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EFFECT OF GABAPENTIN ON ATTENUATION OF HEMODYNAMIC REPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION UNDER BIS CONTROLLED ANAESTHESIA: A PLACEBO CONTROLLED PROSPECTIVE RANDOMIZED CONTROLLED STUDY

Anaesthesiology

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ABSTRACT

Background and Aims: Laryngoscopy and intubation cause sympathetic stimulation and arousal reactions. We evaluated the role of gabapentin on hemodynamic responses to laryngoscopy and intubation as compared to placebo, when depth of anaesthesia was maintained at a constant bispectral index (BIS) range 40-50 (±5). **Methods:** Sixty patients were randomised to receive either gabapentin (Group G), or multivitamin tablet (Group P) orally 120 min before induction of anaesthesia in a double blind manner. After achieving BIS 40–50 (±5), laryngoscopy and intubation were performed. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded pre-drug, after premedication, after induction, and at 1,3,5 and 10 min following intubation. Statistical analysis was done using Chi-square test and t-test. Results: HR remained elevated than baseline till 10 min after intubation in both groups. Blood pressure rise was seen only at one minute after intubation which was insignificant in gabapentin group and then became lower than baseline in both groups till 10 min after intubation. Difference in BP in both groups was statistically significant ($p<0.05$) till 5 min after intubation and not significant at 10 min ($p>0.05$). **Conclusion:** Gabapentin is safe and effective method for attenuation of blood pressure in response to direct laryngoscopy and endotracheal intubation. Gabapentin does not attenuate heart rate.

KEYWORDS

Gabapentin, Bi-spectral index, hemodynamic response, laryngoscopy, tracheal intubation

INTRODUCTION

Laryngoscopy and intubation, being noxious stimuli, incite remarkable sympathetic activity. The pressor response, represented by an abrupt rise in the arterial blood pressure and heart rate (HR), arising 30s after laryngoscopy and intubation, returns to baseline values steadily within 5–10 min.[1] These transitory responses usually produce no consequences in healthy individuals but may be harmful to the patients having reactive airways, hypertension, coronary artery disease, myocardial insufficiency and cerebrovascular diseases.[2]

Common factors precipitating the pressor response to laryngoscopy and intubation are light planes of anaesthesia, prolonged time for the procedure, anatomically difficult view, greater force used to displace the tongue and more manipulations/attempts at laryngoscopy and intubation.[3] Several drugs and manoeuvres have been used for mitigating this stress response with variable benefits and side effects.[4]

Gabapentin (1-aminomethyl cyclohexane acetic acid), a structural analogue of gamma amino butyric acid and an anticonvulsant drug, is also used in the treatment of neuropathic pain. It inhibits the membrane voltage gated calcium channels[5], just like calcium channel blockers and may be due to its inhibitory action it is helpful in attenuating the cardiovascular responses to tracheal intubation[6],[7]. Other proposed mechanism is by decreasing the neurotransmitter glutamate.

Laryngoscopy and intubation can cause sympathetic stimulation and arousal reactions. We therefore designed this study to evaluate the attenuation of this pressor response by gabapentin as compared to placebo, when the depth of anaesthesia was maintained at bi-spectral index (BIS) range 40–50 (±5) in all the patients.

METHODS

After approval from the Institutional Ethical Committee, the present study enrolled 60 patients of American Society of Anesthesiologists (ASA) physical status I and II, aged 18–60 years, of either sex, scheduled for elective surgery under general anaesthesia using induction with propofol and maintenance with atracurium and isoflurane. The exclusion criteria were refusal of consent; patients having history of treatment with gabapentin; psychiatric patients; patients having chronic pain complaint; hepatic, renal or cardiovascular dysfunction; uncontrolled hypertension; epilepsy; pregnancy; anticipated difficult airway; anticipated major blood losses and fluid shift; patients on sedatives and drug allergies.

Pre-anaesthetic evaluation and relevant investigations were carried out in all patients. Informed written consent was obtained and patients were fasted for 6 h.

Sixty patients were divided into 2 groups of 30 patients in each group to receive either gabapentin 800mg (Group G) or multivitamin capsule/placebo (Group P). One person with randomization chart gave the drug to the patient on a particular day 120 min before induction. Laryngoscopy, intubation and monitoring of vitals were done by another person who was blinded to the drug used in each group.

In preoperative room, the study drug was administered with a sip of water 120 mins before surgery. Continuous monitoring of pulse rate, respiratory rate, blood pressure and arterial oxygen saturation was done in the preoperative period and recorded at an interval of 5 mins by a nurse posted in preoperative room.

In operation theatre, routine monitoring was done which included Heart Rate, Electrocardiogram (ECG), SpO2, Non Invasive Blood Pressure (NIBP), EtCO2 and Bispectral Index monitoring (BIS).

Inj. Glycopyrrolate 0.004mg/kg, inj. midazolam 0.05mg/kg, Inj. fentanyl 1 µg/kg were administered as premedication. 100% oxygen was administered to all patients for 3 mins before induction. Induction was done with Inj. propofol iv titrated to achieve BIS value in range of 40-45 (±5). Inj. succinylcholine 1mg/kg was given to facilitate endotracheal intubation with proper size cuffed endotracheal tube by same person each time.

Anaesthesia was maintained with 60 % N2O in oxygen and isoflurane 0.5-1 MAC. Muscle relaxation was achieved with atracurium 0.5mg/kg iv as loading dose and 0.1mg/kg as maintenance doses. Mechanical ventilation was adjusted to normocapnia (EtCO2 values of 35-38 mm of Hg). BIS was adjusted to maintain a value between 40-45 (±5). Surgical procedure was started after 10 minutes of intubation i.e. after recording of all readings. After completion of surgery, Inj. neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01mg/kg were administered to reverse the residual neuromuscular blockade.

Haemodynamic parameters like Heart Rate, Systolic, Diastolic and Mean Blood Pressures were recorded before administration of study drug (baseline), after premedication, immediately after induction, and at 1, 3, 5 and 10 min following intubation.

After operation, the patients were monitored in recovery room for 1 hour, and then in post operative ward for next 24 hours. Complications like nausea, vomiting, bradycardia, hypotension, hypertension, respiratory depression, allergic reaction, sedation, restlessness if any, were also recorded.

The primary outcome of interest were changes in BP and HR from baseline, at intubation and upto 10 min after intubation. Secondary outcome were minimal complications in intraoperative and postoperative period.

Sample size was calculated at 80% study power and alpha error of 0.05 assuming a standard deviation of 6.5 mmHg in systolic blood pressure after 2 h of 800 mg gabapentin per oral administration as per results of pilot study conducted before this study on ten patients. For difference of 5 mmHg to be detected in mean systolic blood pressures between the groups, 28 patients in each group were required as sample size. It was further enhanced and rounded off to thirty patients in each group as the final sample size for the present study.

Data was expressed as mean value ± standard deviation (SD). Quantitative data was analysed using t-test and qualitative by chi square test. Statistical calculations were carried out using Microsoft Office Excel 2010 and Graph Pad Prism 6.05 (quickcale) Software (Graph pad software Inc. La Jalla CA USA). Changes in haemodynamic variables from baseline and a comparison of means were analysed by unpaired t-test for each time interval. A P-value < 0.05 was considered statistically significant. P value < 0.001 was considered highly significant. P value > 0.05 was considered not-significant.

RESULTS

Both the study groups were identical in terms of age, gender distribution, weight and ASA status [Table 1].

Table 1: Demographics

Variable	Group G	Group P	P value
Age(years),mean± SD	33.03±9.36	30.23±9.16	0.246#
Weight (kg),mean±SD	59.13±9.05	59.13±11.92	1.00#
Gender (male/female) (n=30)	20/10	18/12	0.789*
ASA grade (Ⅰ / Ⅱ) (n=30)	17/13	14/16	0.606*

#Unpaired t-test; *Fisher's exact test. n – Number of patients; SD – Standard deviation; ASA – American Society of Anesthesiologists

Difference in hemodynamic parameters at baseline, after premedication and after induction was not statistically significant amongst both groups(P>0.05).

In both groups maximum rise in heart rate was seen after 1 minute of intubation (group G – 99.17±9.51, group P –103.63±12.52) and HR remained elevated above baseline value in both groups till 10 minutes after intubation. Changes in heart rate were not statistically significant between both groups (P>0.05). [Table 2]

Table 2: Heart Rate at various points of time (beats/min)

HEART RATE	G	P	P value
	MEAN ±SD	MEAN±SD	
BASELINE	78.70±10.06	82.63±11.39	0.16
AFTER PREMEDICATION	79.5 ±9.65	82.83±9.40	0.18
AFTER INDUCTION	81.37±10.52	83.6±8.86	0.38
1 MIN AFTER INTUBATION	99.17±9.51	103.63±12.52	0.13
3 MIN AFTER INTUBATION	97.80±8.04	102.53±12.29	0.08
5 MIN AFTER INTUBATION	94.33±9.63	100.43±14.88	0.06
10 MIN AFTER INTUBATION	87.00±8.61	88.27±10.89	0.62

SBP increased from baseline in both gabapentin and placebo group 1 min after intubation and increase was highly significant between both groups and then it decreased and became lower than baseline in both groups till 10 min after intubation. Changes in SBP among both groups were statistically highly significant at 1minute after intubation (P<0.001) and statistically significant at 3, 5 minutes after intubation (P<0.05). Changes in SBP were not statistically significant (P>0.05) at 10 minutes after intubation.[Table3]

Table 3: Systolic Blood Pressure at various points of time (mmHg)

SBP	G	P	P value
	MEAN ±SD	MEAN±SD	
BASELINE	123.83±8.64	128.37±9.60	0.06
AFTER PREMEDICATION	121.80 ±8.71	125.4±9.75	0.14
AFTER INDUCTION	109.97±8.76	109.03±8.50	0.68
1 MIN AFTER INTUBATION	125.90±7.59	137.83±13.39	0.0001
3 MIN AFTER INTUBATION	109.80±7.71	118.63±14.09	0.004
5 MIN AFTER INTUBATION	104.10±7.85	109.60±11.52	0.03
10 MIN AFTER INTUBATION	107.13±8.67	108.2±8.03	0.62

DBP increased at 1 min following intubation when compared to baseline in both groups. Changes in DBP were statistically significant till 5 minutes after intubation (P<0.05) between both groups. Changes in DBP were not statistically significant (P>0.05) in both groups at 10 minutes after intubation.[Table 4] MAP followed same trends.[Table 5]

Table 4: Diastolic Blood Pressure at various points of time (mmHg)

DBP	G	P	P value
	MEAN ±SD	MEAN±SD	
BASELINE	77.93±8.03	81.27±9.49	0.15
AFTER PREMEDICATION	76.53 ±5.18	78.23±11.48	0.46
AFTER INDUCTION	68.90±7.37	67.27±8.73	0.44
1 MIN AFTER INTUBATION	81.33±6.49	87.83±12.48	0.014
3 MIN AFTER INTUBATION	69.83±8.81	75.47±10.95	0.03
5 MIN AFTER INTUBATION	65.13±7.46	69.33±8.62	0.048
10 MIN AFTER INTUBATION	65.70±7.41	65.93±7.70	0.91

Table 5: Mean Blood Pressure at various points of time (mmHg)

DBP	G	P	P value
	MEAN ±SD	MEAN±SD	
BASELINE	97.23±7.64	99.50±10.00	0.33
AFTER PREMEDICATION	95.07±6.32	98.17±10.01	0.16
AFTER INDUCTION	86.00±7.02	83.97±9.03	0.33
1 MIN AFTER INTUBATION	100.5±6.54	108.80±13.27	0.003
3 MIN AFTER INTUBATION	86.93±7.99	93.77±12.03	0.01
5 MIN AFTER INTUBATION	81.90±7.59	86.37±9.14	0.04
10 MIN AFTER INTUBATION	83.50±6.28	84.70±8.35	0.53

BIS value was kept between 40-50(±5) during intubation and till 10 minutes after intubation. BIS value was on higher side of selected range at 1 min after intubation and difference was statistically

significant between both groups. At 3,5,10 minutes post intubation BIS values were statistically not significant between both groups (P>0.05). [Table 6]

Table 6: BIS at various points of time

DBP	G	P	P value
	MEAN ±SD	MEAN±SD	
BASELINE	97.47±0.97	97.57±0.86	0.67
AFTER PREMEDICATION	90.90±1.21	90.87±1.46	0.93
AFTER INDUCTION	40.4±1.92	40.4±1.57	1.00
1 MIN AFTER INTUBATION	50.63±1.13	51.47±1.53	0.018
3 MIN AFTER INTUBATION	43.9±1.27	44.47±1.2	0.08
5 MIN AFTER INTUBATION	40.3±1.37	40.8±1.03	0.11
10 MIN AFTER INTUBATION	42.33±4.30	43.37±3.37	0.30

Table 7: COMPLICATIONS

	G	P
INTRAOPERATIVE		
Bradycardia	--	--
Hypotension	1	1
Arrhythmia	--	--
Bronchospasm	--	--
POSTOPERATIVE		
Bradycardia / Tachycardia	--	--
Hypotension / Hypertension	--	--
Arrhythmia	--	--
Respiratory depression	--	--
Restlessness	--	--
Bronchospasm	--	--
Nausea / vomiting	1	1

Hypotension was observed in 1 patient in each group, it was treated with IV fluid and Inj. Phenylephrine 50µg bolus. Post-op nausea, vomiting was observed in 1 patient in each group and it was treated with inj. Ondansetron 4 mg i.v. No significant side effects, such as intraoperative bradycardia, arrhythmias, bronchospasm, or postoperative respiratory depression, bronchospasm, bradycardia/tachycardia, arrhythmias or any other side effects were noted in any of the groups.[Table 7]

DISCUSSION

Laryngoscopy and intubation are known to cause an increase in HR and blood pressure.[1,3,8] In the present study, the effect of oral gabapentin on the hemodynamic responses was compared to oral multivitamin group (placebo) after achieving an adequate depth of anaesthesia, that is BIS value 40–50 (±5). In our pilot study, we observed that BIS levels of 40–50 provided better conditions for laryngoscopy than BIS 40–60. Since laryngoscopy and endotracheal intubation, similar to any other peripheral noxious stimulus, might produce a reflex response in the reticular activating system of brainstem, it can lead to wakefulness, making the planes of anaesthesia lighter.[9] Hence, maintaining the BIS values at 40–50 during the induction of anaesthesia may decrease such responses.

Gabapentin has been used to attenuate the pressor response to laryngoscopy and intubation, mechanism of which is not fully known. One of the proposed mechanisms is by inhibition of membrane voltage gated calcium channels, thus acting in a manner similar to calcium channel blockers. Other is by decreasing the synthesis of neurotransmitter glutamate. A.Fassoulaki & colleague(2006)[6] found that oral gabapentin used as premedication attenuate the hemodynamic response to laryngoscopy & intubation. Memiş and colleagues (2006)[7] showed that oral administration of gabapentin 800 mg but not 400 mg given 1 h before operation blunted the arterial pressure and HR increase in the first 10 min after endotracheal intubation.

HR remained elevated above baseline value in both groups till 10 minutes after intubation and maximum rise in HR was seen after 1 minute of intubation. Between both groups, changes in heart rate were not statistically significant after intubation (P>0.05). Thus our study suggested that gabapentin does not attenuate heart rate as compared to placebo. This is supported by A.Fassoulaki & colleague (2006)[6] and Montazeri K et al (2011)[10] in their study. While Serhat Koc and colleague (2007)[11] observed that oral gabapentin 1000 mg given 1 h prior to operation resulted in significant decreases in MAP and HR during study period (p<0.05). This effect was considered to be dose dependent.

SBP increased as compared to baseline in gabapentin and placebo group 1min after intubation but more in placebo group and then it decreased and became lower than baseline in both groups till 10 min after intubation. Changes in SBP were statistically significant till 5 min after intubation (P<0.05) between both groups. Changes were not statistically significant (P>0.05) at 10 minutes after intubation. DBP and MBP followed same trends. Thus our study suggests that gabapentin attenuate SBP, DBP, MBP as compared to placebo till 5 min after intubation. In another study, Kaya et al (2008)[12]reported that gabapentin 800 mg given 2 hours prior to surgery prevented the increase in MAP after tracheal intubation but not the HR. In a recent study comparing 600 mg and 1000 mg doses of gabapentin, Bafna et al (2011)[13] found that gabapentin 1000 mg given before operation significantly attenuated the hemodynamic response to laryngoscopy and intubation, whereas gabapentin 600 mg had no effect. Bala I et al (2015)[14] showed that the pretreatment with gabapentin 800 mg in single or double doses is equally effective in attenuating the hypertensive response associated with laryngoscopy and tracheal intubation in treated hypertensive patients.

BIS value was kept between 40-50(±5) during intubation and till 10 minutes after intubation. BIS value was on higher side of selected range at 1 min after intubation. Difference in both groups was statistically significant at 1 minute after intubation. After that BIS value was comparable in both groups till 10 minutes post intubation. Keeping BIS at lower range, there was a decrease in blood pressure throughout in placebo group also which may actually be desirable in certain surgeries where induced hypotension may be beneficial. BIS monitoring serves the goal of maintaining adequate depth of anaesthesia well and reducing the requirement of i.v. induction agents, volatile agents and analgesics.[15] Since, the BIS values increase with unpleasant stimuli, it can be utilised as an objective marker for quantifying hypnosis that proved advantageous to assess the blunting of the pressor response.[16]

Contrary to other studies, here the pressor responses have been assessed using BIS, whereas, in the past obtunding of pressor responses with various drugs was studied without confirming adequacy of depth of anaesthesia. BIS monitoring during laryngoscopy and intubation should be made a part of healthcare policy, since it not only produces stable condition but also reduces the cost of drugs to obtund pressor responses. In future, research can be planned on evaluating the pressor responses with or without BIS monitoring. Further, the impact of BIS on haemodynamic variability during laryngoscopy and intubation can be compared between different BIS ranges of 40–50 and 50–60.

Gabapentin is well tolerated with a favourable side-effect profile. There were no significant side effects noted. Advantages of using gabapentin is easy administration and availability at low price. Limitations of our study are that we did not compare different doses of gabapentin and their effects at different time intervals of administration, we did not assess sedation and anxiety scores and post op pain score, we did not assess extubation responses, we did not measure plasma catecholamines levels.

CONCLUSION

Gabapentin 800mg, given 120 minutes prior to laryngoscopy and intubation is safe and effective method in attenuating the blood pressure response to direct laryngoscopy and endotracheal intubation. Gabapentin does not attenuate heart rate.

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