



Original Research Article

Comparative efficacy of oral gabapentin versus melatonin for attenuation of haemodynamic response to direct laryngoscopy and endotracheal intubation

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ABSTRACT

Introduction: Several drugs have been tried and used to attenuate the haemodynamic response to direct laryngoscopy and endotracheal intubation. In this study, we have compared the efficacy of Gabapentin and Melatonin, an endogenous hormone, in attenuating the haemodynamic response to direct laryngoscopy and endotracheal intubation.

Materials and Methods: 60 patients of ASA physical status I and II scheduled to undergo elective surgeries were randomly allocated to three groups: the Control group, Melatonin group and Gabapentin group. Placebo, 6mg melatonin, or 300mg gabapentin respectively were administered orally to the patients in the three groups 120min before surgery. Pre-operative anxiety score, induction dose of propofol and the patient's heart rate and blood pressure were recorded. The haemodynamic parameters were recorded every minute for 5 minutes after intubation and then at 10 and 15min after intubation.

Results: Patients in the study groups were found to have significantly reduced pre-operative anxiety scores and dose of propofol required for induction was also significantly lower than control. Heart rate was found to be significantly lower in the study groups at all time points. Systolic blood pressure was significantly lower in the study groups at 1, 2, 3, 4, 10 and 15min after intubation. Diastolic and Mean blood pressures were significantly lower in the study groups at 1 and 2min after intubation. Post-hoc tests showed no significant differences between the two study groups.

Conclusion: Both melatonin and gabapentin are effective in attenuating the haemodynamic response to direct laryngoscopy and endotracheal intubation. Both drugs are also effective in reducing pre-operative anxiety and also reduce the induction dose of propofol.

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1. Introduction

Direct laryngoscopy and endotracheal intubation are very potent noxious stimuli. They provoke adrenergic responses leading to marked increases in heart rate and blood pressure. This puts a strain on the heart and is especially detrimental in patients who have diagnosed or undiagnosed Coronary Artery Disease. Several drugs have been found to be useful in attenuating the haemodynamic response to intubation. But the search is still on for a drug which can give consistent results with minimum side effects.

Gabapentin was introduced as an antiepileptic but proved to be effective in controlling neuropathic pain. The drug is well tolerated with limited side-effect.¹ More recently gabapentin has been used in randomized controlled trials to treat acute postoperative pain and to reduce the postoperative opioid requirements.² While using gabapentin as premedication for patients undergoing elective surgeries, it was noticed that these patients were also haemodynamically stable. Subsequently, studies have demonstrated that gabapentin attenuates the pressor response to direct laryngoscopy and endotracheal intubation.^{3,4}

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Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone secreted by the pineal gland. Exogenous administration of melatonin facilitates sleep onset and improves the quality of sleep. Melatonin is a safe drug with minimal side effects and is classified under the heading of "dietary supplement". Melatonin administered pre-operatively has been found to reduce anxiety in patients undergoing surgery.^{5,6} Attenuation of haemodynamic responses to endotracheal intubation^{7,8} and reduction of induction dose of propofol⁹ with preoperatively administered melatonin has been demonstrated in recently published studies.

We decided to compare the effects of gabapentin and melatonin pre-medication on the haemodynamic response to direct laryngoscopy and endotracheal intubation.

2. Materials and Methods

After obtaining Institutional Ethical Committee Approval, patients were enrolled for this study. The study was done in 60 patients who were randomly allocated to three groups using a computer generated random number table: Group C- Control group, Group M- Melatonin group and Group G- Gabapentin group.

2.1. Inclusion criteria

1. ASA physical status I and II patients.
2. Age between 20-60 years.
3. Patients undergoing elective surgery under general anesthesia.

2.2. Exclusion criteria

- ASA physical status 3 or more
- Patients already taking Gabapentin or Melatonin
- Patients having anticipated difficult airway.
- Patients not giving consent for the study.

2.3. Preparation and procedure

2.3.1. Preoperative

Routine preoperative assessment was done as for all elective surgeries. Patients were explained about the study in their own language and written informed consent to participate in the study was obtained.

2 hr before the start of surgery, the patient was administered the oral pre-medication according to his/her group allocation. Patients in group C were administered placebo, those in group M were administered tab. Melatonin 6mg, and those in group G were administered tab. Gabapentin 300mg. The tablets were kept in identical opaque envelopes labelled only with the study number and were administered by the pre-operative room nurse. The patient, the anaesthesiologist conducting the case and the investigator conducting the study were unaware of the group

allocation of the patients.

The pre-operative anxiety score of the patient was recorded using the VAS Anxiety scale¹⁰ 2 hours after administration of the study drug.

2.4. Intraoperative

Routine monitoring was done with ECG, pulse oximetry and NIBP. Baseline HR and Blood Pressure were noted (systolic, diastolic and mean).

Venous access was secured with an 18G venous canula. All patients received preloading with 500ml of Ringer Lactate before induction of anesthesia. Inj fentanyl 2µg/kg intravenously was administered to all patients.

After pre-oxygenating with 100% oxygen for 4 mins, induction of anaesthesia was started with inj. Propofol (10mg/ml). Propofol was administered 20mg every 15 sec till anaesthesia was induced. The end point of induction was taken as loss of verbal contact. Thereafter, after checking the adequacy of mask ventilation, inj Atracurium 0.5mg/kg was administered for achieving neuromuscular blockade. Patient's lungs were ventilated with 33% oxygen in nitrous oxide through face mask for 4min before intubation.

Intubation was done using Macintosh laryngoscope. Portex cuffed endotracheal tube size 7.0mm ID was used for female patients and size 8.0mm ID for male patients. Heart rate and blood pressure were recorded after induction, and every 1 min for 5 min and at 10 and 15 min after intubation.

3. Observations and Results

The Normality of the variables was tested with the Shapiro-Wilk test /Kolmogorov Smirnov tests of normality. ANOVA followed by Post Hoc Multiple Comparisons test were carried out for comparisons of Normally distributed data. Group comparisons of values of skewed data were made with Kruskal Wallis test. Categorical variables were compared using the Chi-Square test or Fisher's exact test. A p-value < 0.05 was considered significant. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Analyses were conducted using IBM SPSS STATISTICS (version 22.0).

There was no statistically significant difference observed in the patients of the three groups with respect to Age, Sex Distribution, Weight and ASA Physical Status.

There was a significantly reduced Anxiety Score (p-value < 0.001) observed in the study groups compared to the control group. Post-hoc test showed no difference between the two study groups.

Induction dose of Propofol (mg/kg) was found to be significantly reduced (p-value 0.001) in the study groups compared to the control group. Post-hoc test showed no difference between the two study groups.

Heart rate was found to be significantly lower at all time points, namely baseline, post-induction, post-intubation

Table 1: Demographics

Demographics	Control group	Melatonin group	Gabapentin group	p- value
Age	38.90 ± 13.11	40.60 ± 14.39	42.00 ± 11.08	0.751
Sex (M: F)	10 : 10	12 : 8	10 : 10	0.765
weight	62.20 ± 12.16	61.75 ± 13.56	56.70 ± 11.72	0.311
ASA Status (I : II)	12 : 8	9 : 11	10 : 10	0.627

Table 2: Anxiety score and induction dose of propofol

	Control Group	Melatonin Group	Gabapentin Group	p- value
Anxiety Score	4.85 ± 1.04	3.15 ± 1.27	3.20 ± 0.95	<0.001
P1		<0.001	<0.001	
P2			0.842	
Induction dose of propofol (mg/kg)	2.20 ± 0.19	1.96 ± 0.20	1.99 ± 0.17	0.001
P1		0.001	0.003	
P2			0.625	

P1: p- value of post-hoc test when compared with control

P2: p- value of post-hoc test between study groups

Table 3: Heart rate

Heart rate	Control Group	Melatonin Group	Gabapentin Group	p- value
Base-line	98.95 ± 17.99	79.10 ± 7.64	86.60 ± 8.6	<0.001
P1		0.000	0.008	
P2			0.179	
Post-induction	84.35 ± 17.895	69.85 ± 4.45	78.45 ± 8.64	0.001
P1		0.001	0.354	
P2			0.073	
Post-intub. 1min	109.70 ± 11.97	75.25 ± 7.59	92.60 ± 14.43	<0.001
P1		0.000	0.000	
P2			0.000	
2min	101.7 ± 11.86	74.10 ± 6.95	90.35 ± 13.67	<0.001
P1		0.000	0.007	
P2			0.000	
3min	98.45 ± 12.83	72.95 ± 6.59	88.70 ± 13.27	<0.001
P1		0.000	0.026	
P2			0.000	
4min	95.00 ± 12.89	72.65 ± 6.42	86.65 ± 12.27	<0.001
P1		0.000	0.057	
P2			0.000	
5min	91.75 ± 12.55	72.7 ± 5.32	85.15 ± 11.28	<0.001
P1		0.000	0.137	
P2			0.001	
10min	87.45 ± 11.79	74.00 ± 5.22	83.65 ± 11.22	<0.001
P1		0.000	0.686	
P2			0.009	
15min	85.25 ± 11.19	74.35 ± 5.01	83.90 ± 11.06	0.001
P1		0.002	1.00	
P2			0.007	

P1: p- value of post-hoc test when compared with control

P2: p- value of post-hoc test between study groups

Table 4: Systolic blood pressure

Systolic BP	Control Group	Melatonin Group	Gabapentin Group	p- value
Base-line	131.2 ± 15.33	131.2 ± 11.33	130.1 ± 13.13	0.96
Post-induction	106.6 ± 16.32	106.2 ± 13.76	107.6 ± 13.28	0.948
Post-intub. 1min	147.2 ± 20.27	130.6 ± 11.66	135.2 ± 10.41	0.0023
P1		0.002	0.038	
P2			0.99	
2min	135.2 ± 14.73	123.3 ± 10.49	130.3 ± 10.55	0.0023
		0.008	0.615	
			0.217	
3min	129.9 ± 10.21	121.1 ± 9.57	125.9 ± 12.03	0.038
P1		0.033	0.703	
P2			0.479	
4min	125.1 ± 9.47	117.5 ± 8.41	121.0 ± 10.71	0.048
P1		0.043	0.528	
P2			0.758	
5min	117.8 ± 10.42	122.9 ± 8.77	116.8 ± 8.90	0.098
10min	123.0 ± 7.20	113.7 ± 9.89	114.4 ± 10.78	0.004
P1		0.009	0.016	
P2			1.000	
15min	122.9 ± 7.74	114.1 ± 10.57	114.6 ± 12.14	0.014
P1		0.028	0.041	
P2			1.000	

P1: p- value of post-hoc test when compared with control

P2: p- value of post-hoc test between study groups

Table 5: Diastolic blood pressure

Diastolic BP	Control Group	Melatonin Group	Gabapentin Group	p- value
Base-line	82.10 ± 10.37	84.05 ± 10.33	79.80 ± 13.125	0.500
Post-induction	71.50 ± 11.22	73.50 ± 11.91	68.00 ± 13.27	0.358
Post-intub. 1min	93.30 ± 13.67	81.05 ± 9.04	82.30 ± 13.31	0.004
P1		0.007	0.018	
P2			1.000	
2min	87.80 ± 12.60	79.60 ± 8.55	79.80 ± 13.56	0.050
P1		0.095	0.108	
P2			1.000	
3min	84.25 ± 11.49	78.85 ± 8.13	78.10 ± 13.01	0.168
4min	81.40 ± 10.35	78.10 ± 8.57	76.80 ± 12.23	0.367
5min	79.45 ± 10.66	77.95 ± 8.99	76.15 ± 11.04	0.599
10min	79.15 ± 9.57	78.0 ± 8.20	76.4 ± 10.62	0.669
15min	78.05 ± 9.69	78.10 ± 7.42	75.25 ± 10.48	0.544

P1: p- value of post-hoc test when compared with control

P2: p- value of post-hoc test between study groups

1min, 2min, 3min, 4min, 5min, 10min and 15min in the study groups as compared to the control group. Also, post-hoc test showed that patients in the Melatonin group had lower heart rates than the Gabapentin group at all time points after intubation.

The baseline and post-induction Systolic Blood Pressures were comparable in the three groups. The study groups were found to have significantly lower Systolic Blood Pressures at 1, 2, 3, 4, 10 and 15 min after intubation. Post- hoc test did not show any difference between the two study groups.

Diastolic Blood Pressure was comparable in the three groups at Base-line and post-induction. At 1 min and 2 min post-intubation, there was a significantly lower Diastolic Blood Pressure in the study groups. There was, however, no difference between the two study groups.

The three groups had comparable Mean Blood Pressures at Base-line and post-induction. At 1 min and 2 min post-intubation, there was a significantly lower Mean Blood Pressure in the study groups. There was, however, no difference between the two study groups.

Table 6: Mean blood pressure

Mean BP	Control Group	Melatonin Group	Gabapentin Group	p- value
Base-line	98.5 ± 10.13	97.6 ± 12.53	97.3 ± 11.16	0.946
Post-induction	83.0 ± 11.61	86.7 ± 10.22	82.4 ± 11.6	0.425
Post-intub. 1min	109.5 ± 15.48	96.9 ± 15.04	99.4 ± 10.89	0.015
P1		0.019	0.078	
P2			1.000	
2min	101.9 ± 11.05	94.8 ± 6.91	94.5 ± 10.95	0.0315
P1		0.075	0.059	
P2			1.000	
3min	97.1 ± 9.97	95.5 ± 8.50	92.9 ± 10.71	0.387
4min	94.0 ± 10.28	94.5 ± 7.76	91.6 ± 10.18	0.600
5min	92.6 ± 8.74	94.1 ± 7.69	90.5 ± 9.49	0.425
10min	90.6 ± 8.84	93.6 ± 6.87	89.5 ± 9.01	0.279
15min	89.7 ± 8.15	93.6 ± 6.25	88.5 ± 8.35	0.095

P1: p- value of post-hoc test when compared with control

P2: p- value of post-hoc test between study groups

4. Discussion

Fassoulaki et al³ studied the effect of gabapentin premedication on the pressor response to direct laryngoscopy and tracheal intubation. Gabapentin in the dose of 1600 mg at 6 hourly intervals starting the day (noon) before surgery was found to attenuate the pressor response but not the tachycardia associated with laryngoscopy and tracheal intubation. In our study, Gabapentin attenuated both the tachycardia as well as the hypertension associated with laryngoscopy and tracheal intubation.

Memis et al⁴ compared the effects of gabapentin on arterial pressure and heart rate at induction of anaesthesia and tracheal intubation in a randomized double-blind study. They concluded that given 1 h before operation, gabapentin 800 mg blunted the arterial pressure and heart rate increase due to endotracheal intubation. These results are consistent with those of our study. In our study, the reduction in heart rate was found to be more significant with both melatonin and gabapentin pre-medication.

Gupta et al⁷ studied the role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. Melatonin in the dose of 6mg given 120min before surgery was found to be an effective drug for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation. These results are consistent with those of our study.

Mohamed et al⁸ studied the effects of melatonin premedication on the hemodynamic responses and perfusion index during laryngoscopy and endotracheal intubation. Melatonin in the dose of 6mg or 9mg given 1 hr before surgery was found to significantly decrease the hemodynamic parameters and perfusion index in response to direct laryngoscopy and endotracheal intubation. In this study, patients receiving melatonin were also found to have lower preoperative anxiety scores. These results are

consistent with those of our study where we have found significantly reduced pre-operative VAS anxiety scores in patients receiving melatonin or gabapentin, when compared to placebo.

In a study done by Turkistani et al,⁹ melatonin premedication, in an oral dose of either 3 or 5 mg, reduced the required dose of propofol to achieve a BIS score of 45, reflecting a sufficient level of hypnosis for tracheal intubation without prolongation of postoperative recovery room stay. In our study, the induction dose of propofol was found to be significantly reduced in patients receiving both melatonin and gabapentin.

5. Source of Funding

None.

6. Conflict of Interest

None.

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