%) or nausea (3%). Dizziness, headache and irritability may be seen in some patients with use of very high doses in some previous studies of melatonin done for its anxiolytic action.[26] Thus, proving that melatonin is a useful drug for use as an adjunct in anaesthesia. The correct dosage in humans seems largely unknown and requires further studies.

The role of melatonin in anaesthesia and critical care[27] has been elaborately discussed in the literature; it has been mentioned as a wonder drug with a wide spectrum of beneficial uses in anaesthesia and critical care including antioxidant and neuroprotective properties besides hypnosis, anxiolysis, analgesia and others. The use of melatonin for attenuation of haemodynamic responses before laryngoscopy and intubation is superior to few other drugs studied for the same purpose. For instance, melatonin is superior to dexmedetomidine since the latter is associated with significant bradycardia and hypotension.[28] On the other hand, esmolol has more selective action on heart rate than blood pressure.[29] As compared to remifentanil, melatonin is easily available and easy to administer. Moreover, remifentanil is associated with severe hypotension thus limiting its use for the purpose.[30]

The limitations of our study were that we did not compare different doses of melatonin and effects at different time intervals of administration of melatonin. We also did not assess sedation and anxiety scores and did not perform psychoanalytic tests in the

Number of participants included: 60

⇓

Randomised based on computer-generated tables

⇓

Control group (*n* = 30)	Melatonin group (*n* = 30)
⇓	⇓
All received intended treatment	All received intended treatment
⇓	⇓
All analysed for primary outcomes	All analysed for primary outcomes
⇓	⇓
Dropout nil	Dropout nil

Details of flow of participants

post-operative period, extubation responses and plasma norepinephrine levels.

CONCLUSION

Pre-treatment with 6 mg melatonin administered orally 120 min before induction of anaesthesia is effective for attenuating haemodynamic responses to laryngoscopy and intubation.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Announcement

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30 June 2016	Dr. Y. G. Bhoj Raj Award	Hon. Secretary, ISA
30 Sept. 2016	Kop's Award	Chairperson, Scientific Committee ISACON 2016 with Copy to Hon. Secretary, ISA
30 Sept. 2016	Prof. Dr. Venkat Rao Oration 2017	Hon. Secretary, ISA
30 Sept. 2016	Ish Narani Best poster Award	Chairperson, Scientific Committee ISACON 2016
30 Sept. 2016	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2016
10 Nov. 2016	Late Dr. T. N. Jha Memorial & Dr. K. P. Chansoriya Travel Grant	Hon. Secretary, ISA, copy to Chairperson Scientific Committee of ISACON 2016
20 Oct. 2016	Awards (01 Oct 2015 to 30 Sept 2016) 1. Best City Branch 2. Best Metro Branch 3. Best State Chapter 4. Public Awareness – Individual 5. Public Awareness – City / Metro 6. Public Awareness - State 7. Ether Day (WAD) 2016 City & State 8. Membership drive 9. Proficiency Awards	Hon. Secretary, ISA
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