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Original Research Paper

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TO OBSERVE EFFECTS OF MELATONIN PREMEDICATION ON HAEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

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ABSTRACT Laryngoscopy using rigid metal blade produces noxious stimuli that causes stimulation of sensory receptors which in turn causes release of endogenous catecholamines, which in turn provokes hemodynamic changes called stress response. Due to its inhibitory action on CNS which causes sedation and anxiolysis as well as suppression of catecholamine release, we hypothesized that oral melatonin tablet 10 mg, administered orally about 120 minutes before the procedure should provide hemodynamic stability and blunt this response. The primary objective of the study was to observe magnitude and duration of changes in vital parameters before, during and after laryngoscopy and intubation, in a group of patients who were premedicated with 10 mg mouth dispersible tablet melatonin 120 min anesthesia. Continuous numeric data on pulse rate, blood pressure, SPO2 were analyzed as mean and standard deviation. Significance of observation was derived by applying student's t-test. Non parametric data on complication of study drug was reported as number of patients exhibiting the complication and also as percentage. One group of 35 patients received 10 mg of oral melatonin as mouth dispersible tablet 120 minutes before conduct of anesthesia and other group did not received the study drug and acted as control group for comparison. Pre induction hemodynamic parameters after 120 minutes of oral melatonin administration were recorded and after induction of anesthesia and intubation hemodynamic parameters were recorded. In group of patients who received melatonin the magnitude of rise of heart rate, systolic, diastolic and mean arterial pressure was less returning to pre induction value within 3 minutes. .In control group patients we observed a statistically significant rise in magnitude of heart rate and blood pressure that remained elevated till 10 minutes after laryngoscopy and intubation. The rate pressure product, an indicator of myocardial oxygen demand and consumption was significantly higher in control group and lasted for longer time. While in melatonin treated patients insignificant rise of RPP occurred. The clinical observations made in the present study allow us to conclude that oral melatonin administered 120 minutes before induction of anesthesia effectively controlled the stress response to laryngoscopy and endotracheal intubation and shown cardio-protective effect.

KEYWORDS : melatonin premedication, hemodynamic response, stress response, laryngoscopy, endotracheal intubation

INTRODUCTION: -

Placement of tube inside trachea called "endotracheal intubation" is an essential step in initiation of artificial respiration for the purpose of conduction general anesthesia, controlled ventilator care in intensive care unit and in extended post anesthesia care unit. An important step for endotracheal anesthesia is laryngoscopy visualizing larynx. Laryngoscopy using rigid metal blade produces noxious stimuli that causes stimulation of sensory receptors which in turn causes release of endogenous catecholamines[1], which in turn provokes hemodynamic changes called stress response[2, 3, 4]. This needs to attenuated in all patients but particularly in those who are at risk of complications following laryngoscopy and endotracheal intubation i.e. patients with prior history of compromised cardiovascular reserve.

Some of the drug regimes that anesthesiologists have in their arsenal include lignocaine (intravenous and tropical) [5], narcotic analgesics (fentanyl[6], remifentanyl[7] alfentanyl[8]), vasodilators (nitroglycerine[9] and sodium nitroprusside), sympatholytic (clonidine, dexmedetomidine[10]), beta blockers (esmolol[11], propranolol), benzodiazepines (midazolam) [12], calcium channel blockers (verapamil[12], diltiazem[11]). Techniques like pre cruarization, minimizing the duration of laryngoscopy to less than 15 seconds, placing supragolttic device like laryngeal mask airway have also been tried to blunt this stress response[13].

Melatonin is a naturally occurring substance mainly produced by pineal gland. It is a potent chronobiotic agent that causes sedation via action on MT1 and MT2 receptors at suprachiasmatic nucleus[14]. Unlike benzodiazepines, the sleep produced by melatonin is natural and does not cause impairment of cognitive function[15]. Clinically it has been used in psychiatry, ICU to relieve anxiety, agitation, deranged cognitive function and psychomotor abnormalities and sleep disorders [16]. Due to its inhibitory action on CNS which causes sedation and anxiolysis as well as suppression of catecholamine release, we hypothesized that oral melatonin tablet 10 mg, administered orally about 120 minutes before the procedure should provide hemodynamic stability. Melatonin is available in our country as over the counter medicine as various preparations.[17]

The primary objective of the study was to observe magnitude and duration of changes in vital parameters before, during and after laryngoscopy and intubation, in a group of patients who were premedicated with 10 mg mouth dispersible tablet melatonin 120 min anesthesia.

AIMS AND OBJECTIVES:-

Primary Objective:

- To evaluate cardiovascular protection offered by attenuation of hemodynamic stress response to laryngoscopy and tracheal intubation in patients premedicated with 10 mg oral melatonin.

Secondary Objective

- To observe changes in vital parameters after premedication patients with 10 mg oral melatonin given 120 minutes before shifting patients to operating room.

MATERIAL AND METHODS:-

The present study entitled "To observe the effect of melatonin

premedication on hemodynamic responses to laryngoscopy and intubation" was undertaken in the department of Anesthesiology at R.D. Gardi Medical College and Associated hospitals Ujjain, after permission of institutional ethics committee and institutional research guidance committee. The study was conducted on 70 patients; divided in two groups of 35 patients each. Group A patients did not receive test drug whereas Group B patients received mouth dissolving tablet of melatonin 10 mg 120 minutes before the induction of general anesthesia.During pre-anesthetic visit the patients included in the study were explained the purpose of study demographic data like age, sex, weight and height were recorded and were examined to note data on cardiovascular system and clinically systemic examination was done. Airway assessment was also done for noting the ease of intubation.

To rule out co-morbid condition before including the patient in study all the patients were also investigated to find out hemoglobin concentration, complete blood count, random blood glucose level, serum creatinine level, x-ray chest and Electrocardiogram.

Patients classified as belonging to ASA physical status 1 or 2 were included in the study.

Vitals and hemodynamic parameters, heart rate, systolic and diastolic blood pressure, mean blood pressure, RPP were recorded just before giving the study drug and 120 minutes before shifting the patient to operating room, and again checked on operation table, during laryngoscopy and intubation, and thereafter at 1, 3, 5, 10, 20, 30 minutes of laryngoscopy and intubation.

Inclusion Criteria:-

1) Patients belonging to ASA1 and ASA2
2) 18-60 years of age
3) All patients scheduled for routine elective surgeries to be performed under general anesthesia

Exclusion Criteria:-

1) Patient refusal for the procedure for inclusion in study
2) Patients belonging to ASA grade 3 and 4
3) Patients with systemic disease like respiratory, cardiac, hepatic, renal and neurological disorders, diabetes and hypertension.
4) Patients with difficult airway.
5) Pregnant and lactating patients

Statistical Methods:-

1) Case definition for inclusion in the study – All patients fulfilling the inclusion criteria and given general anesthesia at our institute.
2) Study Design – Clinical observational study.
3) Source of data – Patient's records and observation charts for individual study subject. Data on individual stud subject were tabulated on excel sheet to prepare master chart of observations.
4) Sample size calculation – To calculate the sample size based on the mean difference with an approximate 99% confidence interval, we used the following formula:

$$n = \frac{o^2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\left(\mu_0 - \mu_a\right)}$$

2 means – Hypothesis Testing	
Standard deviation (σ)	6.000
Expected difference	5.000
Significance level (α)	0.010
Power (1-β)	0.800
Sample size	34 cases in each group

5) Study parameter – Changes occurring in hemodynamic parameters during and after laryngoscopy and endotracheal intubation and up to 30 minutes of laryngoscopy and endotracheal intubation.
6) Statistical method – Demographic data of study group patients has been presented as number of patients included in the study. Individual patient's data and observed parameters have been transferred on a master chart of observation. Continuous numeric data on pulse rate, blood pressure, SPO2 were analyzed as mean and standard deviation. Significance of observation was derived by applying student's t-test. Non parametric data on complication of study drug was reported as number of patients exhibiting the complication and also as percentage.
7) Hypothesis for conducting the study – We assumed that the inhibitory action of melatonin on CNS and peripheral melatonin receptors will result in sedation and anxiolysis that can attenuate hemodynamic response to laryngoscopy and intubation hence is expected to provide hemodynamic stability.
8) Statistical tool used for analysis – SPSS version 25.
9) Data management plan – The data on individual patients was recorded in case record proforma and was transferred on master chart of observation on excel sheet which subjected to appropriate statistical tests as described above.

OBSERVATION AND RESULTS:-

Majority of the patients , 75.7% (53), included in the study were between age of 21 – 50 years while 20% (14) of the patients were above 50 years whereas 4.3% (3) of patients were less than 20 years of age. Of the patients included in the study, 44.3% were male and remainders were females. Out of 70 patients included, pre-operative diagnosis was renal calculi 45.7% (32), cholelithiasis 22.9% (16), Ca breast 5.7% (4), acute appendicitis 5.7%

(4), chronic appendicitis 4.3% (3), upper ureteric calculus 2.9% (2), right parotid swelling 2.9% (2), renal disease 2.9% (2) and lastly inguinal hernia, ovarian mass, renal cyst, right non-functioning kidney, right PUJ obstruction each sharing 1.4% i.e. 1 patient for each of these diagnosis among the patients included in this study.

Comparison study of the hemodynamic parameters mentioned above are as follows depicted in the tables below.

Table 1: Comparison of mean SBP between groups at different stages

GROUP		No. of patients	Mean (mmHg)	Std. Deviation	T	P
SBP just before drug	B	35	124.41	8.613	1.996	0.050
	A	35	119.76	10.485		
SBP 120 minutes After drug	B	35	129.47	11.101	5.345	0.000
	A	35	115.74	10.064		
SBP pre Induction	B	35	126.06	8.971	1.251	0.215
	A	35	122.74	12.623		
SBP intubation	B	35	151.91	10.388	5.796	0.000
	A	35	134.26	14.396		
SBP 1 min	B	35	138.00	10.351	0.997	0.322
	A	35	135.35	11.499		
SBP 3min	B	35	132.26	11.174	0.312	0.755
	A	35	131.38	12.066		
SBP 5min	B	35	129.74	10.788	0.832	0.408
	A	35	127.56	10.760		
SBP 10min	B	35	126.35	8.366	0.843	0.402
	A	35	124.18	12.501		
SBP 20min	B	35	124.50	7.597	0.957	0.342
	A	35	122.26	11.301		

SBP 30min	B	35	123.06	7.905	0.893	0.375
	A	35	121.24	8.890		

Table 1 indicated that mean SBP mean before administration of melatonin in group B was 124.41±8.81 mmHg and in group A was 119.76±10.48 mmHg. Critical value 't' indicate that there was no significant (p = 0.05) SBP mean difference found between group B and group A before administering melatonin and was more or less same. When systolic blood pressure was compared between two groups at 120 minutes after administration of drug, it was observed that there was significant decrease in SBP in group A (mean-115.74±10.064 mmHg) as compared to group B (mean- 129.47±11.101 mmHg) and this difference was statistically significant. Similarly comparing the SBP values, during laryngoscopy and intubation, the SBP in group of patients who received melatonin had mean-SBP of 134.26±14.3 mm of Hg was found to be lesser than those who did not receive melatonin. (151.91±10.388 mmHg) and thus a differential increase by mean rise of 25 mm of hg occurred in group of patients who did not receive melatonin and this was statistically significant. After 1 minute of intubation the rise in mean systolic pressure in group of patients receiving was less than 1 mm hg as compared to mean difference of 13 mm of hg at same period of observation in patients who did not receive melatonin.

Thus the raised systolic pressure settled within one minute of intubation in patients who received melatonin. Rest of the observations showed decreased mean SBP in group of patients who received melatonin as compared to group B, but this difference was not found to be statistically significant. After 5 minutes in patients who received melatonin mean SBP was close to pre induction mean value. (122.7 ± 74 mmHg v/s 127.5 ± 10.7 mmHg). At 20 and 30 minutes of post intubation in both groups the mean SBP was near pre intubation value.

Table 2: Comparison of mean DBP between groups at different stages

GROUP		Number of patients	Mean (mmHg)	Std. Deviation	T	P
DBP just before test drug	B	35	81.41	6.140	1.112	0.270
	A	35	79.41	8.493		
DBP 120 minutes after drug	B	35	85.12	6.158	6.288	0.000
	A	35	75.18	6.860		
DBP pre induction	B	35	86.88	5.553	1.215	0.229
	A	35	79.85	8.001		
DBP intubation	B	35	95.41	6.542	4.148	0.000
	A	35	87.56	8.891		
DBP 1 min	B	35	90.09	8.163	0.195	0.846
	A	35	89.71	7.972		
DBP 3min	B	35	87.56	8.880	0.072	0.943
	A	35	87.41	7.878		
DBP 5min	B	35	84.18	8.526	0.177	0.860
	A	35	83.85	6.392		
DBP 10min	B	35	81.65	4.578	0.690	0.493
	A	35	80.38	9.661		
DBP 20min	B	35	81.18	5.385	0.920	0.361
	A	35	79.71	7.602		
DBP 30min	B	35	80.44	6.243	2.623	0.011
	A	35	76.24	6.959		

Table 2 indicated that just before melatonin in group B mean DBP was higher 81.41± 6.14 mmHg and in group A and Group B patients was similar 79.41±8.49 mmHg. Critical value t indicate that difference in DBP was not significant (p = 0.27).When diastolic blood pressure was compared between two groups at 120 minutes after administration of study drug, it was observed that there was statistically significant decrease in DBP in group A (mean-75.18±6.860 mmHg) as compared to group B (mean- 85.12±6.158 mmHg) and this difference observed was statistically significant. Mean DBP during laryngoscopy and intubation in group B was 95.41 ± 6.54 mmHg and in group A was 87.56 ± 8.89 mmHg. Critical value t indicate that this observation was significant (p=0.000) only rise of 7.7 mm mean rise was recorded in melatonin treated group than 8.6 mm in control group patients who did not receive melatonin. Raised DBP in melatonin settled in next observation at 3 minute post intubationand returned close to preoperative mean after 20 minutes (79.7 mmHg v/s 79.4 mmHg) when compared to those who did not receive melatonin mean DBP returned near to base line value after 30 minutes (80.4 v/s 80.4 mmHg) Similarly comparing the DBP values, 30 minutes after laryngoscopy and intubation, the DBP of group A (mean-76.24 mmHg) was found to be significantly less than B. At remaining intervals of the observations showed that DBP in group remained lower than group B but it was not found to be statistically significant.

Table 3: Comparison of mean MAP between groups at different stages

GROUP		Number of patients	Mean MAP	Std. Deviation	T	P
MAP just before drug	B	35	95.71	5.036	1.641	0.106
	A	35	92.88	8.679		
MAP 120 minutes after drug	B	35	99.85	6.238	6.696	0.000
	A	35	88.65	7.503		
MAP pre induction	B	35	96.59	5.527	1.368	0.176
	A	35	94.18	8.667		
MAP intubation	B	35	114.21	6.646	5.250	0.000
	A	35	103.15	10.328		
MAP 1min	B	35	105.82	7.720	0.335	0.738
	A	35	105.15	8.877		
MAP 3min	B	35	102.44	8.822	0.177	0.860
	A	35	102.06	9.018		
MAP 5min	B	35	99.15	7.484	0.235	0.815
	A	35	98.68	8.933		
MAP 10min	B	35	96.56	5.338	0.819	0.416
	A	35	94.94	10.201		
MAP 20min	B	35	95.65	5.570	1.037	0.304
	A	35	93.88	8.216		
MAP 30min	B	35	94.62	6.272	2.143	0.036
	A	35	91.24	6.738		

Table 3 and accompanying line diagram number 6 shows mean MAP between two groups after 120 minutes of administration of drug, it was observed that there was significant decrease in MAP in group A (mean- 88.65±7.503 mmHg) as compared to group B (mean- 99.85±6.238 mmHg) and this difference was statistically significant. MAP during laryngoscopy and intubation in group B was 114.21 ± 6.646 mmHg and in group A was 103.15 ±10.328 mmHg. Critical value t indicate that difference observed was significant (p= 0.000).

Elevated MAP in patients who received melatonin settled at 3 minutes of observation in comparison to group of patients who did not received the study drug elevated mean MAP settled after 5 minutes. On comparing the mean MAP values, 30 minutes after laryngoscopy and intubation, the MAP of group A (mean-91.24±6.738 mmHg) was found to be less than group B (mean-94.62±6.272 mmHg) and this difference was considered to be statistically significant.

During rest of the observations at different intervals showed that MAP in group A remained less than mean values at similar time of observations in group B patients.

Table 4: Comparison of mean Pulse between groups at different stages

GROUP			Number of patients		Mean pulse (bpm)		Std. Deviatio	t	P
pulse just before drug		B	35		88.3714		11.47654	2.879	0.005
		A	35		81.8000		7.11585		
pulse minutes	120 after	B	35		90.8571		10.77072	3.370	0.001
		A	35		82.9714		8.69579		
Pulse Induction	pre	B	35		91.2857		10.07785	0.394	0.695
		A	35		90.3714		9.32450		
pulse intubation	during	B	35		101.5429		9.95975	1.639	0.106
		A	35		97.7143		9.58114		
pulse 1min		B		35	102.6000	9.23930	3.593		0.001
		A		35	94.8857	8.71703			
pulse 3min		B		35	98.7143	8.77688	5.256		0.000
		A		35	89.2000	6.13476			
pulse 5min		B		35	95.2000	7.96241	6.280		0.000
		A		35	84.9714	5.42589			
pulse 10min		B		35	92.9143	8.40998	6.017		0.000
		A		35	82.4000	6.01077			
pulse 20min		B		35	90.8571	7.65869	6.224		0.000
		A		35	80.2286	6.58914			
pulse 30min		B		35	89.1143	8.17014	5.357		0.000
		A		35	80.0857	5.71567			

Table 4 shows mean pulse rate observed at various time intervals in group A and group B patients. Comparing the mean pulse rate values, 120 minutes after administration of study drug, the mean pulse rate of group A (mean 82.97±8.695 bpm) was found to be less than group B (mean 90.857±10.770 bpm) and this difference was found to be statistically significant. On comparing the mean pulse rate values one minute after intubation, the mean pulse rate of group A raised to a mean of 94.885±8.717 bpm was found to be less than group B mean value of 102.6±9.239 bpm and this difference was considered to be statistically significant.

Comparing the mean pulse rate values, 3 minutes after intubation, the mean pulse rate of group of patients who received melatonin was 89.2±6.134 bpm and was lesser than group B patients who did not receive study drug with mean pulse rate raised to 98.714±8.776 bpm and this difference was found to be statistically significant. Similarly the mean pulse rate recorded after intubation at 5,10,20,30 minutes were all found to be significantly less in group A as compared to group B and the difference was found statistically to be highly significant ($p<0.001$).

In patients who received melatonin mean rise in pulse rate settled at 3 minutes of observation when compared to the time taken to settle the mean pulse rate to pre-induction value in patients who did not receive melatonin, which was 10 minutes. Thus the mean pulse rate remained elevated for about 3 minutes in patients who received study drug and for about 20 minutes in patients who did not receive test drug. At 30 minutes mean pulse rate was slightly lower 1.75 bpm than pre induction mean value.

Table 5: Comparison of mean RPP between groups at different stages

GROUP		Number of patients	Mean RPP	Std. Deviation	t	P
RPP just before melatonin	B	35	10992.0857	1494.64250	3.768	0.000
	A	35	9788.4286	1156.48853	3.768	0.000
RPP 120 minutes after drug	B	35	11758.4857	1720.11960	5.868	0.000
	A	35	9606.8571	1321.50452	5.868	0.000
RPP pre induction	B	35	11518.0571	1556.82707	1.049	0.298
	A	35	11120.0000	1618.39201	1.049	0.298
RPP intubation	B	35	14818.3429	1828.58573	2.365	0.021
	A	35	13700.7714	2115.40420	2.365	0.021
RPP 1min	B	35	13948.0286	1904.88367	2.067	0.043
	A	35	13080.8857	1590.41546	2.067	0.043
RPP 3min	B	35	13028.5143	1767.78207	3.278	0.002
	A	35	11799.1429	1340.66781	3.278	0.002
RPP 5min	B	35	12157.7714	1516.22765	3.346	0.001
	A	35	11049.4286	1241.78804	3.346	0.001
RPP 10min	B	35	11553.1429	1585.79765	3.335	0.001
	A	35	10441.5429	1171.97933	3.335	0.001
RPP 20min	B	35	11099.8857	1306.18114	3.707	0.000
	A	35	10010.1429	1148.19506	3.707	0.000
RPP 30min	B	35	10819.7143	1226.08148	3.363	0.001
	A	35	9870.7429	1133.25633	3.363	0.001

Table 5 shows The Rate Pressure Product, an indicator of oxygen requirement by heart, recorded at various time intervals was compared between study and control groups. Comparing the RPP values, 120 minutes after administration of study drug, the mean RPP of group A was 9606.85±1321.5 and was found to be lesser than group B patients mean observed was 11758.48±1720.1 and this difference was found to be statistically significant. Comparing the RPP values, during intubation, the mean RPP of group A (mean-13700.77±2115.4) was found to be lesser than in group B (mean-14818±1828.58) and this difference was considered to be statistically significant. Comparing the RPP, one minute after intubation, the RPP of group A (mean- 13080.885±1590.4) was found to be lesser than group B (mean-13948.028± 1904.883) and this difference was considered to be statistically significant. Similarly the RPP recorded after intubation at 3,5,10,20,30 minutes were found to be significantly less in group A as compared to group B and this difference was considered to be statistically very significant ($p<0.001$).Although in both group of patients the rate pressure product was less than critical value of 25,000, but it remained lower in melatonin treated group, even during laryngoscopy and intubation its mean value was 13700 ± 1618 as compared to 14818 ± 1828, thus melatonin offered better cardio protective effect. Thus the findings of our study allow us to conclude on the basis of above observations that pre medication with 10 mg melatonin provided better cardiovascular stability and considerably decreased myocardial oxygen demand in comparison to those who were not pre medicated with oral melatonin.

DISCUSSION:-

Laryngoscopy and intubation are one of the most noxious stimuli that elicit stress response in patients undergoing surgery under general anesthesia. This stress response occurs due to reflex sympathetic discharge caused by epi-pharyngeal and laryngo-pharyngeal stimulation which

results in major hemodynamic changes, seen in the form of increasing heart rate and systolic blood pressure. The increased sympathetic adrenal activity can cause tachycardia, arrhythmias and hypertension which are more often than not unpredictable. The transient hypertension and tachycardia response is non consequential in healthy patients but in those suffering from coronary artery disease, arrhythmias, congestive cardiac failure, hypertension, raised intracranial pressure, cerebral aneurysm, and these responses may have disastrous consequences[4].The magnitude of this response is proportional to strength and duration of laryngoscopy. Within five seconds of laryngoscopy the rise in blood pressure begins, peaking in 1-2 minutes and returning to normal within 5 minutes[18]. The first report on circulatory response to laryngoscopy was made in 1940 by Reid and Brace[19].The aim of the present study was to observe the effects of melatonin premedication on hemodynamic responses to laryngoscopy and intubation and extent to which this drug offers protective effect. Melatonin, N-acetyl-5-methoxytryptamine, is a hormone produced by pineal gland, which controls the circadian rhythm. The drug as oral formulation was introduced to treat jet lag. Later this found clinical application in treatment of sleep disorders, to induce perioperative anxiolysis and sedation, and for cognitive and psychomotor functions[20,21]. In their study on modification of surgical stress response by perioperative administration of melatonin, Rosenberg et al[22] found that melatonin had sympatholytic activity, which could be beneficial in attenuating stress response induced by noxious stimuli of laryngoscopy and intubation. The peak effect of orally administered melatonin occurs within 60-150 minutes[23] and hence we decided to give the drug 120 minutes before the anticipated noxious stimuli produced by laryngoscopy and intubation. In their study, Ismail and Mowafi[24] used oral melatonin 10 mg premedication for patients undergoing cataract surgery under tropical anesthesia and found that, melatonin provided anxiolysis, enhanced analgesia and decreased IOP. So in our study we decided to use oral melatonin 10 mg as the test drug. We observed that in patients who received melatonin; systolic, diastolic and mean blood pressures were lower as compared to those who did not receive. This result was found clinically and statistically highly significant at two occasions that is at 120 minutes after giving melatonin and during laryngoscopy and intubation.

Rest observations though showed a decrease in group A, the difference was not considered to be statistically significant. Arangino et al[25] in a study on healthy male volunteers and found that melatonin reduced blood pressure, pulsatility index of internal carotid and catecholamine levels, suggesting the possibility of blunting of activity of cardiovascular response by melatonin. Sewerynek[26] also found that melatonin reduced blood pressure in healthy volunteers. Zanobani et al[27] conducted an animal study on rats and found that pinealectomy resulted in hypertension. Mohamed AA et al[28] studied the effect of melatonin premedication on hemodynamic response and perfusion index during laryngoscopy and intubation. The study was conducted on 90 patients who were divided into three groups, control group, melatonin 6 mg group and melatonin 9 mg group with the drug administered 1 hour before the surgery. Authors observed decrease in systolic, diastolic and mean blood pressure with both doses of melatonin groups in comparison to control group. The mechanism by which the circulatory system is affected by melatonin is complicated and also not very well understood. As suggested by Wan Q et al[29] specific melatonin receptor its subtypes mel1a and mel1b in blood vessels, interfered with their vascular reactivity to catecholamines. Anwar et al[30] similarly found that melatonin caused endothelium dependent vasorelaxation and potentiated the relaxant effect of acetylcholine. Simko et al[31] advocated that melatonin worked through its antioxidant and scavenging effect, improved endothelial function, increased nitric oxide availability that caused vasodilatation. They also suggested that melatonin could work through itsperipheral receptors to reduce blood pressure. Melatonin could also exert its blood pressure reducing effect through GABA A mediated sedative effect[27].When comparing heart rate, in our study we found that heart rate in group A (melatonin) remained lower than group B at all periods of observations and this difference was statistically significant. However in a similar study done by Mohamed AA et al[32], it was observed that there was no significant difference between heart rates of melatonin and control groups at different times after administration of melatonin except the observation made at one minutes post intubation. In the study by Priyamvada Gupta et. al.[33], authors found that in patients who did not receive melatonin rise in heart rate was observed after laryngoscopy and intubation and this rise persisted till 10 minutes of intubation, while in melatonin group there was insignificant rise in heart rate which settled within one minute of laryngoscopy and intubation. Melatonin probably causes heart rate reduction due to its anxiolytic property[33]. Srinivasan et al[34] found that melatonin has analgesic action and this could contribute to its hemodynamic stability. The extent of hemodynamic stress response induced by laryngoscopy and intubation largely depends on the duration of laryngoscopy, so the patients who required more than 20 seconds of laryngoscopy or more than one attempt were excluded the study. Similarly due to possibility of autonomic neuropathy, diabetics were not included.

Only patients aged less than 60 were included in study as blood vessel wall atherosclerosis increases with age. As antihypertensive medications desensitize the autonomic receptors and this could interfere with the results, hypertensive patients on medications were not included in the present study.Melatonin has an excellent safety profile. Weishaupt JH et al[35]in a clinical safety study administered very high doses of melatonin, up to 300 mg/day for two years, and found it to be a safe drug. Melatonin is also safe in children. As per Pramila Bajaj[36], dose as high as 20 mg has been given in children without any adverse effects except sedation in high doses.

Some adverse effects reported with oral melatonin use include fatigue, nausea, headache, dizziness and irritability[16]. In present study patients reported no such side effects. Kurdi et al[16] discussed the role of melatonin in anesthesia and critical care and described it as a wonder drug with a vast spectrum of beneficial effects including hypnosis, anxiolysis, analgesia, antioxidation, neuroprotection etc. As far as comparison with other drugs is concerned, melatonin is better than some drugs that have been studied in recent for the same purpose. Dexmedetomidine is one such drug and its but use is associated with bradycardia and hypotension[37]. Melatonin, when compared to Remifentanil, is more easily available, and also not associated with severe hypotension which is the case with later[38].

Limitations:-

In present study we did not compare different doses and timing of melatonin administration; effect of night dose in inducing good sleep and did not study the extubation response. Because the present study model was clinical observational study plasma levels of stress hormones cortisol and norepinephrine levels were not ascertained.

SUMMARY AND CONCLUSION:-

The present study entitled "To observe the effect of melatonin premedication on hemodynamic responses to laryngoscopy and intubation" was undertaken in the department of Anesthesiology at R.D. Gardi Medical College and Associated hospitals Ujjain, after permission of institutional ethics committee and institutional research guidance

committee. Present study was carried out to find out the effect of oral melatonin on rate and pressure response occurring in response to laryngoscopy and endotracheal intubation. The study was conducted on 70 patients scheduled to undergo various surgeries under general anesthesia with endotracheal intubation. All patient included in the study belonged to physical status 1 or 2 as per the classification of American Society of Anesthesiologists.All patients were free from co-existing disease and underwent physical and systemic examination to record baseline vital parameters; evaluation of air way and performed essential bio-chemical tests, ECG, and X-ray chest (as detailed in the chapter material and methods). One group of 35 patients received 10 mg of oral melatonin as mouth dispersible tablet 120 minutes before conduct of anesthesia and other group did not received the study drug and acted as control group for comparison. Pre induction hemodynamic parameters after 120 minutes of oral melatonin administration were recorded and after induction of anesthesia and intubation hemodynamic parameters were recorded. In group of patients who received melatonin the magnitude of rise of heart rate, systolic, diastolic and mean arterial pressure was less returning to pre induction value within 3 minutes. .In control group patients we observed a statistically significant rise in magnitude of heart rate and blood pressure that remained elevated till 10 minutes after laryngoscopy and intubation. The rate pressure product, an indicator of myocardial oxygen demand and consumption was significantly higher in control group and lasted for longer time. While in melatonin treated patients insignificant rise of RPP occurred. The clinical observations made in the present study allow us to conclude that oral melatonin administered 120 minutes before induction of anesthesia effectively controlled the stress response to laryngoscopy and endotracheal intubation and shown cardio-protective effect. Although this is not our clinical observation but as a foot note after reviewing the available literature we can assume melatonin to have an important place in perioperative management of patients and in intensive care units. We assume this to be a future drug in the arsenal on anesthetist.

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