Comparative Clinical Evaluation of Preoperative Oral Pregabalin and Melatonin for Attenuation of Haemodynamic Responses to Laryngoscopy and Intubation.

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Abstract
Background: Laryngoscopy and endotracheal intubation are considered potent noxious stimuli which provoke haemodynamic responses leading to a marked increase in heart rate and blood pressure. These events are especially detrimental in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmias, congestive heart failure, hypertension, cardiomyopathy and geriatric age group. Hence, it is mandatory to take measures to attenuate these pressor responses.
Material and methods: A total of 90 patients undergoing surgeries requiring general anaesthesia for more than 30 minutes were enrolled in this comparative study of preoperative pregabalin and melatonin for attenuation of haemodynamic responses to laryngoscopy and intubation. The patients were randomly assigned in equal numbers to Group P (n=30) – receiving pregabalin 150 mg group, Group M (n=30) – receiving melatonin 6 mg group and Group C (n=30) – receiving placebo drug 120 minutes before surgery. The study groups were then evaluated for efficacy as premedication for attenuation of haemodynamic responses and post operative sedation.
Results: It was observed that in the control group, there was a significant increase in heart rate and blood pressure at laryngoscopy and intubation and persisted till 10 minutes post‑intubation. In melatonin group, there was an insignificant increase in heart rate at the time of laryngoscopy and intubation which however settled within1minute post‑intubation and the blood pressure remained stable throughout . At induction, all haemodynamic parameters showed significant increase in pregabalin group which started receding 1minute post-induction and at 10 minutes after induction these parameters returned back to normal values.
Conclusion: Premedication with oral pregabalin (150 mg) and oral melatonin (6 mg) before surgery can be safely used to attenuate haemodynamic response to laryngoscopy and intubation with acceptable levels of sedation.
Key words: Haemodynamic pressor response, intubation, laryngoscopy, melatonin, pregabalin, sedation.

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I. Introduction

Laryngoscopy and endotracheal intubation are synonymous with modern anaesthesia. They are considered potent noxious stimuli which provoke haemodynamic responses leading to a marked increase in heart rate and blood pressure [1]. This is probably of no consequence in healthy individuals. However, these events are especially detrimental in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmias, congestive heart failure, hypertension, cardiomyopathy and geriatric age group [2]. Hence, it is mandatory to take measures to attenuate these pressor responses. During intubation of trachea, the laryngeal and tracheal sensory receptors are stimulated which result in the release of endogenous catecholamines resulting in tachycardia and hypertension [3].

Many pharmacological techniques have been introduced and evaluated either in the premedication or during induction to attenuate the haemodynamic pressor response to airway instrumentation, but results are not uniform. More attention is given to the use of selective beta- adrenergic blockers to prevent the reflex sympatho-adrenal discharge mediated tachycardia and hypertension during laryngoscopy and intubation. Hypotensive agents, including sodium nitroprusside, nitroglycerine, adrenoreceptor blockers, calcium channel blockers and opioids, have been used effectively to attenuate these haemodynamic responses. Intranasal nitroglycerine tends to block the hypertensive response to airway instrumentation. The intravenous lidocaine (1.5 mg/kg) prevents the increase in mean arterial blood pressure with no effect on heart rate. Among opioids, remifentanil (1μg/kg), alfentanil (10–20 μg/kg) or fentanyl (0.5–1 μg/kg) have been used successfully to attenuate haemodynamic

pressor response to laryngoscopy and tracheal intubation, but these are associated with bradycardia, hypotension and post operative respiratory depression [4].

Pregabalin, a gabapentinoid compound, is described structurally as (S)-3 aminomethyl-5-methylhexanoic acid. Pregabalin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but is not functionally related to it. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system, and possesses analgesic, anticonvulsant and anxiolytic activity and is effective in preventing neuropathic component of acute nociceptive pain of surgery. It is well absorbed and tolerated after oral administration, with peak plasma concentrations occurring within 1 hour. It undergoes negligible hepatic metabolism. It is non narcotic, with clinically important reduction in pain and adverse haemodynamic response to larygoscopy and intubation [5]. Favourable pharmacokinetics of pregabalin makes it a valuable premedicant for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia [6].

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 as it produces natural sleep pattern and does not lead to impairment of cognitive functions [7]. Various researchers have used this drug in different dose patterns as premedication in both adults as well as children. It has been mainly studied in view of pre-operative anxiolysis, sedation in Intensive Care Unit, pre-operative cognitive and psychomotor functions [8]. It has been assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have role in attenuating haemodynamic responses to laryngoscopy and intubation.

II. Methods

After obtaining approval from the institutional ethical committee, a randomized controlled study was conducted which included 90 patients of ASA grade I and II, age between 18 and 65 years of either sex, 45-90 kg of body weight / BMI 18 -30kg/m^2 ,patients undergoing surgeries requiring general anaesthesia for more than 30 minutes.

The patients who were excluded in this study were patients with uncontrolled diabetes, uncontrolled hypertension, any psychiatric illness, who were taking antipsychotics, sedatives, anxiolytics or antiepileptic drugs, any sleep disorders, obesity, known allergy to the drug, an ASA status III or IV, pregnant or lactating females, some coagulopathy or on anticoagulant medications, anticipated difficult intubation , those requiring more than one attempt or more than 20 sec for laryngoscopy.

They were randomly assigned according to computer generated table of randomization into three groups.

GROUP P(n=30)- Patients in this group received pregabalin 150 mg orally 120 mintues before induction of anaesthesia, **GROUP M(n=30)**- Patients in this group received melatonin 6mg orally 120 minutes before induction of anaesthesia, **GROUP C(n=30)-** Patients in this group received a placebo drug orally 120 minutes before induction of anaesthesia.

Pre-anaesthetic check-up was done one day prior to surgery and included a detailed history, general physical as well as systemic examination and airway assessment of all patients. All the routine investigations and any other specific investigations deemed necessary for the patient were undertaken. Basic demographic profile like age, sex, weight, height, BMI were noted. All the patients were kept fasting 6 hours prior to surgery. Tab Alprazolam 0.25mg and Tab Pantoprazole 40mg were given orally night prior to surgery. Haemodynamic parameters such as heart rate: systolic, diastolic and mean blood pressures were recorded before the administration of drug (baseline).

The drug was given according to the groups allocated to the patients with sips of water 120 mins before the procedure. Continuous monitoring of the pulse rate, respiratory rate, blood pressure and arterial oxygen saturation (SpO2) was done in the pre-operative period at an interval of 10 min in the pre operative room.

An intravenous line with an 18 G cannula was established and patients were preloaded with 10 ml/kg of Ringer Lactate solution. Injection Ondansetron 0.1mg/kg and Injection Ranitidine 50 mg were given.

After receiving the patient in the operation theatre, monitors like ECG, NIBP, Pulse oximetry were attached. All base line parameters heart rate, systolic, diastolic blood pressure and mean arterial pressure were recorded. After adequate preoxygenation, anaesthesia was commenced with Fentanyl 1µg/kg and Propofol 2mg/kg. Laryngoscopy and intubation was facilitated with Rocuronium 0.6mg/kg. Anaesthesia was maintained with 33% Oxygen & 66% Nitrous Oxide mixture& 0.5-1% Isoflurane. At the end of the surgery, the residual neuromuscular paralysis was antagonized with Neostigmine (0.05 mg/kg) and Glycopyrolate (0.01 mg/kg) and the patients were extubated. The patients were shifted to the postanaesthesia care unit for observation. The time of arrival in the post-operative unit is defined as 0 hour post-operatively.

After the surgery all the patients were transferred to the post-anaesthesia care unit (PACU). There the patients received the standard post-operative care which includes oxygen administration via face mask at 4–6

L/min and monitoring of heart rate, NIBP, respiratory rate and SpO_2. Besides this, post operative analgesia level of sedation was assessed according to Ramsay Scale for Assessment of Sedation.
Any side effects e.g., vomiting, blurring of vision, and excessive sedation were also checked for.

STATISTICAL ANALYSIS:

Comparison of mean value according to treatment groups were done using students t-test and percentage comparison was done using the chi square test. To compare more than two variables ANOVA test was used. The P value of less than 0.05 were considered statistically significant.

III. Results

A total of 90 patients undergoing surgeries requiring general anaesthesia for more than 30 minutes were enrolled in this comparative study of preoperative pregabalin and melatonin for attenuation of haemodynamic responses to laryngoscopy and intubation . The patients were randomly assigned in equal numbers to Group P, Group M and Group C . The three study groups were then evaluated for efficacy as premedication for attenuation of haemodynamic responses and for post operative sedation.

Data from 120 patients was analysed. Patients in the three groups were comparable with respect to the baseline demographic characteristics as depicted in Table (1).

Table (1) Demographic data of patients

Demographic Parameters	Group P (n=30)	Group M (n=30)	Group C (n=30)
Age (years) Mean ± SD	42.43 ± 11.32	46.06 ± 13.89	40.53 ± 13.67
Male: Female ratio	1:1.72	1:1.30	1:1.14
ASA I/II	17/13	18/12	17/13

Table (2) Distribution of patients according to Mallampati grade

MPG	Group P (n=30) No. (%)	Group M (n=30) No. (%)	Group C (n=30) No. (%)
I	15 (50.00)	11 (36.67)	13 (43.33)
II	8 (26.67)	14 (46.67)	11 (36.67)
III	7 (23.33)	2 (6.66)	5 (16.67)
IV	0	3 (10.00)	1 (3.33)
Total	**30**	**30**	**30**

Table (2) shows the distribution of patients according to Mallampati grade. Majority of patients in Group P, Group M and Group C had MPG I/II (76.67%, 83.34% and 80% respectively), while difficulty in intubation (MPG III/IV) was observed in 23.33%, 16.67% and 20% patients in Group P, Group M and Group C respectively.

Table (3) Comparison of three groups according to

Parameter	Group P (n=30) Mean ± SD	Group M (n=30) Mean ± SD	Group C (n=30) Mean ± SD	Statistical inference (ANOVA)
Heart Rate (beats/min)				
Baseline	82.16 ± 7.41	82.43 ± 9.26	82 ± 5.76	p=0.82
At induction	97.80 ± 4.04	83.90 ± 10.61	87.40 ± 8.89	p<0.0001
At 1 min	93.52 ± 5.78	79 ± 10.02	89.87 ± 11.65	p<0.0001
At 3 mins	87.68 ± 4.28	75.43 ± 9.05	86.57 ± 8.83	p<0.0001
At 5 mins	82.88 ± 5.91	74.03 ± 9.02	84.03 ± 8.10	p<0.0001
At 10 mins	81.52 ± 7.64	74.60 ± 8.87	83.27 ± 7.08	p<0.0001
Systolic blood pressure (mmHg)				
Baseline	126.88 ± 11.30	124.43 ± 6.65	123.63 ± 5.79	p=0.16
At induction	140.12 ± 3.36	120.60 ± 9.73	132.05 ± 5.88	p<0.0001
At 1 min	136.52 ± 6.66	112.83 ± 7.52	140.10 ± 11.54	p<0.0001
At 3 mins	132.12 ± 7.29	104.93 ± 9.56	132.23 ± 6.85	p<0.0001
At 5 mins	128.36 ± 8	104.23 ± 8.63	129.70 ± 6.86	p<0.0001
At 10 mins	126.88 ± 7.13	105.47 ± 8.39	127.07 ± 5.92	p<0.0001
Diastolic blood pressure (mmHg)				
Baseline	79.76 ± 8.08	79.17 ± 6.34	80.87 ± 4.52	p=0.23
At induction	93.04 ± 4.36	79.43 ± 6.75	90.10 ± 4.69	p<0.0001

At 1 min	88.84 ± 4.79	73 ± 7.35	95.53 ± 6	p<0.0001
At 3 mins	85.08 ± 4.57	66.03 ± 6.14	88.27 ± 3.78	p<0.0001
At 5 mins	80.84 ± 5.16	65.43 ± 6.25	85.53 ± 3.41	p<0.0001
At 10 mins	80.72 ± 3.95	65.67 ± 5.76	84.87 ± 3.43	p<0.0001
Mean blood pressure (mmHg)				
Baseline	95.51 ± 8.60	94.27 ± 5.58	95.10 ± 4.71	p=0.51
At induction	108.31 ± 3.45	93.10 ± 6.65	104.27 ± 4.49	p<0.0001
At 1 min	104.49 ± 5.42	86.27 ± 5.97	110.33 ± 6.99	p<0.0001
At 3 mins	100.63 ± 5.37	78.97 ± 6.35	102.87 ± 4.25	p<0.0001
At 5 mins	97.09 ± 5.81	78.47 ± 5.72	100.17 ± 4.19	p<0.0001
At 10 mins	95.88 ± 4.72	78.97 ± 5.45	98.97 ± 3.91	p<0.0001
Oxygen saturation (%)				
Baseline	98.39 ± 0.60	98 ± 1.38	98.45 ± 0.92	p=0.14
At induction	98.7 ± 0.70	98.46 ± 0.97	98.83 ± 0.83	p=0.23
At 1 min	98.73 ± 17.56	98.56 ± 17.55	98.86 ± 17.60	p=0.42
At 3 mins	98.8 ± 17.21	98.76 ± 17.22	98.96 ± 17.25	p=0.58
At 5 mins	98.86 ± 16.87	98.63 ± 16.83	99.06 ± 16.91	p=0.10
At 10 mins	98.93 ± 15.98	98.8 ± 15.97	99.2 ± 16.03	p=0.07

Table (3) shows a comparison of three groups according to haemodynamic parameters. Base-line values for heart rate, systolic, diastolic and mean arterial blood pressures were comparable between the three groups. At induction, all haemodynamic parameters showed significant increase in pregabalin and control groups. In the melatonin group, there was a rise in heart rate from baseline values at the time of induction, but it was not statistically significant. The difference in mean values of haemodynamic parameters (heart rate, SBP, DBP, MAP) at induction between the three groups was statistically highly significant (p<0.0001). One minute after intubation, mean heart rate in pregabalin group started receding though it was significant compared to baseline value. At 3 minutes after intubation in the pregabalin group, fall in mean heart rate was still significant compared to that of baseline, but at 5 and 10 minutes mean heart rate attained stability. In the melatonin group, there was no rise and the patients were stable at all points of time after the intubation. In the control group, there was a rise in heart rate from baseline values after intubation which attained statistical significance at 1 minute and persisted thereafter till 10 minutes when the increase became non-significant. At 1, 3, 5 and 10 minutes, difference in mean heart rate between the three groups was highly significant (p<0.0001). Mean systolic blood pressure in pregabalin group started decreasing after intubation and by 10 minutes it attained attenuation. Similar trend was seen in mean diastolic blood pressure and mean arterial pressure. In the melatonin group, there was no rise and the patients were stable at all points of time after intubation. Similar trends were observed for diastolic and mean arterial blood pressure. In control group, mean systolic blood pressure was high from baseline value after intubation and this increase persisted at 1, 3, 5 and 10 minutes. Similar trends were observed for diastolic and mean arterial blood pressure. At all time intervals, difference in mean values of haemodynamic parameters between the three groups were statistically highly significant (p<0.0001) and the difference in the oxygen saturation levels at all times were insignificant.

Table (4). Comparison of post-operative sedation

Variable	Group P (n=30)	Group M (n=30)	Group C (n=30)
Mean RSS score ± SD (Range)	3.63 ± 0.49 (3 – 4)	1.53 ± 0.50 (1 – 2)	1.5 ± 0.50 (1 – 2)

Table (4) shows a comparison of post-operative sedation between the three groups. Post operative sedation score was high in pregabalin group as compared to Melatonin and Control groups.

IV. Discussion

The haemodynamic pressor response during laryngoscopy and intubation occurs frequently. Laryngoscopy increases the blood pressure and catecholamine levels, while intubation significantly increases heart rate which could lead to dangerous sequelae. Though various agents have been used to prevent these pressor responses, but still the search for ideal agent continues[9].

The present study was conducted on 90 patients undergoing surgeries requiring general anaesthesia. Thirty patients each were randomly assigned to pregabalin 150 mg group, melatonin 6 mg group and placebo drug group. The three study groups were evaluated for efficacy as premedication for attentuation of haemodynamic responses, post-operative analgesic effects and side effects of both drugs, if any.

In the present study, base-line values for heart rate, systolic, diastolic and mean arterial blood pressures were comparable between the three groups. At induction, all haemodynamic parameters showed significant

increase in pregabalin and control groups. In the melatonin group, there was a rise in heart rate from baseline values at the time of induction, but it was not statistically significant. The difference in mean values of haemodynamic parameters (heart rate, SBP, DBP, MAP) at induction between the three groups was statistically highly significant (p<0.0001).

One minute after intubation, mean heart rate in pregabalin group started receding though it was significant compared to baseline value. At 3 minutes after intubation fall in mean heart rate was still significant compared to that of baseline, but at 5 and 10 minutes mean heart rate attained stability. In the melatonin group, there was no rise and the patients were stable at all points of time after the intubation. In the control group, there was a rise in heart rate from baseline values after intubation which attained statistical significance at 1 minute and persisted thereafter till 10 minutes when the increase became non-significant. At 1, 3, 5 and 10 minutes, difference in mean heart rate between the three groups was highly significant (p<0.0001).

Mean systolic blood pressure in pregabalin group started decreasing after intubation and by 10 minutes it attained attenuation. Similar trend was seen in mean diastolic blood pressure and mean arterial pressure. In the melatonin group, there was no rise and the patients were stable at all points of time after intubation. Similar trends were observed for diastolic and mean arterial blood pressure. However, in control group, mean systolic blood pressure was higher from baseline value after intubation and this increase persisted at 1, 3, 5 and 10 minutes. Similar trends were observed for diastolic and mean arterial blood pressure. At all time intervals, difference in mean values of haemodynamic parameters between the three groups were statistically highly significant (p<0.0001). The present study showed that pregabalin (150 mg) and melatonin (6 mg) effectively reduced the hemodynamic responses to intubation and laryngoscopy.

In a study by Bhandari G *et al.* investigated the effect of pregabalin premedication on hemodynamic responses to laryngoscopy and intubation. They found that during laryngoscopy and intubation there was significant attenuation of SBP, DBP and MBP in pregabalin group as compared to placebo group [10].

Our study also confers to the study done by Chaudhary A *et al.* who did a comparative study between pregabalin and clonidine. They observed that pregabalin was equally efficacious in stabilizing the haemodynamics during laryngoscopy[11].

The present study concurs with the study conducted by Rastogi B *et al.* who found that 150 mg of pregabalin successfully attenuated the haemodynamic response to airway instrumentation[12].

Gupta K *et al.* showed significant increase in heart rate and blood pressure immediately after laryngoscopy in placebo group, whereas no such changes were observed in pregabalin group and in clonidine group. There was statistically significant attenuation of heart rate in premedicated groups (p<0.0001)[13].

Inhibitory actions of melatonin on central nervous system responsible for sedation and anxiolysis may have a role in attenuating haemodynamic responses to laryngoscopy and intubation[14].

Mohammed AA *et al.* compared the role of oral melatonin 6 mg and 9 mg with placebo administered 1 hour before surgery in attenuating pressor response to laryngoscopy and intubation. They observed that there was a reduction of blood pressure with regard to systolic, diastolic and mean blood pressure in both melatonin groups as compared to the placebo group[15].

Rosenberg J *et al.* studied the role of perioperative melatonin in the modification of surgical stress response indicating that melatonin has sympatholytic activity[16].

The attenuation of pressor response of airway instrumentation of direct laryngoscopy and intubation with near stable haemodynamic variables during the present study is an indication of clinically effective and safe analgesia and sedation with oral pregabalin (150 mg) premedication. Several mechanisms may contribute to the beneficial effects, which includes the modulation of visceral pain and central sensitization [17,18]. Favourable pharmacokinetics of pregabalin makes it a valuable premedicant for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia **[19]**.

Melatonin 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 [20]. As compared to remifentanil, melatonin is easy to administer. Moreover, remifentanil is associated with severe hypotension thus limiting its use for the purpose [21].

In the present study, postoperative sedation was observed to be higher in pregabalin group compared to melatonin and placebo groups (p<0.0001).

Our study concurs with the studies done by Ghai A *et al.* who observed that sedation scores were more in the pregabalin premedicated group than after gapapentin premedication[22].

Our study revealed that pregabalin produces sedation and hence reduces the anxiety, as assessed by Ramsay sedation scores. Preoperative anxiety is an important problem because it not only changes the drug dosages needed for induction, maintenance and recovery of anaesthesia, but it also affects the physiological

condition of the patient. Stress releases hormones like cortisol, catecholamines which increase negative nitrogen balance and catabolism and ultimately delay wound repair and weaken immune system[23].

Yucel A *et al*. and Agarwal A *et al.* noted that pregabalin premedication result in higher sedation scores as compared to the placebo group[24,25].

Pregablin (150 mg) and melatonin (6 mg) effectively attenuates heamodynamic stress responses to intubation, with adequate sedation and analgesia when compared to placebo.

V. Conclusion

Premedication with oral pregabalin (150 mg) and oral melatonin (6 mg) before surgery can be safely used to attenuate haemodynamic response to laryngoscopy and intubation with acceptable levels of sedation.

CONFLICTS OF INTEREST
There are no conflicts of interest.

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