Original Research Paper

Volume - 12 | Issue - 03 | March - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Anaesthesiology

EFFECT OF ORAL MELATONIN IN ATTENUATION OF HAEMODYNAMIC STRESS RESPONSE DURING ENDOTRACHEAL INTUBATION AND LARYNGOSCOPY IN PATIENTS UNDERGOING ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA: A RANDOMIZED CONTROLLED STUDY.

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ABSTRACT **INTRODUCTION:** During laryngoscopy and intubation there is an increase in both heart rate and blood pressure due to sympathetic response mediated by catecholamines and activation of tracheal nociceptors due to its manipulation. Melatonin has been used for sleep regulation and ICU sedation but there are very few studies to evaluate its effect on reducing haemodynamic stress response during laryngoscopy and intubation. In our study we evaluated the effects of melatonin in reducing the haemodynamic changes during laryngoscopy and intubation.**METHODOLOGY**: 100 patients belonging to ASA grade 1 and 2 of either gender, of age 18 to 60 years who were planned for elective surgery under general anaesthesia were randomly divided into two groups: Group M (n=50) was given 6 mg oral melatonin (two capsules of 3 mg each) and Group C (n=50) was given multivitamin capsules with a sip of water 90 minutes before induction of anaesthesia. General anaesthesia was induced using standard method for both the groups and changes in heart rate and blood pressure were noted in pre operative period, during intubation and at 1, 3, 5 and 10 min after intubation. **RESULTS:** The mean pulse rate was comparable between the two groups at baseline. During intubation heart rate was increased in both groups but rise was significant in control group which persisted upto10 minutes, while in melatonin group it started settling within 3 minutes. There was a significant rise in SBP, DBP and MAP in control group during and after intubation till 5 minutes as compared to melatonin group. **CONCLUSION:** Oral melatonin can be used in pre operative period to effectively reduce the hemodynamic stress response during and after laryngoscopy and intubation.

KEYWORDS : Melatonin, hemodynamic stress response, endotracheal intubation

INTRODUCTION

General anaesthesia is preferred mode of anaesthesia for many elective and emergency surgeries. Laryngoscopy and intubation is the most important and crucial step during administration of general anaesthesia for securing the airway. It produces the sympathetic response through activation of nociceptors present in trachea due to tracheal manipulation **[1]** and increase in catecholamine activity. **[2,3]**

Transient rise in heart rate and blood pressure are probably of no consequence in healthy individuals. But either or both may be deleterious to those with hypertension, myocardial insufficiency, cerebral vascular diseases, raised intracranial pressure, geriatric age group or aneurysmal vascular disease. **[4]** Various techniques and methods have been used to attenuate this response in high-risk individuals, such as lignocaine, beta blockers, opioids, calcium channel blockers **[5,6,7]** a2 agonists, but each agent comes with their own set of adverse effects such as bradycardia, respiratory depression, hypotension, tachycardia, rebound hypertension or allergic reactions. Hence, there has always been a search for a better agent for this purpose.

Melatonin is an endogenous hormone secreted by pineal gland, primarily associated with regulation of sleep-wake cycle which is its chrono biotic action. It is known for its hypnotic actions [8] as well as potent analgesic properties in a dose dependent manner.[9]

It produces no hangover effect and lacks negative effects like addiction, dependence and does not produce any cognitive impairment. It has got anti-inflammatory, antioxidant and antihypertensive effects. **[10]** Melatonin binds to specific receptors (M1 and M2 receptors) present on the blood vessels and reduces mean blood pressure by enhancing the nitric oxide availability which causes smooth muscle relaxation in arterial wall and interferes with the catecholamine induced response. [11,12,13]

Melatonin, currently is being used primarily for sleep regulation and has been evaluated for sedation in ICU and as preoperative anxiolytic agent. The literature currently available, provides varied conclusions for its use as well as doses and very few studies have been conducted to evaluate and explore its potential to attenuate hemodynamic stress response to laryngoscopy and intubation.

AIMS AND OBJECTIVES

The aim of this study is to evaluate the foresaid beneficial effects of melatonin in reducing the haemodynamic changes during laryngoscopy and intubation.

MATERIALS AND METHODS

This prospective, randomized, controlled study was conducted over the duration of one year after the approval from Institutional Ethics and Scientific Review Committee.

100 patients belonging to ASA grade 1 and 2 of either gender, of age 18 to 60 years, mallampati class I and II, planned for elective surgery under general anaesthesia of duration 1 to 2 hours and intubation of duration < 20 seconds were included in the study. Patients with unanticipated difficult intubation, multiple intubation (>1) attempts at laryngoscopy and/or duration > 20 seconds, known hypersensitivity to Melatonin , surgery of time duration of <1 hour and > 2 hours , pregnancy and lactation and patients on chronic neuroleptic medications, tricyclic antidepressants, serotonin and nor epinephrine reuptake inhibitors, alcohol abuse, immunosuppressants, oral contraceptives, anticoagulants, antidiabetic medications and antihypertensives were excluded from the study.

Written informed consent was taken from all patients. On the morning of surgery, the patients were assigned into either Group M (study group) or Group C (control group) randomly by chit method. Before administration of drugs, baseline haemodynamic parameters (heart rate, systolic and diastolic blood pressure, mean blood pressure and Oxygen saturation) were recorded for both the groups. Group M was given oral Melatonin capsules 6 mg (two capsules of 3mg each) and Group C was given two oral multivitamin capsules with a sip of water, 90 min before surgery by the nurse. 90 minutes after the administration of drugs, pre operative hemodynamic values (HR, SBP, DBP, MAP, SPO2) were recorded and then shifted to operation theatre. Multipara monitor was connected .

After preoxygenation with 100% oxygen, intravenous Inj. Midazolam 0.05 mg/kg and inj. Fentanyl 2 mcg/kg was given and induction was done with Propofol 2 mg/kg. Laryngoscopy and intubation was facilitated with intravenous Inj. Succinylcholine 1.5 mg/kg. Time

Duration of laryngoscopy and intubation was limited to <20 seconds for all patients and was done by same experienced anaesthesiologist. Hemodynamic parameters were noted at the time of intubation, at 1, 3, 5 and 10 minutes after intubation.

Anaesthesia was maintained with 60% Nitrous oxide in Oxygen along with Isoflurane and muscle relaxation was maintained with intravenous inj. Atracurium loading dose 0.5mg/kg and maintenance dose 0.1mg/kg. Inj. Paracetamol was given one hour after induction of anaesthesia to all the patients. At the end of the surgery, residual blockade was reversed with inj. Neostigmine 0.05mg/kg and inj. Glycopyrrolate 0.01mg/kg and extubation was done after return of reflexes.

In post operative period, if there was vomiting, Inj. Ondansetron was given and inj. Paracetamol was given for treatment of headache.

Statistical Analysis:

Statistical analysis was done using Statistical Package of Social Science (SPSS Version 20; Chicago Inc. USA). Mini tab version 17.0 was used for calculating the P values. Comparison of means between the two groups was done using unpaired 't' test. Descriptive statistics was presented in the form of numbers and percentages. P value of <0.05 was taken as statistically significant. The final data was presented in the form of tables, graphs and bar diagrams.

OBSERVATIONS AND RESULTS

This study included total of 100 patients scheduled for elective surgeries under general anaesthesia with details given in **Table 1.**

Table 1. Demographic Data

Variable	Group M [Mean±SD]	Group C [Mean±SD]	P value
ASA grade I/II n=50	41/9	42/8	0.790
Gender M/F n= 50	26/24	27/23	0.841
Duration of surgery in mins	102.30	103.68	0.620
Age	36.26 ± 12.74	38.28 ± 13.47	0.443

Fisher's exact test; Unpaired t-test. n – Number of patients; SD – Standard deviation

Table No. 2 mean heart rate at different point of times

Point of time	Group M [Mean±SD]	Group C [Mean±SD]	P value
Baseline	80.88 ± 8.75	79.16 ± 8.24	0.314, NS
Preoperative	76.9 ± 6.24	83 ± 7.42	0.001*
At the time of intubation (Ta)	90.6 ± 10.88	97.16 ± 14.15	0.011*
1 Min (T1)	96.06 ± 9.89	103.04 ± 13.45	0.004*
3 min (T3)	85.36 ± 9.51	100.02 ± 13.12	0.001*
5 min (T5)	84.74 ± 9.19	99.56 ± 14.67	0.001*
10 min (T10)	79.2 ± 8.09	93.64 ± 13.34	0.001*

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Table No. 3 Comparison of mean systolic blood pressure between the two groups

Point of time	Group M [Mean±SD]	Group C [Mean±SD]	P value
Baseline	122.04 ± 12.68	120.48 ± 13.97	0.560, NS
Preoperative	116.54 ± 10.63	122.68 ± 11.66	0.007*
At the time of intubation (Ta)	120.94 ± 5.93	126.84 ± 12.44	0.003*
1 Min (T1)	114.34 ± 8.97	121.04 ± 15.71	0.010*
3 min (T3)	112.22 ± 9.55	117.8 ± 12.15	0.012*
5 min (T5)	112.30 ± 7.14	117.4 ± 14.98	0.032*
10 min (T10)	112.18 ± 8.28	117.1 ± 14.63	0.041*

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Table No. 4 Comparison of mean diastolic blood pressure between the two groups

Point of time	Group M [Mean±SD]	Group C [Mean±SD]	P value
Baseline	78.16 ± 9.11	77.2 ± 8.48	0.587, NS
Preoperative	74.84 ± 7.14	78.94 ± 9.18	0.014*
At the time of intubation (Ta)	79.06 ± 8.88	83.72 ± 11.79	0.028*
1 Min (T1)	78.14 ± 8.19	82.82 ± 10.73	0.016*
3 min (T3)	74.58 ± 8.9	80.28 ± 10.65	0.005*
5 min (T5)	71.14 ± 7.55	78.8 ± 10.66	0.001*
10 min (T10)	72.08 ± 8.4	75.96 ± 9.96	0.038*

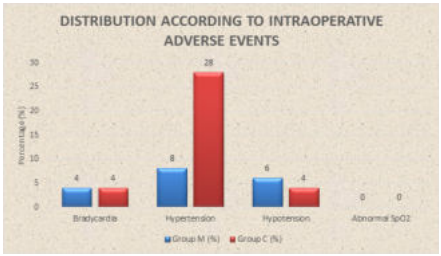
Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Table 5 Mean Arterial Pressure at various points of time

Points of time	Group M [Mean±SD]	Group C [Mean±SD]	P value
Baseline	92.78 ± 9.48	91.58 ± 9.45	0.528, NS
Preoperative	88.74 ± 7.73	93.52 ± 9.29	0.006*
At the time of intubation (Ta)	93.02 ± 7.25	98.09 ± 11.21	0.008*
1 Min (T1)	91.54 ± 7.88	95.56 ± 11.19	0.040*
3 min (T3)	87.79 ± 8.58	92.79 ± 10.36	0.010*
5 min (T5)	84.86 ± 6.81	91.67 ± 11.47	0.001*
10 min (T10)	85.42 ± 7.6	89.11 ± 10.65	0.049*

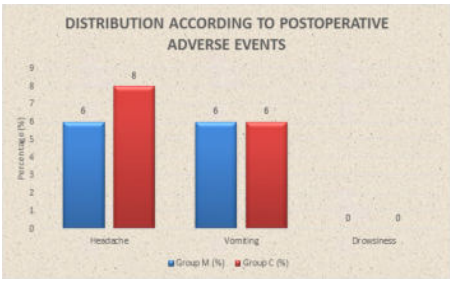
Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Graph 1



Bar diagram showing distribution according to intraoperative adverse events

Graph 2



Bar diagram showing distribution according to postoperative adverse events

DISCUSSION

General anaesthesia is preferred mode of anaesthesia for many elective and emergency surgeries, in which laryngoscopy and intubation forms the most important step to secure the airway. Laryngoscopy and intubation is a noxious stimulus which poses the patients towards sympathetic stimulation and causes an increase in heart rate and blood pressure. While this response is tolerated fairly in young people but it can provoke untoward cardiovascular response in patients with associated hypertension or cardiac diseases.

With several attempts to minimise this stress response with various drugs there have been associated adverse effects too.

The primary objective of our study was to assess the attenuation of hemodynamic stress response during endotracheal intubation by Melatonin by comparing the haemodynamic parameters (HR, SBP, DBP, MAP, SpO2) to control group.

All the patients were comparable in age, gender, ASA status and duration of surgery.

In our study, the mean heart rate was comparable between the two groups at baseline which was 80.88 ± 8.75 for Group M and 79.16 ± 8.24 in Group C (P>0.05). In preoperative period there was a reduction

in mean heart rate after 90 minutes in Group M (76.9 ± 6.24) while in Group C there was an increase in mean heart rate (83 ± 7.42). There was significant rise in heart rate during intubation till 1 min after intubation in both the groups but heart rate started settling within 3 minutes in Melatonin group where mean heart rate was 85.36 ± 9.51, while it remained significantly higher in Group C till 10 min (P<0.05)

Our findings were comparable with a similar study done by Priyamvada Gupta & Durga Jethava [14] they found that in control group there was a rise in heart rate during intubation which attained significant value at 1 min post intubation and persisted till 10 minutes. While in melatonin group there was slight but insignificant rise in heart rate during intubation, which returned to previous values within 1 min and maintained lower values till 10 min at all points.

Our findings were also comparable to recent study done by R. Kumar & K. Kumari et al. [15] in which they divided 64 patients into two equal groups, Melatonin Group (6 mg) and placebo group, undergoing elective laparoscopic cholecystectomy and found that postintubation rise in heart rate (HR) was less in the Melatonin group compared to the placebo group (p < 0.0001).

Our findings were contradictory to findings of the study done by Ahmed A. Mohamed et al [16] in which they did not find significant difference in heart rate in comparison to control group except after one minute post intubation.

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.

The mean systolic blood pressure at baseline was 122.04 ± 12.68 mm Hg in Group M and in Group C it was 120.48 ± 13.97 mm Hg which was comparable to each other. After administration of drugs there was a fall in mean SBP of Group M which was 116.54 ± 10.63 while mean SBP of Group C was 122.68 ± 11.66 in which was higher than baseline. There was a slight rise in mean SBP during intubation 120.94 ± 5.93 in Melatonin group while mean SBP in Group C was 126.84 ± 12.44 which was significantly higher than Group M (P= 0.003). At all the other time intervals the mean systolic blood pressure was significantly higher in Group C in comparison to the Group M (P<0.05).

The mean diastolic blood pressure was comparable between the two groups at baseline (Group M= 78.16 ± 9.11 mm Hg, Group C= 77.2 ± 8.48 mm Hg). There was a slight increase in DBP in Group M during intubation (79.06 ± 8.88) which returned to near baseline within 1 min after intubation while there was significant increase in DBP in Group C at the time of intubation (83.72 ± 11.79) (P=0.028). At all the other time intervals the mean diastolic blood pressure was significantly higher in Group C in comparison to the Group M (P<0.05).

The mean MAP was comparable between the two groups at baseline (Group M- 92.78 ± 9.48 mm Hg; Group C- 91.58 ± 9.45 mm Hg) (P>0.05). MAP was reduced from baseline in Group M after administration of melatonin while it slightly increased in Group C. There was a slight rise in MAP during intubation in Group M (93.02 ± 7.25) and returned to baseline within 1 min. while it was significantly higher in Group C (98.09 ± 11.21). The mean MAP was significantly higher in Group C in comparison to Group M at all the other time intervals (P<0.05).

Our findings are comparable with the study done by Dr. Krishnendu Chandra et al [17] in which they compared effect of melatonin (6 mg) and pregabalin (150 mg) with control group, given 2 hours before surgery and found that SBP, DBP and MAP were significantly lower in melatonin group as compared to placebo group (P<0.05).

Similar results were observed by Sarmila Guha Banerjee et al [18] in 2021 when they compared the efficacy of orally administered Melatonin and Clonidine for Attenuation of Hemodynamic Response During Laryngoscopy and Endotracheal Intubation in gastrointestinal surgeries.

This lowering of blood pressure can be explained by two main mechanisms. It acts on specific melatonin receptors present on blood vessels and interferes with the action of catecholamines and hence vascular response to sympathetic stimulation is reduced. It increases the availability of nitric oxide leading to relaxation of smooth muscles of arterials walls leading to vasodilation and reduced blood pressure.

Intraoperative bradycardia was seen in 3 (5.9%) patients in Group M and in 2 (4%) patients in Group C. Hypotension was seen in 3 (5.9%) patients in Group M and in 2 (4%) patients in Group C. The proportional comparison was found to be statistically not significant for both (P=1.000).

Hypertension was seen in 4 (7.8%) patients in Group M and in 14 (28%) patients in Group C which was statistically significant (P=0.010). (Graph 1) Our findings were similar to study done by Santosh Choudhary & Sandeep Sharma et al [19] in which no significant adverse effects were found in melatonin group (6 mg) given 120 min before surgery.

No adverse effects were found by Tushar Patel & Madhuri S. Kurdi in. [20] in melatonin group in their study of 120 patients comparing melatonin 0.4 mg/kg and midazolam 0.2 mg/kg with placebo, on pre operative anxiety, cognitive and psychomotor function.

Headache was seen in 3 (5.9%) patients in Group M and in 4 (8%) patients in Group C and vomiting was seen in 3 (5.9%) patients in Group M and in 3 (5.9%) patients in Group C, which were statistically not significant (P=1.000) (Graph 2).

In study done by Priyamvada Gupta & Durga Jethava et al [14], they compared 6 mg oral melatonin to placebo in attenuation of hemodynamic response to laryngoscopy and intubation and found nausea/vomiting in one patient in each group and restlessness was found in 2 patients in control group.

CONCLUSION

From our observations and results we can conclude that melatonin can reduce hemodynamic stress response during laryngoscopy and intubation when given preoperatively without producing any significant adverse effects.

Limitations Of Study:

1. This was a single centered study and we did not measure the catecholamine level which would have been a better and appropriate criteria than hemodynamic parameters to assess sympathetic stimulation.
2. We assessed the effects of a single dose of melatonin given 90 min prior to induction. It would have given more clarity regarding the function of melatonin if different doses given at different time intervals were also assessed.

Conflict Of Interest:

None.

Source Of Funding:

None.

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