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Comparative study of Melatonin and Pregabalin for attenuation of hemodynamic stress response to laryngoscopy and endotracheal intubation in Laparoscopic Cholecystectomy

[1]Dr.Debkamal Mukherjee,MD,DNB *Critical Care Trainee,CMRI*
[2]Dr.Krishnendu Chandra ,MD,IDCCM(Critical Care) *Associate Professor, Dept Of Anaesthesiology,VIMS,RKMSP, KOLKATA*
Corresponding Author: Dr.Krishnendu Chandra

Abstract
Background and Aim
Laryngoscopy and intubation are painful stimuli which invoke responses like tachycardia, hypertension and arrhythmias. The study aimed at comparing efficacy of pregabalin and melatonin for attenuation of hemodynamic stress response to laryngoscopy and intubation in patients posted for Laparoscopic Cholecystectomy.
Methods
It was a randomised prospective double blinded controlled study. 90 ASA Status 1 and 2 patients were divided into three equal groups. Group M received 6mg melatonin tablet, Group P received 150mg pregabalin tablet and Group C received placebo tablet orally 2 hours prior to induction of GA. Anaesthesia technique was standardised for all groups. Primary outcome measures were HR, SBP, DBP, MAP,RPP (Rate Pressure Product) before and after induction,at intubation and 1,2,4,6,8,10 minutes after intubation. Secondary outcome measures were any adverse effects associated with the drugs.
Results
Statistically significant difference ($P<0.05$) between melatonin and pregabalinwas found in HR 1 min after intubation onwards till 6 min, in SBP and RPP at 1 min after intubation onwards till 8 mins,in MAP at 6 and 8 mins after intubation.
Statistically significant difference was observed in SBP, DBP, MAP and RPP at all time points after induction and in HR at intubation and all time points after intubation in Melatonin and Pregabalin groups compared to placebo group.
Sedation scores were significantly more in melatonin and pregabalin group compared to placebo group. No significant adverse effects were noted with both drugs.
Conclusion
Melatonin and pregabalin both attenuate intubation response but melatonin does it better.
Keywords: *Pregabalin,Melatonin,Laryngoscopy,Heamodynamic response*

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I. Introduction

Direct rigid laryngoscopy and tracheal intubation have remained the gold standard in airway management in spite of the emergence of new airway devices in recent years. The hemodynamic stress response resulting from airway instrumentation are due to sympatho-adrenergic response caused by epipharyngeal and parapharyngeal stimulations, which lead to a significant rise in the catecholamine level that increases blood pressure (BP) and pulse.

These hemodynamic responses may be fatal in susceptible patients such as those with coronary artery disease, hypertension, intracranial aneurysm, and cerebrovascular disease and may cause myocardial infarction, arrhythmias, left ventricle failure, and rupture of aneurysm.

Various pharmacological agents such as opioids (fentanyl, alfentanyl), beta-adrenergic blockers (esmolol, propranolol), calcium channel antagonists (verapamil, diltiazem), and alpha-2 agonists (clonidine, dexmedetomidine and methyldopa) benzodiazepines (midazolam, alprazolam), barbiturates, propofol, lignocaine and peripheral vasodilators (sodium nitroprusside, nitroglycerine) have been used to attenuate the hemodynamic stress response to laryngoscopy and intubation, but they all had limitations such as respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension or allergic reactions. So, it is desirable to use a drug with early, rapidly recognizable, and easily treatable adverse effects. The technique should be simple so that it can be useful as a routine practice.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous sleep regulating hormone secreted by pineal gland. Exogenous administration of melatonin facilitates sleep onset and improves the quality of sleep. It is different from benzodiazepines and their derivatives in that it produces natural sleep pattern and does not lead to impairment of cognitive functions[1]. Various researchers have used this drug in different dose patterns as premedication in both adults as well as children. This drug has been mainly studied as a sedative agent in Intensive Care Unit and pre-operatively as an agent for anxiolysis.[2]

Pregabalin, a gabapentinoid compound appears to produce an inhibitory modulation of neuronal excitability particularly in neocortex, amygdala and hippocampus of CNS.It binds to the $\alpha_2\delta$ subunit of voltage dependent calcium channels and inhibits the channel[3]. It possess analgesic, anticonvulsant and anxiolytic activity by reduction of neurotransmitter glutamate, nor-adrenaline, serotonin, dopamine and substance P.

There are numerous studies which have shown the efficacy of melatonin[4, 5] or pregabalin[6,7] to reduce the stress response associated with laryngoscopy and tracheal intubation, but very few data are available comparing the efficacy of pregabalin and melatonin in controlling haemodynamic stress response throughout the peri-intubation period. The primary objective was to study the changes in heart rate, blood pressure during laryngoscopy and intubation.

Methods

This randomised prospective double blinded controlled study was conducted after obtaining the clearance of the Ethical Committee.

Sample size was calculated at 80% study power and α error of 0.05 assuming a standard deviation of 6.1032 in heart rate after 2 hours of oral melatonin administration as per the result of the pilot study conducted on 10 patients.For a difference of 5 beats per min to be detected in heart rate between the groups 24 patients in each group were required as sample size. It was further increased and rounded off to 30 patients in each group.

$$N=[(Z_\alpha+Z_\beta)^2*2*S^2]/L^2$$

N= number of subjects in each group, Z_α= 1.96 as confidence limit is 95%, Z_β=0.84 as power of trial is 80%, L= Difference to be detected, S= Standard Deviation.

Thus 90 patients posted for laparoscopic cholecystectomy were enrolled for this study after taking their informed consent. These patients were randomly divided into three groups each containing 30 patients with help of computer generated random number list. Group C received 2 placebo tablets orally 2 hours prior to surgery, Group M received Melatonin 6 mg (two 3 mg tablets) and Group P received Pregabalin 150 mg (two 75 mg tablets) orally 2 hours before surgery.Each patient received the drug based on the generated list in a similar looking envelope by the pre-operative nurse. Both patient and investigator were unaware of the type of drug. Antacid tablets were used as placebo and looked similar to the melatonin and pregabalin tablets. Inclusion Criteria were the patients of American Society of Anaesthesiologists (ASA) physical status Grade I and II, age 18– 50 years of either gender, surgery requiring general anaesthesia for duration longer than 30 min but less than 90 minutes.Exclusion Criteria were sleep disorders, BMI>30 allergy to study drugs, patients with anticipated difficult intubation,pregnant and lactating females,physically dependent on narcotics, patients with cerebrovascular, neurologic, psychiatric, cardiovascular, respiratory, endocrine, renal and hepatic dysfunction, intraoperative surgical complications which may alter vital parameters.

Before administration of the oral premedication, each patient's baseline heart rate, mean arterial blood pressure, DBP, SBP, Rate Pressure Product were measured, in addition Ramsay Sedation Score was also noted for each patient. The premedication was administered in the preoperative area and the vitals were monitored at regular intervals.

On arrival at the operation theatre, Standard monitors like NIBP, ECG, Pulse oximetry, Capnography were connected to the patients and a crystalloid intravenous infusion of 6 to 8 ml $kg^{-1}hr^{-1}$ was started after securing an i.v access. All patients were premedicated with glycopyrrolate (0.4 μg kg^{-1}), and fentanyl (1 μg kg^{-1}). After preoxygenation for 3 minutes, anaesthesia was induced with propofol 2 mg kg^{-1} or in a dose sufficient to abolish the eyelash reflex. After achieving proper mask ventilation atracurium 0.5 mg kg^{-1} was given to facilitate tracheal intubation. Then the patient was mask ventilated for 3 minutes followed by laryngoscopy and endotracheal intubation. Anaesthesia was maintained with sevoflurane, 60% nitrous oxide in oxygen. The patients' lungs were mechanically ventilated with minute ventilation adjusted to maintain normocapnia ($EtCO_2$ between 35 to 40 mm Hg). Supplemental neuromuscular blockade was achieved with atracurium 0.1 mg kg^{-1} at regular intervals. All patients received Diclofenac 1.5 mg kg^{-1} and Paracetamol 15 mg kg^{-1}iv and Tramadol 2 mg kg^{-1}i.v intra operatively for analgesia. Intraoperatively, patients were observed for any complications like hypotension/hypertension, tachycardia/bradycardia, arrhythmias, hypercapnia, and bronchospasm. Ondansetron (0.15mg/kg) was also administered and residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg kg^{-1}) and glycopyrrolate (0.01 mg kg^{-1}). The extubation was performed when reversal was adequate.

Hemodynamic parameters like systemic mean arterial blood pressure, systolic BP, diastolic BP, heart rate, rate pressure productwere recorded before and after induction of general anaesthesia, at intubation and 1, 2, 4, 6, 8 and 10 mins after intubation. Ramsay sedation scores were recorded before induction, and at 60 mins after extubation. Rate pressure product was calculated from recordings of SBP and PR (formula: SBP × HR), This RPP is an index of myocardialoxygen demand.

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

The results of the observations thus obtained in each group of patients were tabulated, compiled and statistically analysed using SPSS Statistics version 25 [Illinois, Chicago: SPSS Inc., 2008], Microsoft Office Excel 2013. Data was analaysed for normality of distribution by Shapiro-Wilk test. Qualitative data (sex, ASA grade and postoperative complications) were compared between groups with Chi-Square ($\chi 2$) test. Quantitative data (age, body weight, HR, SBP, DBP,MAP, RPP, Ramsay sedation score) were presented as median ± standard deviation and 3 groups were compared using Kruskal-Wallis and post hoc Dunn test with Bonferroni correction(for non-normal distribution) and ANNOVA with post hoc Tukey test(for normal distribution) for comparing a pair of groups.A p value < 0.05 was considered as statistically significant.

II. Results

The groups were analysed for normality of distribution by Shapiro-Wilk test which revealed that the data for all variables were not normally distributed ($P<0.05$)except for HR at 1min after intubation for which data was found to be normally distributed

The groups were comparable with respect to age, sex, weight, ASA status. There were no significant differences in demographic profile among the three groups (Table 1).

DEMOGRAPHIC VARIABLES	GROUP M n=30 (Median±SD)	GROUP P n=30 (Median±SD)	GROUP C N=30 (Median±SD)	*p value*
SEX (M:F)	11:19	12:18	10:20	.866
AGE (YEARS)	41 ± 8.272	38.5 ± 7.770	42± 8.150	.846
BODY WEIGHT (KG)	56.5 ±9.769	55 ± 9.522	55 ± 9.042	.792
ASA GRADE (I:II)	24:6	24:6	23:7	.936

Table 1

S.D= Standard Deviation

A statistically significant reduction in HR at intubation and 1 min, 2 min, 4 min, 6min, 8 min and 10 min after intubation in both melatonin and pregabalin group ($P< 0.005$) compared to the placebo group. However there was statistically significant reduction in HR at 1 min ($P< 0.05$), 2 min ($P<0.005$), 4 min($P<0.005$), 6 min ($P<0.05$) after intubation in melatonin group when compared with pregabalin group, as depicted in Figure 1.

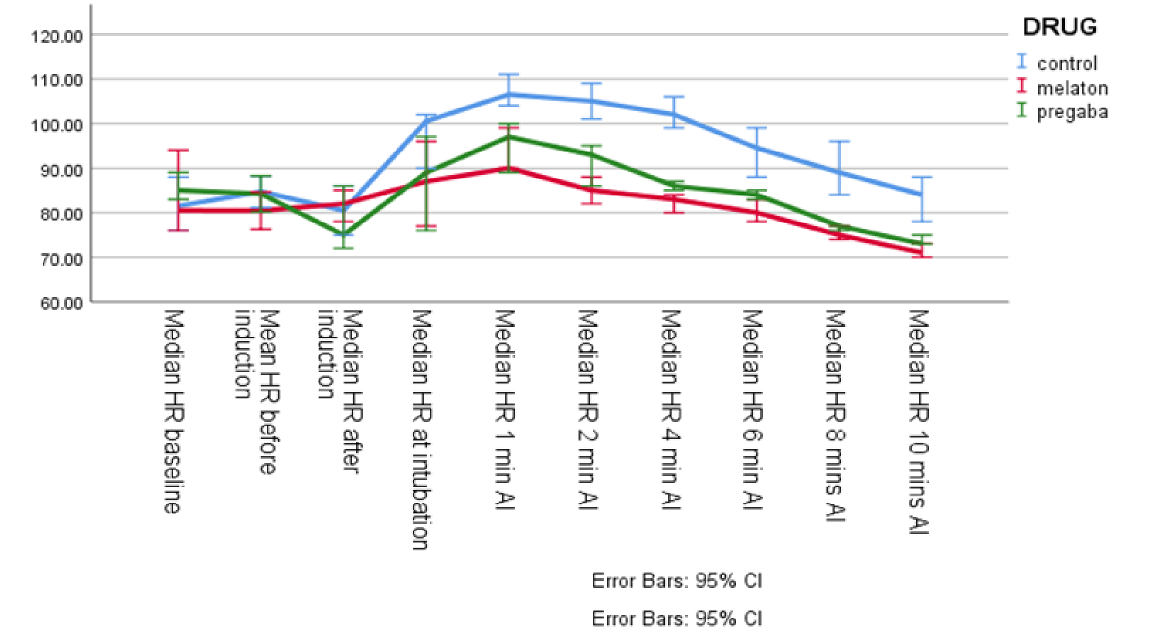

Figure 1. Showing Heart Rate Variation

AI: after intubation

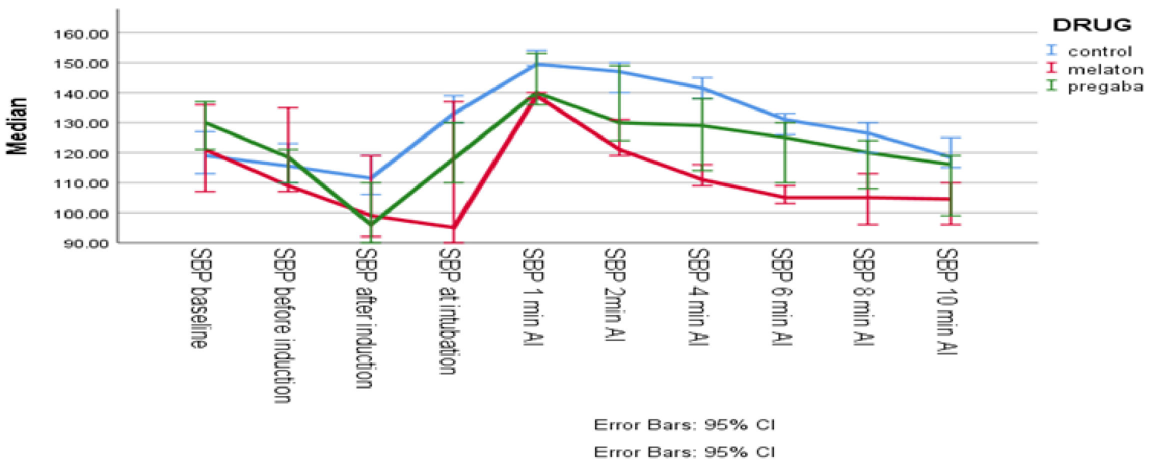

Figure 2. Variation of Systolic Blood Pressure

SBP after induction, at intubation and at 1 min, 2 min, 4 min, 6min, 8 min and 10 min after intubation was found to be significantly lower in both melatonin and pregabalin group as compared to placebo group (*P<0.001*). But statistically significant lowering of SBP was found at 1min (*P<0.05*), 2 min (*P<0.05*), 4 min (*P<0.01*), 6 min (*P<0.001*), 8 min (*P<0.001*) after intubation when melatonin group was compared with pregabalin group as shown in the Figure 2.

Statistical significant decrease in DBP was seen after induction, at intubation and at 1 min, 2 min, 4 min, 6 min, 8 min and 10 min after intubation in melatonin and pregabalin group when compared with placebo group (*P<0.05*). However when melatonin group was compared with pregabalin group no statistical difference was noted as shown in Figure 3.

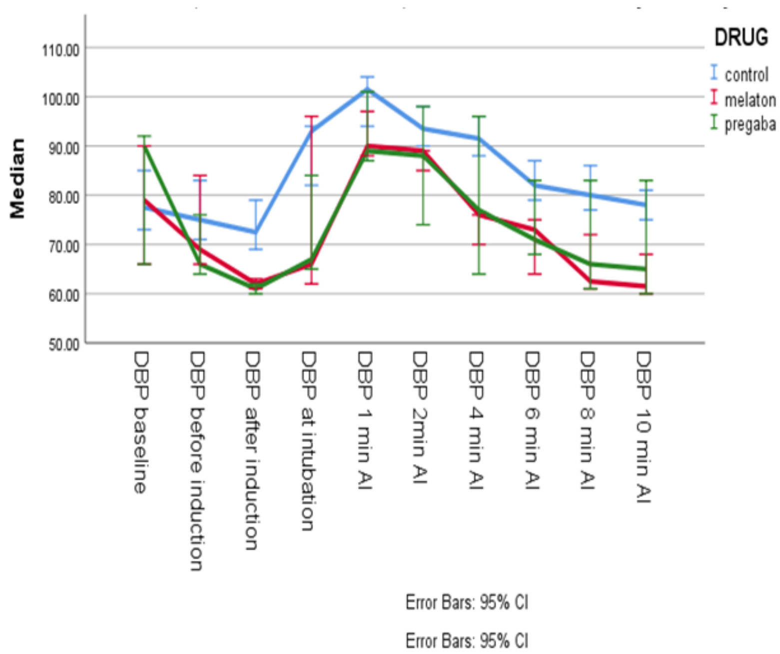

Figure 3. Showing variation in Diastolic Blood Pressure

Significant decrease in Mean Arterial Pressure was noted after induction, at intubation and 1 min, 2 min, 4 min, 6 min, 8 min and 10 min after intubation(*P<0.001*) in melatonin and pregabalin group in comparison with placebo group. When melatonin group was compared with pregabalingroup statistically significant decrease in MAP was seen at 6 min (*P<0.05*), 8 min (*P<0.05*) after intubation as depicted in Figure 4.

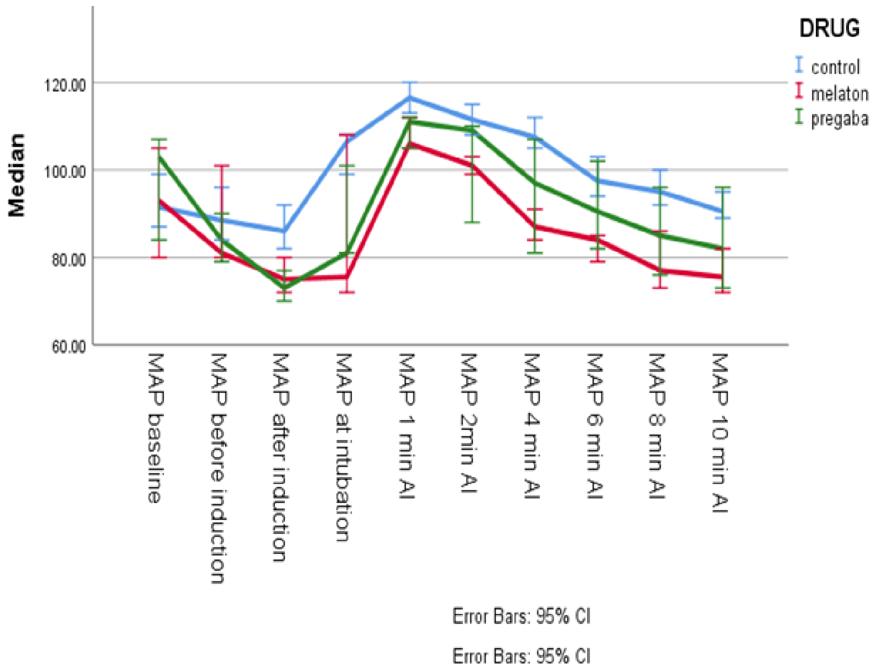

Figure 4. Showing Variation of Mean Arterial Blood Pressure

Statistically significant reduction in Rate Pressure Product was found in melatonin and pregabalin group compared to placebo group after induction, at intubation and 1 min, 2 min, 4 min, 6 min, 8 min and 10 min after intubation(*P<0.005*). However at 1 min (*P<0.05*), 2 min (*P<0.005*), 4 min (*P<0.005*), 6 min (*P<0.001*) and 8 min (*P<0.05*) after intubation there is significant reduction in RPP in melatonin group in comparison with pregabalin group as illustrated in Figure 5.

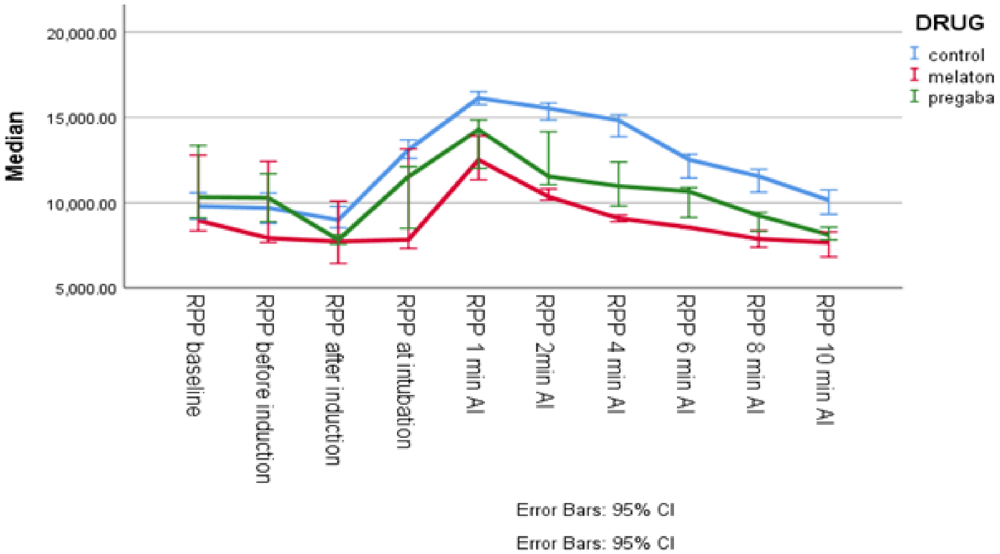

Figure 5. Showing variation in Rate Pressure Product

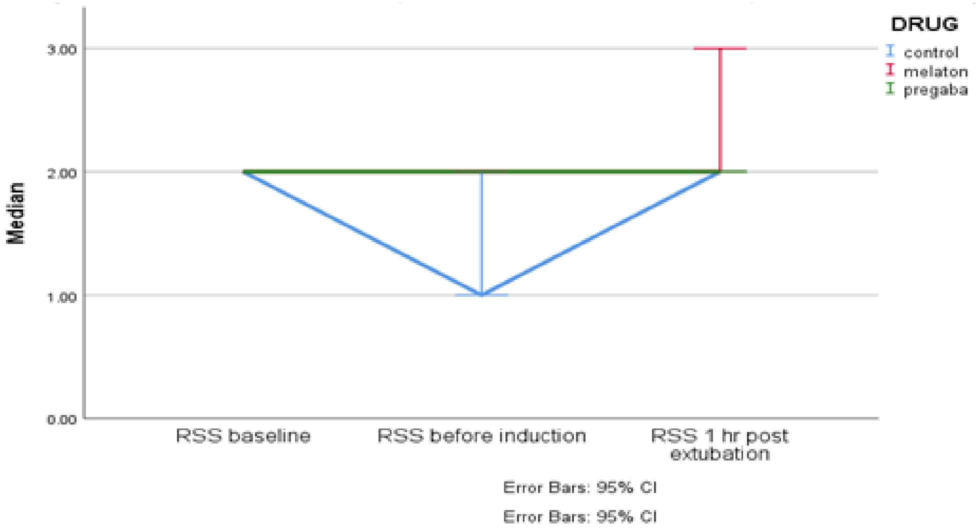

Figure 6. Showing variation of Ramsay Sedation Score

The sedation level as measured by Ramsay Sedation Score was found to be siginificantly more in both melatonin and prgabalin group in comparision to placebo group both before induction and 1 hour post extubation. But no significant difference was found in sedation levels when the two drug groups were compared with each other as demonstrated by Figure 6.

When HR was less than 60 bpm it was considered as bradycardia and SBP less than 90mmHg, or DBP less than 60 mmHg, or both were considered as hypotension. No patient enrolled in the study developed bradycardia or hypotensionin the intraoperative period or in the post-operative period. Hypoxaemia was adjudged by any drop in SpO_2 below 90% and it was seen in 3 patients (1 in each group) in the early postoperative period. 1 patient in each group complained of shivering in the recovery room. Postoperative nausea was complained by 1 patient in Group M, 2 patients in Group P and 4 patients in Group C. When these complications were compared between three groups with Chi-Square ($\chi 2$) test, no statistically significant difference was found (*p* value 0.902) as illustrated in Table 2 and Figure 7.

Table 2. Comparison of complications between three study groups

Post-operative complications	Group M (n =30)	Group P (n =30)	Group C (n =30)	Statistical Analysis
Hypoxaemia	1	1	1	Chi-Square (χ^2) value 2.182
Shivering	1	1	1	
PONV	1	2	4	*P* value 0.6688

PONV: postoperative nausea and vomiting

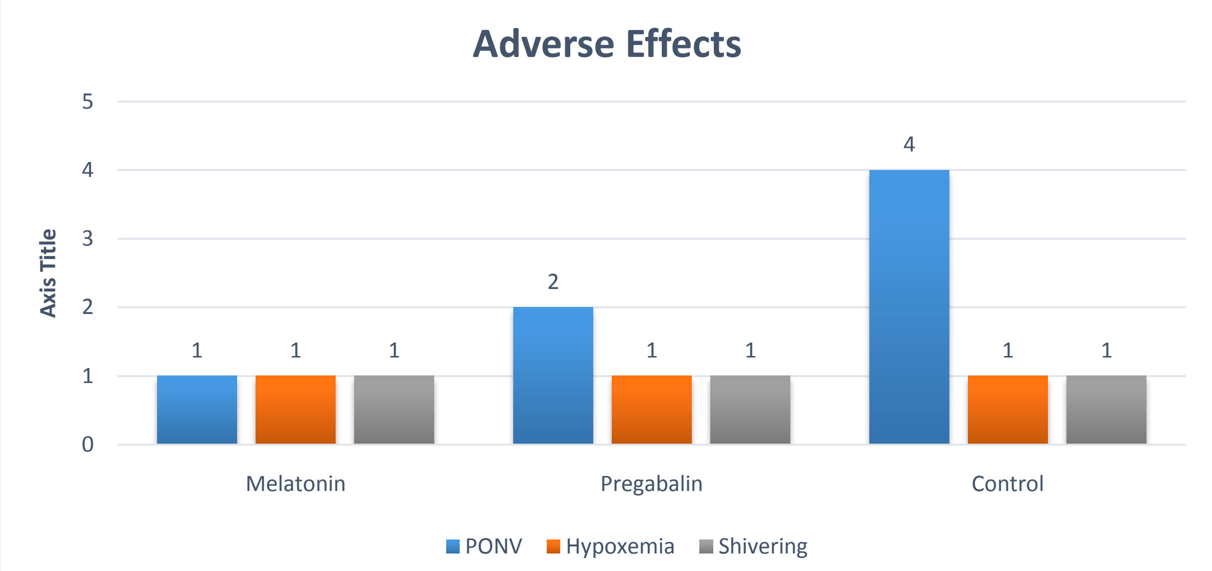

Figure 7

III. Discussion

The present study is aimed at comparing the efficacy of pregabalin and melatonin for attenuation of hemodynamic stress response to laryngoscopy and intubation in patients posted for Laparoscopic Cholecystectomy.

Laryngoscopy and tracheal intubation are associated with haemodynamic stress responses due to sympathetic stimulation, which results in marked increase in heart rate, blood pressure, circulating catecholamines [8] and arrhythmias [9]. This can also lead to increased risk of myocardial ischemia during tracheal intubation [10]. These effects are transient but can be detrimental to the patients, especially in presence of coronary artery disease and cerebrovascular disease. Numerous studies have been done to find out ways to reduce or abolish the stress response. Many drugs like fentanyl , intranasal nitroglycerine , sublingual nifedipine , diltiazem , esmolol , alfentanyl , remifentanyl , lignocaine , dexmedetomidine have been evaluated to reduce stress response with varying results.

Melatonin (N-acetyl-5-methoxytryptamine) is a pineal gland hormone which controls the circadian rhythm. It has been used for sleep disorders, jet lag, perioperative anxiolysis and sedation, cognitive and psychomotor functions. It is assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have a role in attenuating haemodynamic responses to laryngoscopy and intubation[4]. Rosenberg et al. studied the role of perioperative melatonin in the modification of surgical stress response indicating that melatonin has sympatholytic activity.[11] The peak effect of exogenous melatonin ranges from 60 to 150 min.[12] Priyamvada Gupta et al administered 6 mg melatonin 120 min before induction of anaesthesia in their study to assess attenuation of hemodynamic response to laryngoscopy and intubation[4].

We observed that in melatonin group, heart rate,systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product was lower at all points of time after induction till 10 min after intubation as compared to the placebo group in which there was a significant rise. It has been studied that melatonin reduces mean blood pressure in healthy volunteers.Mohammed et al. compared the role of oral melatonin 6 mg and 9 mg with placebo administered 1 h before surgery in attenuating pressor response to laryngoscopy and intubation. Their observations corroborate with our findings except the heart rate.[5] The observations of study conducted by Priyamvada Gupta et al to evaluate the role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation were also similar to our study[4].

The mechanism of effect of melatonin on circulation is complex. The blood pressure lowering effect may be attributed to the specific binding of melatonin to melatonin receptors in the blood vessels, interfering with the vascular response to catecholamines.[13] It may interfere with the peripheral as well as central autonomic system, causing a reduction in adrenergic outflow and resulting catecholamine levels.[14] Furthermore, it may induce relaxation of arterial wall smooth muscle by enhancing the availability of nitric oxide.[15] In addition, it may also act via specific receptors melatonin type 1 or melatonin type 2 located peripherally in the blood vessels and centrally in blood pressure regulating area of the brain.[16] It also has free radical scavenging effect leading to dilatation of blood vessels, and it may work via epigenetic mechanism at area postrema in the brain. The blood pressure lowering effect could also be due to the sedative action of orally administered melatonin. The sedative effect is mainly due to binding at GABA-A receptor and exerting its anaesthetic effect.[13]

We observed that heart rate was found to be lower at all points of time in melatonin group as compared to the control group. However, in a similar study, no difference was observed in the changes of heart rate in the melatonin groups as compared to the placebo group. The heart rate lowering effect of melatonin may be attributed to its anxiolytic actions. The underlying mechanism is probably the synergy between melatonergic and GABAergic systems. It also has analgesic effects as observed by various investigators and this may also contribute to the haemodynamic stability.

Pregabalin is congener of gabapentine, an antiepileptic drug, acts by inhibiting membrane voltage-gated calcium channels in central nervous system. It does not interact with GABA receptors. It has analgesic, anticonvulsant, and anxiolytic properties. It is effective in controlling neuropathic pain. Effect of pregabalin on attenuating stress response to laryngoscopy and tracheal intubation has been evaluated previously in many studies [6,7]. It was found to be very useful and effective premedicant to blunt haemodynamic stress response to tracheal intubation in all those studies.

We observed in our study that in pregabalin group, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product was lower at all points of time after induction till 10 min after intubation as compared to the placebo group in which there was a significant rise. These findings are similar to the study conducted by Bhawna Rastogi et al and Sundar AS et al [6,7]

The role of melatonin in anaesthesia and critical care[17] has been elaborately discussed in the literature; it has been mentioned as a wonder drug with a wide spectrum of beneficial uses in anaesthesia and critical care including antioxidant and neuroprotective properties besides hypnosis, anxiolysis, analgesia and others. The use of melatonin for attenuation of haemodynamic responses before laryngoscopy and intubation is superior to few other drugs studied for the same purpose. For instance, melatonin is superior to dexmedetomidine since the latter is associated with significant bradycardia and hypotension.[18] On the other hand, esmolol has more selective action on heart rate than blood pressure.[19] As compared to remifentanil, melatonin is easily available and easy to administer. Moreover, remifentanil is associated with severe hypotension thus limiting its use for the purpose.[20]

No study has been conducted before our study to compare the efficacy of melatonin and pregabalin for attenuation of hemodynamic stress responses to laryngoscopy and intubation. It is clear from our study that melatonin is able to attenuate the rise in SBP from 1 min till 8 min after intubation compared to pregabalin. The rate pressure product is also significantly lower from 1 min till 8 min after intubation in melatonin group in comparision to pregabalin which signifies that melatotin has a significant role in decreasing the myocardial oxygen demand. But ability of melatonin to control the rise in DBP and HR is similar to pregabalin. The sedation scores of melatonin is equivalent to the scores found in pregabalin. Further studies are required to establish the mechanism in which melatonin is helpful in attenuating the stress response.

IV. Conclusion

We found that oral melatonin 6 mg as well as oral pregabalin 150mg is effective in blunting haemodynamic stress response to laryngoscopy and tracheal intubation. Melatonin was found to be more effective than pregabalin in lowering of blood pressure and heart rate changes and myocardial oxygen demand associated with laryngoscopy and tracheal intubation without any significant adverse effect. Pregabalin and melatonin has similar sedation profile. To summarize, both the drugs are effective in attenuating stress response to laryngoscopy and tracheal intubation but melatonin does it better.

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