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Effect of Preoperative Oral Melatonin on Attenuating Haemodynamic Responses of Laryngoscopy, Intubation and Sternotomy in Patients Undergoing CABG.

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Abstract: *Laryngoscopy and endotracheal intubation may result in a haemodynamic response that causes unwanted tachycardia and hypertension. In patients with poor myocardial reserve, this can cause detrimental impact. Melatonin, also known as N-acetyl-5-methoxy tryptamine, was used in numerous researches including intensive care unit sedation, pre-operative anxiolysis, laryngoscopy and intubation. METHOD- Sixty patient undergoing coronary artery bypass graft surgery (CABG) of NYHA grade II-III, either sex, aged below 70 years divided into two groups : Group S(study) who received oral Melatonin 10mg and Group P(placebo) received oral placebo, 2 hours prior to surgery. Haemodynamic parameters were noted at the time of induction of anaesthesia (baseline), during laryngoscopy, after 1, 2, 3, 5, 10, 15, 30 minutes of laryngoscopy and during sternotomy. Collected data was analysed statistically. It was observed that there was a substantial increase in heart rate and blood pressure at the time of laryngoscopy and intubation and at sternotomy in placebo group, compared with melatonin group. Conclusion–Melatonin is an effective drug to attenuate cardiovascular responses of laryngoscopy, endotracheal intubation and sternotomy in patients undergoing CABG.*

Key words: *CABG, Stress Response, Melatonin, Laryngoscopy, Intubation, Sternotomy*

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I. Introduction

Laryngoscopy and endotracheal intubation are regarded to be powerful abnoxious stimuli that cause haemodynamic reactions leading to marked changes in heart rate and blood pressures[1]. This is less likely to produce significant detrimental effects on healthy people. However, in people with poor myocardial reserve owing to coronary artery disease and geriatric patients, these occurrences are of particular concern for heart failure, cardiac dysrhythmias, hypertension and cardiomyopathy[2].Accordingly, measures to attenuate these pressurizing reactions are compulsory. The causes of these haemodynamic changes are believed to be due to sympathetic stimuli of somato-visceral reflexes, leading to release of endogenous catecholamines[3]. Various drug regimens and methods have been used from time to time to attenuate the stress response to laryngoscopy and intubation[4]. Recently melatonin, also known as N-acetyl-5-methoxy tryptamine, is used as a pre medication agent for its sedative and anxiolytic properties in paediatric patients[5]. In one previous study, melatonin administered 120 minutes prior to the preoperative period provides haemodynamic stability during laryngoscopy and intubation[6]. That was thought to be due to its inhibitory action on the central nervous system which is also responsible for its sedative and anxiolytic impacts. This study has been designed to evaluate the effect of oral melatonin given preoperatively as premedication drug in cardiac patients. Our hypothesis is that melatonin will be effective in attenuating haemodynamic effects caused by laryngoscopy, intubation and during sternotomy.

II. Material and Methods

This prospective comparative double blinded study was carried out on 60 hemodynamically stable patients of either sex aged less than 70 years planned for elective CABG surgery. Patients with anticipated difficult intubation, who required laryngoscopy duration of more than 20 seconds or those who required more than one attempt for intubation, uncontrolled co-morbidity like diabetes, hypertension and reactive airway diseases were excluded from study.After obtaining ethical committee permission from hospital and informed

consent, patients were divided in two equal groups, group S (study group-melatonin) and group P (placebo group) using computer-generated randomization. Each patient has been undergone thorough pre anaesthetic examination and counseling. As per protocol, either tablet Melatonin 10 mg or tab. Vitamin D3 as placebo was given with a sip of water, 120 minutes prior to surgery randomly by a person other than investigator. After receiving patient in operation theater standard monitoring was done. All the patients have been pre oxygenated with 100% oxygen for 3 min before induction. Induction was done with intravenous thiopentone 5mg/kg, fentanyl 5µg/kg and midazolam 0.03 mg/kg, Vecuronium bromide 0.1mg/kg was used to facilitate endotracheal intubation with proper sized well-lubricated cuffed endotracheal tube in single attempt with less than 20 seconds duration each time. Maintenance of anaesthesia was attained with top up doses of fentanyl, midazolam, vecuronium with inhalation of isoflurane 1 MAC, oxygen: air (60:40) to maintain EtCO2 values of 30-35 mmHg. Haemodynamic parameters such as heart rate, systolic, diastolic and mean blood pressures were recorded at the time of induction of anaesthesia (baseline), at laryngoscopy, at 1,2,3,5,10,15,30 minutes after intubation and at time of sternotomy.

Statistical analysis

Data collected and entered in a Microsoft excel sheet and analysed using Epi info 7.1 and analysed in term of Mean and Standard Deviation. Unpaired T test was used for comparison of change in vital parameters of two groups. Repeated measures ANOVA were used for within group comparison of ratio and interval scale data. Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two groups. The level $P < 0.05$ was considered as the cutoff value or significance.

III. Results

Patients in both the groups were comparable in terms of age, gender distribution, weight, NYHA grade and LVEF. All parameters in respect of two groups were not statistically significant. (Table 1)

Table no 1: Shows Demographics of our study.

DEMOGRAPHICS			
VARIABLE	GROUP S (MELATONIN)	GROUP P (PLACEBO)	P VALUE
AGE (YEARS) , (MEAN±SD)	60.26±8.96	59.26±9.63	0.339
GENDER (FEMALE/ MALE)	6/24	4/26	0.731
WEGHT (Kg) , (MEAN±SD)	65.52±11.62	63.73±12.16	0.281
CO MORBIDITIES • Diabetes mellitus • Hypertension • Br. Asthma • Thyroid	 9/30 19/30 2/30 3/30	 10/30 17/30 1/30 4/30	 >0.5
LVEF	50.06±11.26	50.26±12.19	0.431

SD*- Standard Deviation, Kg*- kilogram, NYHA*- New York Heart Association, LVEF*- Left Ventricular Ejection Fraction.

Heart rates in both groups were comparable at baseline but during laryngoscopy and intubation heart rates were significantly increased in placebo group compared to melatonin group. This trend was persisted till five minutes after intubation. In melatonin group mean heart rates were lower from its baseline value as compared to placebo group till sternotomy. During sternotomy heart rates were significantly lower from its baseline value in melatonin group in comparison with placebo group in which heart rates were significantly increased during sternotomy. (Table 2)

Table no 2: Heart Rate in both Groups at various times.

HEART RATE			
TIME	GROUP S	GROUP P	P VALUE
BASE LINE (MEAN ± SD)	78.43±11.33	75.83±10.45	0.252
AT LARYNGOSCOPY & INTUBATION (MEAN ± SD)	76.1±12.81	84.43±15.26	**0.017**
1 MIN (MEAN ± SD)	76.13±10.81	88.26±13.85	**0.000**
2 MIN (MEAN ± SD)	77.5±12.64	85.5±14.28	**0.0184**
3 MIN (MEAN ± SD)	76.73±10.72	83.1±12.29	**0.033**
5 MIN (MEAN ± SD)	73.83±12.22	80.13±18.05	0.259
10 MIN (MEAN ± SD)	65.86±10.82	74.4±15.47	**0.03**
15 MIN (MEAN ± SD)	65.9±12.2	73.1±16.93	0.12
30 MIN (MEAN±SD)	74.13±12.55	70.83±14.85	0.35
AT STERNOTOMY (MEAN ± SD)	72.36±12.08	78.86±17.13	0.094

SD*- Standard Deviation

Differences in systolic blood pressures in both groups were non-significant at baseline but during laryngoscopy and intubation systolic blood pressures were significantly increased in placebo group compared to melatonin group. This trend was persisted till two minutes after intubation. In melatonin group systolic blood pressures were lower from its baseline value as compared to placebo group till sternotomy. During sternotomy systolic blood pressures were significantly lower from its baseline value in melatonin group and in placebo group systolic blood pressures were significantly increased during sternotomy. (Table 3)

Table no 3: Systolic Blood Pressure (mmHg) in both groups at various times.

SYSTOLIC BLOOD PRESSURE			
TIME	GROUP S	GROUP P	P VALUE
BASE LINE (MEAN ± SD)	145.26±26.85	137.16±16.85	0.167
AT LARYNGOSCOPY & INTUBATION (MEAN ± SD)	119.36±24.60	139.76±27.35	**0.003**
1 MIN (MEAN ± SD)	112.03±19.01	151.66±23.26	**0.000**
2 MIN (MEAN ± SD)	103.06±19.47	140.83±17.08	**0.000**
3 MIN (MEAN ± SD)	115.56±14.53	133.06±19.21	**0.000**
5 MIN (MEAN ± SD)	110.3±19.14	123.63±23.86	**0.02**
10 MIN (MEAN ± SD)	101.2±18.72	113.83±18.5	**0.01**
15 MIN (MEAN ± SD)	104.26±24.75	118.93±24.86	**0.02**
30 MIN (MEAN±SD)	116.5±24.21	118.93±19.65	0.67
AT STERNOTOMY (MEAN ± SD)	126.3±20.42	143.16±18.02	**0.001**

SD* - Standard Deviation

At baseline, diastolic blood pressures in both groups were comparable but during laryngoscopy and intubation diastolic blood pressures were also increased significantly in placebo group compared to melatonin group. This trend was persisted till two minutes after intubation. In melatonin group diastolic blood pressures were lower from its baseline value compared with placebo group till sternotomy. During sternotomy diastolic blood pressures were significantly lower from its baseline value in melatonin group and in placebo group diastolic blood pressures were significantly increased during sternotomy. (Table 4)

Table no 4: Diastolic Blood Pressure (mmHg) in both groups at various times.

DIASTOLIC BLOOD PRESSURE			
TIME	GROUP S	GROUP P	P VALUE
BASE LINE (MEAN ± SD)	77.76±15.50	75±9.01	0.401
AT LARYNGOSCOPY & INTUBATION (MEAN ± SD)	66.73±12.93	78.93±18.09	**0.003**
1 MIN (MEAN ± SD)	64.13±12.06	84.43±14.67	**0.000**
2 MIN (MEAN ± SD)	66.3±18.90	76.93±10.37	**0.009**
3 MIN (MEAN ± SD)	67.4±9.11	74.16±12.25	**0.01**
5 MIN (MEAN ± SD)	63.3±10.88	68.26±13.08	0.115
10 MIN (MEAN ± SD)	58.7±11.24	64.76±12.05	**0.04**
15 MIN (MEAN ± SD)	59.93±14.16	67.23±16.02	0.066
30 MIN (MEAN±SD)	67.2±14.38	67.73±13.33	0.88
AT STERNOTOMY (MEAN ± SD)	72±11.69	79.6±14.31	**0.028**

SD* - Standard Deviation

As shown in table no 5 mean blood pressures had similar response pattern as observed in Systolic and Diastolic blood pressures trends. (Table 5)

Table no 5: Mean Blood Pressure (mmHg) in both groups at various times.

MEAN BLOOD PRESSURE			
TIME	GROUP S	GROUP P	P VALUE
BASE LINE (MEAN ± SD)	101.26±11.86	96.66±10.02	0.11
AT LARYNGOSCOPY & INTUBATION (MEAN ± SD)	86.4±17.64	101.76±21.4	**0.003**
1 MIN (MEAN ± SD)	82.1±14.13	110.06±18.77	**0.000**
2 MIN (MEAN ± SD)	85±10.49	101.33±12.04	**0.000**
3 MIN (MEAN ± SD)	85.46±10.64	95.66±13.49	**0.001**
5 MIN (MEAN ± SD)	81.56±13.26	88.93±17.43	0.07
10 MIN (MEAN ± SD)	74.9±14.25	83.36±14.28	**0.025**
15 MIN (MEAN ± SD)	77±17.87	87.13±11.07	**0.037**
30 MIN (MEAN±SD)	86.33±18.59	87.1±16.06	0.864
AT STERNOTOMY (MEAN ±SD)	93.03±15.43	104.37±15.51	**0.006**

SD* - Standard Deviation

IV. Discussion

The present study was conducted to assess the effect of melatonin in attenuating haemodynamic responses to laryngoscopy and intubation and sternotomy in cardiac surgery patients. Laryngoscopy and endotracheal intubation are abnoxious stimuli capable of producing a huge spectrum of stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, and rhythm disturbances.[7] The peri intubation period is one of the stressful moments during cardiac surgeries. These changes are the maximum at about 45sec. after intubation and last for about five to ten minutes[8]. The mechanisms underlying the hemodynamic responses are not completely understood, although they have been attributed to a reflex sympathetic discharge caused by stimulation of the upper respiratory tract. The magnitude of these haemodynamic changes depends on various factors such as measures taken prior to airway manipulation, depth of anaesthesia, the anaesthetic agent used, duration of laryngoscopy and intubation[9]. In cardiac patients with poor myocardial reserve these changes may cause more detrimental effects[10]. Various drug regimens and techniques such as lignocaine, opioids, nitroglycerine, esmolol and α-2 receptor agonist dexmetomedine have been tried for obtruding the stress response. These agents have their own limitations like respiratory depression, hypotension, bradycardia, rebound hypertension or allergic reaction. Hence, there has always been a need for a better agent. Melatonin is a natural hormone secreted from the pineal gland. It has antinociceptive, antidepressant, anxiolytic, blood pressure-reducing, activity-regulating effects and pain-modulating effects[11]. We assumed that inhibition of excitatory effects by melatonin may have role in attenuating these stress responses. We had designed this study to assess the effect of melatonin on hemodynamic responses to laryngoscopy, intubation and sternotomy in patients undergoing coronary artery bypass grafting surgery. In current study we had included hemodynamically stable patients with ejection fraction of more than 40% to prevent any confounding effect of difference in usual stress response. It has been documented in literature that a single oral dose of melatonin 10 mg before intra venous regional anesthesia lowered patient anxiety; decreased pain associated with tourniquet and enhanced perioperative analgesia[12]. The peak effect of exogenous melatonin ranges from 60 to 150 min based on this, Gupta P et al[6] in their study concluded that pre-treatment with 6 mg melatonin administered orally 120 min before induction of anaesthesia is effective for attenuating haemodynamic responses to laryngoscopy and intubation in patients underwent elective surgical procedures. In our study both groups were comparable in terms of demographic data, comorbidity, pre operative nature of disease and duration of sternotomy. (Table 1)

After first three minutes of laryngoscopy, heart rate increased up to 15% (Table 2) of pre-induction values, systolic blood pressure had difference of about 10% (Table 3), diastolic blood pressure had difference of about 12% (Table 4) and mean arterial blood pressure (Table 5), were increased up to 15% of pre-induction values in placebo group from base line values but remained stable, without any increase in study group. At the time of sternotomy these values were increased by than 7% in placebo group, while there was no increase in values of study group. Our data is in concordance with study done by Gupta P et al. Decrease in systolic, diastolic and mean blood pressures from their baseline values was seen in melatonin group compared with placebo group during first three minutes. Previous studies also showed similar reduction in systolic, diastolic and mean blood pressures after intubation in comparison with placebo group[13].

The reducing impact of blood pressure may be due to the melatonin particular binding in the blood vessels to its receptors and interferes with the vascular reaction to catecholamines and reduces the outflow of adrenals which resulted in reduced concentrations of catecholamine[14].

It can relax the smooth muscle of the arterial wall by raising nitric oxide. It dilates blood vessels through free radical scavenging and can operate through epigenetic mechanisms in the postrema region of the brain[15]. The impact of reducing blood pressure may also be due to binding of melatonin at the GABA- A receptor may result in its sedative impact[16]. During sternotomy protective effects of melatonin premedication were reflected by favourable hemodynamics observed in study group with comparison to placebo group in our study. We have used moderate amount of fentanyl during intubation, this may be one explanation for attenuated stress response in our patients during laryngoscopy in comparison to other studies. Another factor for consideration is most of the patients planned for CABG surgery were one or other time were taking beta blocker and other anti hypertensive drugs , which may affect stress response of laryngoscopy and intubation. We have carefully chosen our study population but still this might be one confounding factor which cannot be eliminated completely. In experimental models cardio protective effects of melatonin in myocardial ischemia-reperfusion and myocardial infarction were documented in past which were thought to be mediated by antioxidant impacts of melatonin[17]. All these factors make melatonin an excellent choice for premedication in comparison to dexmedetomidine which is associated with significant bradycardia and hypotension. Benzodiazepines causes hangover effect or drug dependence, esmolol has more selective action on HR than BP while remifentanil is not easily available. In comparison, melatonin is easily available, has hypnotic, anxiolytic and analgesic properties, easy to administer and has got antioxidant and immune modulatory function. It attenuates surgical stress response and improves surgical outcome and has got an excellent safety profile. Lee YM et al[18] in their study found melatonin decreased infarction size, suppressed the frequency and length of ventricular arrhythmias and

enhanced survival in these models. With these added advantage, authors suggests that melatonin premedication should be considered in all possible patients undergoing cardiac bypass graft surgery.

V. Conclusion

Oral premedication of melatonin in patients undergoing coronary bypass graft surgery is effective in attenuation of haemodynamic responses caused by laryngoscopy & intubation and sternotomy. Melatonin premedication may also have added advantages on myocardial protection due to its anti oxidant effect. Authors suggest large scale multi centre study for evaluation of this effect.

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