

Comparative evaluation of oral melatonin and oral clonidine for the attenuation of haemodynamic response to laryngoscopy and tracheal intubation—A prospective randomised double blind study

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ABSTRACT

Background and Aims: Laryngoscopy and endotracheal intubation cause significant derangement of the haemodynamic parameters proving detrimental for some patients. Clonidine, an α -2 adrenoreceptor agonist, and melatonin, the pineal hormone, have been used for the attenuation of these haemodynamic responses. This study was designed to evaluate the effect of oral melatonin and clonidine in attenuating the haemodynamic responses to laryngoscopy and intubation.

Materials and Methods: In this prospective randomised double-blind study, 60 American Society of Anaesthesiologists (ASA) grade I and II patients aged 20–60 years of either gender scheduled to undergo elective surgery under general anaesthesia were randomly divided into Group M and Group C and orally received 6 mg of melatonin and 0.2 mg of clonidine, respectively, 120 min before the induction of anaesthesia. The haemodynamic parameters—heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate-pressure product (RPP) were recorded before and 120 min after the administration of the study drug, before induction, immediately after intubation and at 1, 3, 5 and 10 min following intubation. Sedation was assessed using the Ramsay Sedation Scale. The qualitative and quantitative variables were analysed using Chi square test and unpaired student t test, respectively. For intragroup comparison of quantitative data, paired t test was applied. A P value <0.05 was considered as statistically significant. **Results:** A significant difference was noted between the groups regarding HR and RPP 0, 1, 3 and 5 min after intubation. The Ramsay sedation score ranged between 2 and 3 at all time intervals. **Conclusion:** Although both the drugs are effective, oral melatonin proved superior to oral clonidine in attenuating the haemodynamic response to laryngoscopy and tracheal intubation without any side effects.

Key words: Clonidine, endotracheal intubation, haemodynamic, laryngoscopy, melatonin

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INTRODUCTION

Laryngoscopy, airway instrumentation and tracheal manipulation can stimulate the sympathetic system and cause an ephemeral derangement of vitals. These powerful noxious stimuli cause adverse haemodynamic responses leading to marked increase in heart rate and blood pressure.^[1] Such haemodynamic changes occurring during intubation may alter the delicate balance between myocardial oxygen demand and supply and precipitate myocardial ischaemia in patients with coronary artery disease.^[2] 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 methods to attenuate the sympathetic response to laryngoscopy and achieve

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smoother manipulation of airway have been evaluated like topical anaesthesia of pharynx, superior laryngeal nerve block, intravenous lidocaine, beta blockers, opioids, calcium channel blockers, benzodiazepines, barbiturates, propofol, pregabalin, magnesium sulphate, nitroglycerin (intranasal and intravenous) and alpha2 adrenoceptor agonists like clonidine and dexmedetomidine (intravenous and intranasal).^[4-6] However, the use of these agents is associated with the respective adverse effects like respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension or allergic reactions; hence, the quest for a better agent is always on.

Clonidine, an α -2 adrenoreceptor agonist, exerts central sympatholytic effect and blunts the stress response to laryngoscopy and intubation.^[7] Administration of exogenous melatonin (N-acetyl-5-methoxytryptamine, a pineal gland hormone) has been used for sleep disorders, perioperative anxiety and sedation.^[8] Recently, melatonin has been used for the attenuation of haemodynamic responses to laryngoscopy and intubation.^[9]

To the best of our knowledge, there is very limited literature available comparing the role of oral melatonin and oral clonidine in attenuating the haemodynamic response to laryngoscopy and intubation. Thus, this study was designed to assess and compare the effects of oral melatonin and oral clonidine on the attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation as well as their effect on preoperative sedation.

MATERIALS AND METHODS

After obtaining the institutional ethical committee approval and Clinical Trials Registry-India (CTRI/2018/07/015112) registration, this randomised, double blinded, comparative study was conducted in a tertiary care institute. Sixty American Society of Anaesthesiologists (ASA) grade I and II patients aged 20–60 years of either gender scheduled to undergo elective surgery under general endotracheal anaesthesia were enrolled in the study period from August 2018 to August 2019.

Patients receiving treatment with either of the study drug (melatonin or clonidine), mental illness, pregnancy, cardiac illness, renal or hepatic disease, morbid obesity, bleeding diathesis, known allergy to the study drugs, anticipated difficult intubation (Modified

Mallampati class three and four) and requiring more than two attempts and more than 15 sec at intubation were excluded from the study.

Sample size was estimated on the basis of a previous study by Gupta P *et al.*,^[9] in which at 80% study power and an alpha error of 0.05 to detect a difference of five mm of Hg in mean systolic blood pressure between the groups required 28 patients in each group. To compensate for the dropouts, 30 patients were included in each group.

After obtaining written informed consent, the patients were divided into two groups (30 patients each) with computer-generated table of random numbers in opaque sealed envelopes. Two anaesthesiologists were involved in the study—one administered the drug while the other conducted the case and recorded the data. To ensure double blinding, both the anaesthesiologists and the patients were kept unaware of group allocation.

All patients were subjected to routine pre-anaesthetic checkup in the preoperative period. All routine investigations as appropriate for the surgeries were obtained and optimised. All the patients were kept fasted overnight after 12 midnight and received Tab Alprazolam 0.25 mg and Tab Ranitidine 150 mg the night before surgery.

In the preoperative room, the study drugs six mg of oral melatonin (two capsules of three mg immediate release melatonin by Healthy Hey nutrition) for group M and 0.2 mg of oral clonidine (two tablets of 0.1 mg clonidine by Unichem Laboratory Ltd.) for group C were administered with a sip of water, 120 min before the induction of anaesthesia by an anaesthesiologist. Continuous monitoring of heart rate, respiratory rate, noninvasive blood pressure and peripheral oxygen saturation (SpO₂) were done at an interval of five min by a staff nurse. At 0 (base line), 30, 60 and 90 min after drug administration and just before induction (120 min after study drug), the level of sedation was assessed by Ramsay's Sedation Scale.^[10]

In the operating room, standard monitoring (heart rate, non-invasive measurement of systolic, diastolic and mean blood pressure oxygen saturation, electrocardiography) was applied, and recorded. Intravenous line was secured with 20 G cannula and infusion of injection Ringer Lactate commenced at the rate of two ml/kg/hr. After three mins of pre-oxygenation

with 100% oxygen, Inj glycopyrrolate 0.004 mg/kg and Inj fentanyl two $\mu\text{g/kg}$ were administered to all patients. Patients were induced with Inj propofol two mg/kg followed by Inj vecuronium 0.1 mg/kg intravenously to facilitate endotracheal intubation. The time taken for laryngoscopy (time from insertion of laryngoscope blade to inflation of endotracheal cuff) was noted.

Anaesthesia was maintained with oxygen and nitrous oxide (50:50), isoflurane upto 1% v/v and intermittent dose of Inj vecuronium 0.02 mg/kg for muscle relaxation. Mechanical ventilation was adjusted to normocapnia (EtCO₂ values of 35–38 mm of Hg). After completion of the surgery, Inj neostigmine 0.05 mg/kg and Inj glycopyrrolate 0.01 mg/kg were administered to reverse the residual neuromuscular blockade.

Haemodynamic parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded before the administration of the study drug (baseline), 120 min after the administration of the study drug (just before induction), immediately just after intubation (0 min) and at 1, 3, 5 and 10 min following endotracheal intubation. Rate-Pressure Product (RPP), defined as the product of heart rate and systolic blood pressure was also calculated for all patients.

Data were entered into MS-EXCEL (Microsoft) and analysed using the Statistical Package for the Social Sciences (SPSS) Version 20 (IBM) and an open-source Social Statistics calculator.^[11] The qualitative/categorical variables like gender and ASA grade were summarised as frequency and percentage and were analysed using Chi square test. Quantitative variables like weight, blood pressure and heart rate were summarised as mean and standard deviation and were analysed using unpaired Student's t test. A *P* value <0.05 was taken as statistically significant.

The primary outcome measured was to assess the effect of melatonin and clonidine on systolic blood pressure in response to laryngoscopy and endotracheal intubation. The secondary outcomes measured were the effect on diastolic blood pressure, mean arterial pressure, rate-pressure product and sedative effects of oral melatonin and clonidine.

RESULTS

The demographic characteristics (age, gender and weight distribution) were comparable between the

Table 1: Characteristics of the study population

Characteristics	Group C (n=30)	Group M (n=30)	<i>P</i>
Gender (M/F)			
Male	14	14	1
Female	16	16	
Age (yr)			
20-45	23	24	0.1141
46-70	7	6	
Weight (kg)			
Mean±SD	62.27±8.22	62.6±7.65	0.8571
Duration of laryngoscopy (sec)			
Mean±SD	12.3±3.5	13.4±2.1	0.070

melatonin and clonidine groups. The duration of laryngoscopy was comparable between the two groups. All the patients in both the groups were intubated in the first attempt of laryngoscopy [Table 1]. The baseline Ramsay sedation score was 1 in both groups. The Ramsay sedation score ranged between 2 and 3 at all intervals after the administration of the drugs [Figure 1].

A significant difference was observed in the mean values of all haemodynamic parameters after 120 min of study drug administration and just before induction as compared to the baseline values *P* < 0.05 [Tables 2 and 3] in both groups. The haemodynamic responses in Group M were comparable to the baseline values immediately after intubation (*P* > 0.05). In Group C, the mean heart rate showed a statistically significant difference from the baseline (*P* = 0.031) while the other parameters were comparable to the baseline values (*P* > 0.05). At 1 min after intubation, group M showed statistically significant difference in mean RPP (*P* = 0.0019) while other parameters were comparable to baseline. However in Group C, the SBP, RPP, DBP and MAP means showed statistically significant difference from baseline (*P* ≤ 0.05). At 3, 5 and 10 min after intubation, the means of all parameters showed statistically significant variation from the baseline values in Group C and M.

Both groups were statistically comparable with regards to the heart rate (HR) (*P* = 0.066), systolic blood pressure (SBP) (*P* = 0.077), diastolic blood pressure (DBP) (0.060), mean arterial pressure (MAP) (*P* = 0.085) and rate pressure product (RPP) (*P* = 0.050) at baseline and 120 mins after administration of study drugs. There was a significant difference between the groups regarding HR and RPP immediately after intubation (*P* = 0.00035, 0.000081), 1 min (*P* = 0.0038, 0.0019), 3 min (*P* = 0.0013, 0.0051) and 5 min (*P* = 0.0156, 0.021) after intubation as

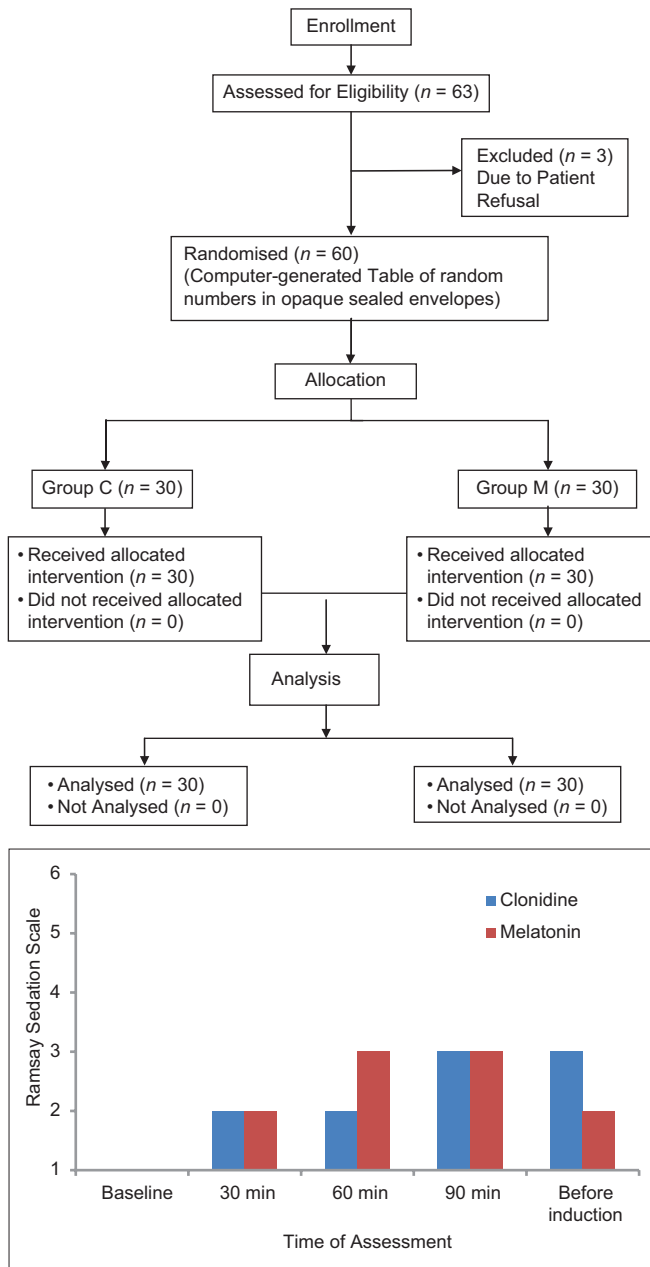


Figure 1: Comparison of preoperative sedation scores at different time intervals among the two groups following administration of clonidine and melatonin

depicted in Table 4. Both the groups were similar when SBP, DBP and MAP were compared between the two groups at all the time durations [Table 4].

DISCUSSION

Laryngoscopy and endotracheal intubation is the most important step during the administration of general endotracheal anaesthesia (GETA) but it is associated with variation in haemodynamic parameters. The attenuation of these changes is of paramount importance to prevent morbidity and mortality.

Melatonin is a pineal gland hormone that regulates various physiological functions like circadian rhythm, reproduction, mood and immune function.^[8] Exogenous melatonin improves sleep quality and has anxiolytic, anti-inflammatory and oxidative effects.^[8,12] Exogenous melatonin has been formulated into various preparations and their pharmacokinetics has been studied,^[13] although their complete range of action, benefits, pharmacokinetics and pharmacodynamics by various routes have not been well described. The wide array of clinical uses of melatonin have not been applied in day to day anaesthesia practice. Hence, this study was conducted to introduce melatonin as a possible premedication with lower side effects and comparable pharmacological action.

Clonidine, which is mainly used as an anti-hypertensive agent, has many properties of an ideal premedicant and it also has beneficial effects on the haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation.^[14] The Tmax value ranges from 15 to 210 min for a dose of two mg and 10 mg oral melatonin^[15] and the maximum plasma concentration (Cmax) following oral administration of clonidine occurs after 1–3 hr.^[16] The oral administration of exogenous melatonin and clonidine approximately two hours before the intended onset of clinical effects, therefore seems reasonable, assuming that clinical efficacy coincides with tmax values.

The demographic data of both groups were similar in terms of mean values of age, gender and weight. Laryngoscopy time and number of attempts of intubation in both the groups were comparable. The magnitude of the haemodynamic response to laryngoscopy and endotracheal intubation is directly proportional to the force applied and the duration of laryngoscopy. Hence, patients requiring more than two attempts and more than 15 sec for laryngoscopy were excluded from the study.

Both the drugs caused sedation without causing respiratory depression. The duration of sedative effects was longer with clonidine as compared to melatonin and appeared to be mediated by α 2A receptor stimulation. Melatonin though induced sleep, did not cause excessive sedation among the patients. Hence, we can say that patients premedicated with melatonin require less preoperative monitoring compared to clonidine. It has been reported that melatonin causes preoperative anxiolysis and increase in the level of sedation without impairing orientation.^[17,18] The sedative effect

Table 2: Intra group comparison of HR and RPP

Observations	Group M		Group C	
	Baseline HR (bpm) (84.7±5.18)		Baseline HR (bpm) (85.53±5.81)	
	Percent change (%)	P	Percent change (%)	P
At 120 min	-3.38	0.00355	-2.45	0.1612
Before induction	-5.19	0.000025	-1.82	0.3512
Immediately after intubation	+1.57	0.113473	+9.98	0.00003
1 min	-1.45	0.12822	-4.99	0.01803
3 min	-4.01	0.001592	-2.10	0.2233
5 min	-5.46	0.000051	-1.35	0.4460
10 min	-5.82	0.000024	-3.65	0.0425
	Baseline RPP (10513.1±708.35)		Baseline RPP (10843.6±950.96)	
At 120 min	-5.53	0.000018	-7.16	0.00044
Before induction	-8.22	<0.00001	-7.20	0.00288
Immediately after intubation	+1.93	0.07386	+10.96	0.00003
1 min	-3.41	0.007053	-2.41	0.2579
3 min	-6.88	0.000016	-2.63	0.17813
5 min	-9.01	<0.00001	-6.29	0.0047
10 min	-9.53	<0.00001	-9.42	0.00013

Table 3: Intra group comparison of SBP, DBP and MAP

Observations	Group M		Group C	
	Baseline SBP (mmHg) (124.40±8.99)		Baseline SBP (mmHg) (126.76±6.89)	
	% change	P	% change	P
At 120 min	-2.25	0.46658	-4.88	0.00001
Before induction	-3.21	0.0081	-5.70	0.00001
Immediately after intubation	-0.37	0.38777	+0.89	0.3845
1 min	-2.03	0.055389	-2.49	0.1988
3 min	-3.07	0.007027	-5.15	0.00003
5 min	-3.85	0.001226	-5.15	0.00006
10 min	-4.04	0.000387	-6.04	0.00003
	Baseline DBP (mmHg) (81.77±6.29)		Baseline DBP (mmHg) (84.06±6.35)	
At 120 min	-2.60	0.02398	-7.70	0.00001
Before induction	-1.25	0.003367	-9.48	0.00001
Immediately after intubation	+1.25	0.1548	-1.39	0.3731
1 min	-1.46	0.111984	-5.5	0.1276
3 min	-4.03	0.000744	-8.01	0.00003
5 min	-4.69	0.000435	-8.96	0.00001
10 min	-4.73	0.000392	-10.11	0.00001
	Baseline MAP (mmHg) (95.87±7.40)		Baseline MAP (mmHg) (98.13±5.76)	
At 120 min	-2.39	0.033328	-6.42	0.00001
Before induction	-3.48	0.00448	-7.67	0.00001
Immediately after intubation	+0.99	0.20822	-0.20	0.8543
1 min	-1.77	0.07992	-4.03	0.00898
3 min	-3.65	0.00155	-6.68	0.00001
5 min	-4.14	0.000666	-7.19	0.00001
10 min	-4.42	0.00023	-7.97	0.00001

of melatonin is mainly due to binding at GABA-A receptor and exerting its anaesthetic effect.^[18] However, our results are contrary to the study on paediatric population by Kurdi MS *et al.*^[19] who observed that the sedation score had no statistically significant difference when melatonin groups 0.5 mg/kg and 0.75 mg/kg were compared with a placebo ($P = 0.4669$ and $P = 0.6276$). This difference from our study may be attributed to the difference in populations studied.

Both melatonin and clonidine caused the attenuation of haemodynamic response. There was a decrease in the mean values of all haemodynamic responses in both groups after 120 min of administering the drugs and just before induction which corresponded to their T_{max} . In our study, melatonin attenuated the stress response to laryngoscopy and intubation better than clonidine as depicted by the changes in heart rate and rate pressure product at 0, 1, 3 and 5 min after

Table 4: A comparison of haemodynamic responses at various intervals between group C and group M

Haemodynamic measurement (mean±SD)	Heart rate (bpm)							
	Baseline	At 120 min	Before induction	Immediately after intubation	1 min	3 min	5 min	10 min
Group M	84.7±5.18	81.83±5.33	80.3±4.98	86.03±5.82	83.47±5.74	81.3±5.69	80.07±5.55	79.77±5.57
Group C	85.53±5.81	83.43±9.24	83.97±10.20	94.07±10.59	89.8±10.93	87.33±8.64	84.37±8.90	82.4±8.68
P	0.281	0.211267	0.0437	0.00035	0.003822	0.001331	0.015597	0.087129
	Systolic Blood Pressure (mm Hg)							
Haemodynamic measurement (mean±SD)	Baseline	At 120 min	Before induction	Immediately after intubation	1 min	3 min	5 min	10 min
Group M	124.40±8.99	121.67±8.48	120.40±8.44	124.87±8.73	121.87±8.29	120.57±7.90	119.60±7.79	119.37±7.22
Group C	126.76±6.89	120.57±8.29	119.53±8.75	127.90±8.48	123.60±7.63	120.70±7.26	120.23±6.59	119.10±6.73
P	0.1271	0.309675	0.351304	0.092397	0.205412	0.473438	0.36972	0.442423
	Diastolic Blood Pressure (mm Hg)							
Haemodynamic measurement (mean±SD)	Baseline	At 120 min	Before induction	Immediately after intubation	1 min	3 min	5 min	10 min
Group M	81.77±6.29	79.57±5.74	78.73±5.60	82.8±5.38	80.57±5.20	78.47±5.06	77.93±5.56	77.9±5.55
Group C	84.06±6.35	77.53±6.88	76.03±6.55	82.83±5.88	79.3±7.68	77.27±5.44	76.47±4.61	75.50±5.89
P	0.08558	0.11332	0.048425	0.49105	0.23255	0.19395	0.13936	0.052
	Mean Blood Pressure (mm Hg)							
Haemodynamic measurement (mean±SD)	Baseline	At 120 min	Before induction	Immediately after intubation	1 min	3 min	5 min	10 min
Group M	95.87±7.40	93.57±6.50	92.53±6.41	96.83±6.31	94.17±6.35	92.37±5.84	91.83±6.12	91.63±5.78
Group C	98.13±5.79	91.87±6.63	90.6±6.36	97.93±5.67	94.17±6.71	91.57±5.80	91.07±4.87	90.30±5.89
P	0.0951	0.16414	0.12684	0.24394	0.5	0.30124	0.29974	0.052
	Rate Pressure Product							
Haemodynamic measurement (mean±SD)	Baseline	At 120 min	Before induction	Immediately after intubation	1 min	3 min	5 min	10 min
Group M	10513.1±708.35	9931.3±641.72	9648.03±657.42	10716.4±736.10	10151.1±746.16	9788.9±791.53	9565.63±789.11	9510.57±748.8889
Group C	10843.6±950.96	10066.8±1395.35	10062.4±1610.29	12032.9±1596.22	11105.3±1539.29	10557.6±1345.09	10160.9±1326.63	9821.9±1238.60
P	0.0643	0.3182883	0.1023267	0.000081	0.0019657	0.0051443	0.0211275	0.125736

intubation. Gupta P *et al.*^[9] observed in their study that in the melatonin group, the heart rate increased from baseline values at the time of laryngoscopy which, however, returned to previous values within 1 min and maintained at lower values at all points of time till 10 min after intubation. SBP, DBP and MAP did not rise after intubation and the patients were stable at all points of time when compared to control group. Manian K *et al.*^[20] compared the effect of oral clonidine 0.3 mg and oral gabapentin 600 mg on stress response to laryngoscopy and intubation and noted that oral clonidine is superior to oral gabapentin.

The mechanism of effect of melatonin on circulation is complex. Melatonin has an endothelium-dependent vasorelaxant effect and potentiates the endothelium-dependent vasorelaxation induced by acetylcholine.^[21] It may interfere with the peripheral and central autonomic system, causing a reduction in the adrenergic outflow and reducing catecholamine levels.^[21] Furthermore, it may induce the relaxation of arterial wall smooth muscles by enhancing the availability of nitric oxide.^[22] In addition, it may also act via specific receptors melatonin type one or type two, located peripherally in the blood vessels and centrally in the blood pressure-regulating area of the brain.^[23] It also exhibits a free radical scavenging effect leading to the dilatation of blood vessels and it may work via an epigenetic mechanism at the area postrema in the brain.^[24]

Clonidine, an imidazole compound is a selective alpha-2 adrenoceptor agonist. It acts on the receptor of medulla and presynaptically on peripheral nerve to reduce the activity of the sympathetic nervous system. Bradycardia and hypotension are the known side effects of clonidine but we did not notice bradycardia and hypotension throughout the study even with 0.2 mg of oral clonidine. This may be due to younger age and healthy patients included in the study. There were no incidences of nausea, vomiting, hypotension, bradycardia and respiratory depression in any of the patients in both the groups. Melatonin is a relatively safe drug. Doses up to 300 mg/day orally for two years have been administered safely.^[25]

The limitations of our study were that we did not compare the effect of different doses of the drugs and the effect of administration of drugs at different time intervals. Further, we did not evaluate the effects of melatonin and clonidine on anaesthetic agent requirement. The effect of these drugs on extubation

response was also not assessed. We did not measure the plasma catecholamine levels which is a better assessment for haemodynamic responses. Further studies should consider these limitations. Future studies on both drugs are required to establish their role in the attenuation of haemodynamic responses to laryngoscopy and intubation with different doses and different time intervals of administration and also their effects on the requirement of anaesthetic agents.

CONCLUSION

Although both the drugs are effective, oral melatonin proved superior to oral clonidine in attenuating the haemodynamic response to laryngoscopy and tracheal intubation without much side effects. Melatonin does not cause prolonged sedation as compared to clonidine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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