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Melatonin versus gabapentin as premedication for anxiolysis and attenuation of hemodynamic response to laryngoscopy and intubation in general anesthesia

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ABSTRACT

Background: Perioperative anxiety adversely affects mental and physical well-being and it is associated with increased pain, stressor responses with general anesthesia (GA), and nausea-vomiting leading to delayed recovery. Recent studies have proven melatonin and gabapentin provide sedation, anxiolysis, and reduced pressure responses. **Aims and Objectives:** This study aimed to compare melatonin and gabapentin as premedication for anxiolysis and attenuation of hemodynamic response to GA. Post-operative pain and sedation were also compared. **Materials and Methods:** A total of 99 subjects (n = 33 in each group) between 18 and 60 year of age, ASA I/II scheduled for elective abdominal surgeries of < 3h under GA were included in the study. Patients in Group A were administered melatonin (10 mg × 2 tab.), those in Group B were administered gabapentin (400 mg × 2 tabs), and those in control Group C were treated with Vitamin C (500 mg × 2) before 2 h of surgery. At 0 min, 30 min, and 60 min assessments of anxiety, sedation, cognition, psychomotor function, and orientation were done. **Results:** There were significantly low anxiety scores in Groups M and G compared to Group C at 60 min and 90 min (P = 0.0000). Sedation score was significantly less in Group C patients compared to Group M and G at 30 min (P = 0.0008), 60 min, and 90 min (P = 0.0000) intervals. Heart rate and mean arterial pressure were increased in Group C patients as compared to Groups M and G. **Conclusion:** This study showed that melatonin had more anxiolytic and less sedative action, so also cognitive functions and orientation were well preserved in melatonin-treated subjects than in gabapentin. Hemodynamic responses were comparable in melatonin- and gabapentin-treated patients.

Key words: Anxiolytics; Melatonin; Gabapentin; General anesthesia; Perioperative pain

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INTRODUCTION

Anxiety before surgery is thought to be an important problem for patients as it can adversely affect emotion, mental condition, and physical well-being.[1] Anxiety-related complications are associated with all aspects of anesthesia including pre-operative visit, induction, perioperative, and recovery period.[2,3] Perioperative anxiety is responsible for increased autonomic reflexes, the requirement of anesthetics, post-operative pain, nausea, and vomiting leading to prolonged duration of recovery and hospital stay.[4-6]

Moreover, laryngoscopy and endotracheal intubation (EI) are known to produce noxious stimulation which significantly increases heart rate (HR) and blood pressure (BP).[7] Except for healthy subjects, this is detrimental in patients with partial myocardial reserve due to coronary

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artery disease, cardiac dysrhythmias, cognitive heart failure, hypertension, cardiomyopathy, and the geriatric age group.[8] Thus, it is essential to prevent these responses. These alterations in hemodynamic are due to sympathetic activation associated with activation of somatovisceral reflexes. During intubation, stimulation of laryngeal and tracheal sensory receptors secret endogenous catecholamine's leading to tachycardia and hypertension.[9]

From the discovery of laryngoscopy and EI, many classes of drugs have been evaluated to attenuate anxiety and stress responses. Widely used analgesics, anxiolytics, and sedatives as premedication are associated with the risk of respiratory depression, post-operative delirium, nausea, and vomiting and increase the risk of serious complications. These classes include opioids, calcium channel blockers, sympatholytic, alpha agonists, β blockers, benzodiazepines, and barbiturates.[10] However, these drugs have their limits including respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension, or allergic reactions. Hence, there has always been a need for a better agent.[11]

Melatonin (N-acetyl-5-methoxytryptamine) hormone is secreted by the pineal gland which regulates sleep.[11] Various studies have reported the action of melatonin as an analgesic, anti-inflammatory, anti-anxiety, and anti-agitation effect.[12] Moreover, pre-treatment of melatonin acts as a sedative and anxiolytic without obvious mental dysfunction including memory recall and driving performances or the quality of recovery.[13] Despite being commonly assessed for analgesic and reduced narcotic intake, the action of melatonin on laryngoscopy and EI-induced hemodynamic alterations is lacking.

Gabapentin is known as one of the new anticonvulsants. It is well-tolerated anti-epileptic drug with low adverse effects and has analgesic, anticonvulsant, and anxiolytic effects.[13] It is a structural analogue of GABA which can also inhibit the calcium influx and subsequent release of excitatory neurotransmitters in pain pathways to presynaptic voltage-gated calcium channels.[14] In recent times, gabapentin was successfully used to attenuate hemodynamic response to laryngoscopy and EI.[15,16] Despite this, there is a paucity of data regarding the comparison of melatonin and gabapentin in the management of anxiety, laryngoscopy, and EI-induced hemodynamic alterations.

The main function of melatonin is to regulate circadian rhythm, but serum melatonin level and sleep phase usually do not correlate.[17] When melatonin is given, externally a dose-dependent shift in the timing of sleep occurs. Sleep benefits associated with the use of melatonin are an increase in total sleep time, sleep efficiency, and Stage 2 sleep with a reduction in slow-wave sleep.[18] Melatonin is mainly metabolized by first-pass metabolism with varying bioavailability. It is a highly lipophilic consequently higher volume of distribution and 70% of plasma melatonin is albumin-bound. The human plasma $T_{1/2}$ of melatonin is around 45 min.[19-23] The common adverse effects of melatonin are headache, dizziness, nausea, and drowsiness.[24] The analgesic, anti-inflammatory, anti-anxiety, and anti-agitation effects of melatonin have been shown in various studies.[12] Although some training indicates that pre-operative use of melatonin can reduce post-operative pain and narcotic administration, its effect on pain and anxiety has not yet been explained to be suggested generally. In addition, few studies have shown contentious findings in this regard.[25-27]

Gabapentin contains a cyclohexyl group. Even though it has a similar structure to GABA, it does not bind to GABA receptors and does not influence the synthesis or uptake of GABA. It has a binding affinity toward voltage-gated calcium channels, particularly alpha-2-delta-1, which inhibit the presynaptic release of excitatory neurotransmitters responsible for epileptogenesis. Despite having paucity of data regarding the direct-action gabapentin on serotonin, dopamine, benzodiazepine, or histamine receptors, studies have suggested that gabapentin increases the blood serotonin level in healthy subjects. The plasma half-life of gabapentin is 5–7 h, with 2 days elimination period. The obvious advantage of gabapentin use is its mild side-effect profile. The well-known adverse effects are fatigue, dizziness, and headache.[28]

Aims and objectives

The present study was undertaken with an aim to compare melatonin and gabapentin as premedication for anxiolysis and attenuation of hemodynamic response to laryngoscopy and EI in general anesthesia (GA). The secondary objectives were to study the role of melatonin and gabapentin as a sedative, and pain in the post-operative period when used as a premedication.

MATERIALS AND METHODS

Hypothesis and sample size

Melatonin or gabapentin when given preoperatively is an effective multimodal approach in reducing anxiety, pressor response, provides sedation, and decreases the post-operative analgesic requirements.

According to Slovin's formula, sample size derived was 66 for Group M (n=33) receiving oral melatonin (10 mg×2 tablets) and Group G (n=33) receiving oral gabapentin (100 mg×2 tablets) in which control group. Group C (receiving Vitamin-C 500 mg×2 tablets) (n=33) will be added to

make a total of 99 patients and then they will be randomly allocated into three groups.

The present prospective randomized placebo-controlled comparative study was performed at our hospital from September 2020 to September 2022 after the Institutional Ethical Committee approval (DYPMCK/320/2020/IEC). The study was registered with the Clinical Trial Registry of India (CTRI/2020/10/028421) having UTR number U1111-1257-9819. All the ASA I and II patients between 18 and 60 years of age, scheduled for elective abdominal surgeries of <3 h were included in the study. Informed consent was obtained before the initiation of the study. Exclusion criteria were any patient with ASA >II, emergency surgery, sedatives, antiepileptic, or antidepressants, antipsychotics, anxiolytics, obesity, neuropsychiatric illness, anticipated difficult intubation, pregnancy, and lactation. Routine pre-operative clinical examinations were performed and patients were kept on overnight fasting. Before 2 h of surgery, subjects were orally administrated with the study drugs based on their group allocation. Patients in Group M were administered melatonin (10 mg×2 tab), those in Group G were administered with gabapentin (400 mg×2 tabs), and those in Group C were treated with Vitamin C (500 mg×2). The tablets were sealed in opaque covers and numbered by a third person who was not involved in the study and was administered by the pre-operative nurse. The subject and the investigator were unaware of the group allocation of the patient.

Preoperatively after drug administration at 0 min, 30 min, 60 min, and 90 min, assessments of anxiety and sedation were done. Anxiety was assessed using Amsterdam's perioperative anxiety and information scale. Sedation was assessed by a 5-point scale such as: (1-alert and wide awake, 2-arousable to verbal command, 3-arousable with gentle tactile stimulation, 4-arousable with vigorous shaking, and 5-unarousable).

On arrival of the patient in the operation room, routine monitoring including HR, electrocardiogram, arterial SpO_2, non-invasive BP, and $EtCO_2$ was performed. All the patients were given 100% oxygen for 3–5 min before induction. Glycopyrrolate 0.004 mg/kg, midazolam 0.05 mg/kg, and fentanyl 1 mcg/kg was administered intravenously (IV). Induction was attained with IV propofol 2 mg/kg followed by 2 mg/kg succinylcholine to facilitate EI with a proper sized well-lubricated cuffed endotracheal tube. Anesthesia was maintained using inhalation of sevoflurane with 50% NO_2 in oxygen. Muscle relaxation was attained with vecuronium administered in the dose of 0.06–0.08 mg/kg IV as loading dose and one-fourth of the initial dose as maintenance doses. Intravenous infusion of paracetamol 1 g was administered intraoperatively. At the termination of the surgery, IV neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg was administered to reverse the residual neuromuscular blockade. Intraoperative pressor responses were assessed by measuring systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and HR at 1, 5, 10, 30, and 60 min and compared with the baseline measurement taken 5 min before intubation. Post-operative data such as assessment of pain using visual analog scale score and the post-operative analgesic requirement was recorded.

Statistical analysis

Data were evaluated using R-Studio with version 1.2.5001 and graphical analysis as well as tabular analysis and graphical analysis were done in MS-Excel. Continuous variables were shown in mean±SD, whereas categorical variables were presented in percentage and frequency. The significant mean difference between the three groups was assessed by one-way analysis of variance as well as Kruskal–Wallis Test. P ≤5% considered as significant.

RESULTS

The mean age of Groups M, G, and C patients was 39.67±10.46, 37.48±10.04, and 40.97±15.83 years, respectively, (P=0.5160) and sex distribution was female/male in Group M 23 (69.70)/10 (30.30), Group G 22 (66.67)/11 (33.33), and 22 (66.67)/11 (33.33) in Group C, respectively, (P=0.9549).

Table 1 shows the pre-operative parameters. There were significantly low anxiety scores (AS) in Groups M and G compared to Group C at 60 min and 90 min (P=0.0000). The sedation score was significantly less in Group C patients compared to Groups M and G at 30 min (P=0.0008), 60 min (P=0.0000), and 90 min (P=0.0000).

There was a significant difference in HR of all groups of patients at all-time intervals at 0 min (P=0.0055), 5 min

Table 1: Pre-operative parameters, anxiety score, and sedation score, in (mean±SD) at 0 min, 30 min, 60 min, and 90 min

Group	0 min	30 min	60 min	90 min
Anxiety score (mean±SD)				
Group M	13.06±2.40	12.21±1.96	7.73±1.33	6.76±0.94
Group G	14.09±2.73	12.15±2.05	6.91±1.28	6.58±1.12
Group C	13.76±2.14	13.03±1.21	12.06±1.03	11.45±0.90
P-value	0.2197	0.0871	0.0000	0.0000
Sedation Score (mean±SD)				
Group M	1.06±0.24	1.36±0.49	1.91±0.38	2.27±0.45
Group G	1±0.00	1.21±042	2.03±0.53	2.39±0.70
Group C	1±0.00	1.00±0.00	1.03±0.17	1.21±0.42
P-value	0.1326	0.000887	0.0000	0.0000

(P=0.0058), 10 min (P=0.000086), 30 min (P=0.0000051), and 60 min (P=0.0000008) intervals, as shown in Figure 1. SBP was significantly increased in Group C patients as compared to Groups M and G at 0 min (P=0.0039), 1 min (P=0.0000107), 5 min (P=0.0000), 10 min (P=0.0000), 30 min (P=0.0000), and 60 min (P=0.0000). DBP was significantly increased in Group C patients than Groups M and G at 0 min (P=0.00415), 1 min (P=0.0000036), 5 min (P=0.0000), 10 min (P=0.0000), 30 min (P=0.0000), and 60 min (P=0.0000) intervals. In Figure 2, MAP was significantly increased in Group C patients than Groups M and G at 0 min (P=0.0034), 1 min (P=0.0000037), 5 min (P=0.0000), 10 min (P=0.0000), 30 min (P=0.0000), and 60 min (P=0.0000) intervals.

Table 2, Post-operative pain was significantly more in Group C patients than Group M and G (P=0.00), and post-operative requirement of a number of analgesic top-ups was significantly more in Group C subjects than Group M and G patients (P=0.03).

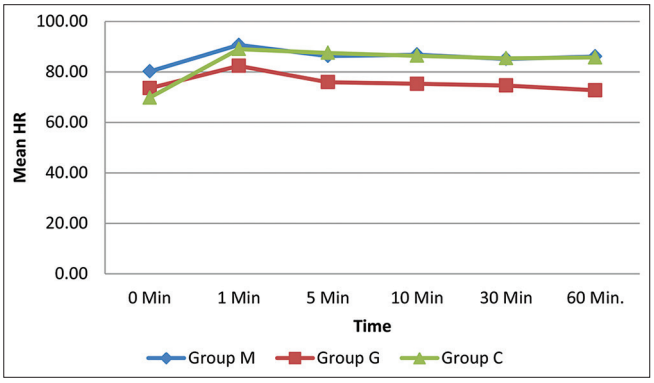

Figure 1: Comparison of heart rate at different time intervals. (P>0.05 Not significant [NS], P<0.05 significant [S])

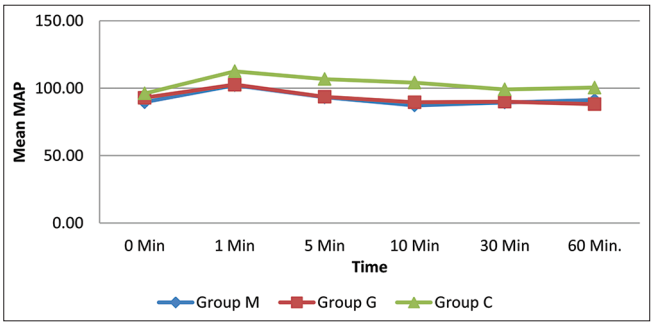

Figure 2: Comparison of mean arterial pressure at different time intervals. (P>0.05 Not significant [NS], P<0.05 Significant [S])

DISCUSSION

Mohamed et al., and Vidhya and Samyukta also showed that melatonin and gabapentin were effective in reducing pre-operative anxiety.[29,30] Furthermore, a systemic review suggested that melatonin was effective in reducing pre-operative anxiety compared to placebo.[31] Similarly, the previous studies showed that melatonin can be effective in reducing anxiety, and the incidence of delirium.[32-35] These findings suggest that melatonin or gabapentin can be used as a pre-operative anxiolytic to make patients more satisfied. The significant findings of our study were that anxiety was significantly less in Groups M and G compared to Group C at 60 min and 90 min intervals (P=0.0000). The sedation scores were significantly increased in melatonin and gabapentin-treated patients than control group patients at 30 min, 60 min, and 90 min intervals. Similarly, Dubey et al., and Bhandari and Shahi also showed a significant difference in sedation scores in the melatonin and gabapentin group than the placebo group.[36,37] Moreover, at 60 min and 90 min, the sedation scores were high in the gabapentin group than the melatonin group. However, the difference was statistically insignificant which is similar to the findings of Khezri et al.[38]

Various studies have suggested that pre-operative melatonin is associated anxiolysis without cognitive dysfunction that includes memory recall and driving performances, orientation, psychomotor skills, and quality of recovery.[39-42] Acil et al., and Kurdi and Muthukalai showed that pre-operative melatonin was associated with anxiolysis and sedation without post-operative impairment of cognition and psychomotor performance compared to midazolam.[43,44] So also Eapen et al., in their study concluded that premedication with melatonin and pregabalin is comparable in their effects on pre-operative anxiety, orientation, sedation, cognition, and psychomotor functions.[45]

Various comparative studies have reported the effects of gabapentin and melatonin on hemodynamic responses.

Table 2: Comparison of post-operative pain and number of top-ups in (mean±SD)

Groups	VAS score (mean±SD)	P-value	Number of top-ups (mean±SD)	P-value
GroupM	2.67±1.29	0.00	2.00±0.83	0.03
GroupG	2.39±1.12		1.88±1.02	
GroupC	3.97±2.17		2.52±1.00	

P>0.05 Not significant (NS), *P*<0.05 Significant (S), VAS: Visual Analog Scale

Vidhya and Samyukta conducted a study that compared the effectiveness of gabapentin and melatonin on hemodynamic responses to direct laryngoscopy and EI. They included 60 subjects undergone elective surgeries, assigned to three groups – control, melatonin group (6 mg), and gabapentin (300 mg). Pre-operative AS, induction dose of propofol, and the HR and BP were recorded. Post-intubation the hemodynamic variables were noted. The results suggested that the study group had significantly decreased pre-operative AS and requirement of doses of propofol than the control group and HR, SBP, and DBP were significantly lower in study group subjects. They concluded that melatonin and gabapentin can in attenuate the hemodynamic response to direct laryngoscopy and EI. These drugs can also reduce the pre-operative anxiety and dose of propofol.[29]

Doddaiah et al., performed a study to compare the hemodynamic changes during laryngoscopy and EI. They included that 120 adult subjects undergone elective surgery under GA into three groups of 40 patients each to receive preoperatively Group C – vitamin capsules, Group G – gabapentin 800 mg, and Group P-pregabalin 150 mg, 90 min before the scheduled surgery. Post-intubation SBP, DBP, MAP, and HR were noted intraoperatively. The results showed that HR was significantly lower in the study groups than the control group ($P<0.05$). There was a statistically significant reduction in SBP, DBP, and MAP in pregabalin and gabapentin group at 1 and 5 min. They concluded that oral pregabalin and gabapentin attenuates hemodynamic responses to laryngoscopy and EI. There was a significant reduction in SBP, DBP, and MAP, but not tachycardia.[30]

Gupta et al., conducted a study on hemodynamic variables during laryngoscopy and EI on 60 ASA I and II subjects. 2 h before surgery subjects were either treated with placebo or melatonin (6 mg). The results showed a significantly increased HR, and BP in the control group till 10 min which was insignificant in melatonin group, and concluded that melatonin is effective for attenuation of cardiovascular responses to laryngoscopy and EI.[11] The present study results showed that the melatonin group had lower HR than the gabapentin group at all-time intervals. Whereas, SBP, DBP, and MAP in the gabapentin and melatonin group were similar to the previous reports.[11,14,29,37-39] Moreover, post-operative pain and requirement of analgesic top-up were significantly more in the control group, whereas, when compared between gabapentin and melatonin groups, post-operative pain and requirement of analgesic top-up were less in the melatonin group; however, the difference was statistically insignificant. These findings are in accordance with the studies of Javaherforooshzadeh et al.,[13] Dubey et al.,[36] and Karri et al.[46]

The strength of the present study was the adequate sample size and uniform application of the protocol. The study showed that melatonin had more anxiolytic and less sedative action than gabapentin. Hemodynamic responses were comparable among melatonin and gabapentin-treated patients. Post-operative pain and the requirement of post-operative analgesics were comparable among gabapentin and melatonin groups.

Limitations of study

The limitations of the study were different doses and routes of test drugs were not studied; generalization could be better if a larger sample size was included. Further, a well-designed study of a large sample size including different doses would provide further evidence to confirm the present study findings.

CONCLUSION

The results of our study showed that pre-operative anxiety and sedation were significantly lower in the melatonin and gabapentin groups. Hemodynamic responses, post-operative pain, and requirement of post-operative analgesics were comparable among gabapentin and melatonin groups. Administration of melatonin or gabapentin can be safely used before laryngoscopy and EI to make patients more satisfied.

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