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Original Article

Oral Gabapentin Pretreatment to Attenuate the Haemodynamic Response to Laryngoscopy and Tracheal Intubation

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ABSTRACT

Introduction: Laryngoscopy and intubation are associated with transient sympathetic responses manifesting as a rise in blood pressure and heart rate. This study was conducted to evaluate the role of oral gabapentin pretreatment in the attenuation of such haemodynamic response.

Materials and Methods: Sixty-two patients aged 16 to 60 years weighing 50 to 75 kg undergoing elective surgeries requiring endotracheal intubation were randomized into two groups. Group G received 900 mg oral gabapentin and group P received a placebo by mouth two hours before induction of anaesthesia. Patients were induced with propofol, fentanyl, and vecuronium. Laryngoscopy was attempted after four minutes and endotracheal intubation was done. Heart rate, systolic, diastolic, and mean arterial pressure at baseline, before intubation, one, three, five, and ten minutes after intubation were compared between two groups. Patients were observed for any adverse events peri-operatively and post-operatively for the first 24 hours.

Results: There was significant attenuation of the rise in blood pressure and heart rate before and after intubation in both groups compared with their corresponding baseline parameters. A significant decrease in heart rate was observed in the gabapentin group only 10 minutes after laryngoscopy and intubation (p=0.022).

Conclusions: Oral gabapentin 900 mg two hours before induction is effective in attenuating the rise in blood pressure and heart rate following laryngoscopy and tracheal intubation, though a statistically significant difference was observed only at 10 minutes after intubation, compared with a placebo group. Besides the significant incidence of pre-induction somnolence, there were no serious perioperative adverse effects.

Keywords: Blood pressure; gabapentin; Heart rate; Intubation; Laryngoscopy

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INTRODUCTION

Laryngoscopy and tracheal intubation are frequently associated with a rise in blood pressure, an increase in heart rate, and dysrhythmia.[1] The cardiovascular response typically begins within five seconds after laryngoscopy, peaks in one to two minutes, and returns to control levels within five minutes.[2] These may result in a variety of complications like myocardial ischemia. It may be well tolerated in healthy adult patients but can result in catastrophe increasing the risk of morbidity and mortality in patients with cardiac disease.[3]

Laryngoscopy and endotracheal intubation also stimulate the central nervous system which is shown by increases in electroencephalographic activity, cerebral metabolic oxygen demand, and cerebral blood flow.[4] The response of the respiratory system to laryngoscopy and intubation may be manifested as activation of the upper airway reflexes leading to laryngospasm, coughing, and bronchospasm.[5]

Deepening anaesthesia can help attenuate these haemodynamic responses.[6] Different drugs like lignocaine, opioids, beta-blockers, calcium channel blockers, vasodilators, dexmedetomidine, and clonidine have been used for the same. [7-16]

Gabapentin is a structural analogue of GABA. It was originally synthesized in the 1970s in Germany, at a pharmaceutical company, Goedecke AG, and was approved by the FDA in 1993 as an antiepileptic drug.[17, 18] This amino acid binds to the $\alpha^{2\text{-}\delta}$ subunit of presynaptic calcium channels and inhibits calcium influx. Subsequent inhibition of smooth muscle contraction might explain the effectiveness in attenuation of a pressor response.[18]

Recently, it has been used to attenuate haemodynamic response to laryngoscopy and tracheal intubation.[19] Thus, we found it worthy of evaluation if gabapentin lessened changes in blood pressure and heart rate following laryngoscopy and intubation.

MATERIALS AND METHODS

This was a prospective double-blinded, randomized study conducted at Kathmandu Medical College Teaching Hospital. Following approval of the study protocol by the Institutional Review Committee of the hospital, a total of 62 patients planned for elective surgeries under general anaesthesia, were enrolled. The sample size was calculated based on the formula:

$\mathbf{N= 2\ [(Z_{1-\alpha/2} + Z_{1-\beta})\ /E]^2}$, where, N = sample size in each group, Z = Z-score, α = level of significance, β = beta error, E = effect size.

The patients were explained about the study and written consent was obtained.

A pre-anaesthetic evaluation was done a day before surgery. Patients of the American Society of Anesthesiologists (ASA) physical status-I were chosen. The patients were allowed to take solid food for 8 hours and clear liquids 2 hours prior to the surgery.

Patients' heart rate (HR) and systolic, diastolic, and mean arterial pressure (SBP, DBP, MAP) were monitored preoperatively. If they developed bradycardia (HR < 50 bpm) and hypotension (BP < 80/60 mmHg), they were excluded.

Simple random sampling was used to allocate the patients into two groups of 31 each. Group G received three gabapentin capsules of 300 mg each. Group P received an oral placebo in the form of three sugar-filled capsules (prepared after meticulous emptying of gabapentin capsules). The drug was given per-oral 2 hours before the induction of anaesthesia. Patients were assessed half hourly for any adverse effects (bradycardia, hypotension, nausea, vomiting, dizziness, headache, somnolence).

On arrival at the operation room, patients' identification was confirmed. Baseline vital parameters: SBP, DBP, MAP, HR, and arterial oxygen saturation (SpO_2) were recorded.

After preoxygenation for three minutes with 100% Oxygen, anaesthesia was induced with fentanyl 2 mcg/kg and propofol in a titrated dose (till eyelash reflex was lost) followed by vecuronium 0.1 mg/kg (muscle relaxant) and inhaled 1% isoflurane in 100% Oxygen. Patients' lungs were manually ventilated with 100% oxygen. After an interval of 4 minutes, direct laryngoscopy was performed using a Macintosh 3 laryngoscope blade and tracheal intubation was accomplished with a cuffed endotracheal tube of 7.0 mm or 7.5 mm internal diameter. The duration of laryngoscopy and intubation was limited to the minimum possible time in all the patients. Patients with a duration of laryngoscopy and intubation > 15 seconds were excluded. After tracheal intubation, the patients' lungs were mechanically ventilated with a tidal volume of 6 ml/ kg and positive end-expiratory pressure of 5 cmH_2O, and the respiratory rate was adjusted to maintain an end-tidal carbon dioxide of 30 to 35 mmHg. The maintenance of anaesthesia was done with isoflurane in 3L/min Oxygen. Muscle relaxation was maintained with vecuronium.

The readings of SBP, DBP, MAP and HR were again noted before intubation and one, three, five, and ten minutes after intubation.

Acetaminophen 1 gm was administered after 10 minutes of intubation to all the patients to supplement analgesia. Additional intraoperative analgesic supplementation, which was judged by increased heart rate during the surgery, was done with ketorolac 30 mg.

At the end of the operation, ondansetron 0.15 mg/kg was administered for prophylaxis against nausea and vomiting. Residual neuromuscular block was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. The patients were extubated once the respiratory efforts were adequate and shifted to post anaesthetic care unit after being fully awake.

Data were collected as per the specified proforma. Data entry and analysis were done with IBM's SPSS Statistics for Windows (version 26, 2019). Paired sample t-test was used for comparison of data amongst the same group. Inter-group comparison between gabapentin and the placebo group was done using an independent sample t-test. A p-value of less than 0.05 was considered statistically significant. The Chi-square test was applied for comparing qualitative variables between the groups.

RESULTS

Out of 62 patients enrolled in the study, one in each group was excluded as they required more than one attempt at intubation. Sixty patients, therefore, with 30 in each group were included for the final analysis.

In the gabapentin group, there was a significant decrease in SBP before intubation and one, three, and five minutes after intubation when compared to the baseline value, as shown in table 1.

Table 1: Comparison of different parameters in two groups

Haemodynamic parameter	Time	Group G	Group P	p-value
SBP Mean ± SD mmHg	Baseline	124.13 ± 14.58	129.80 ± 14.06	0.131
	Pre-intubation	107.63 ± 14.49	111.70 ± 18.97	0.355
	1 min after intubation	111.53 ± 17.84	111.97 ± 20.91	0.931
	3 min after intubation	102.13 ± 8.93	103.40 ± 14.09	0.302
	5 min after intubation	104.33 ± 11.68	111.13 ± 18.64	0.096
	10 min after intubation	120.17 ± 15.36	116.80 ± 18.06	0.440
DBP Mean ± SD mmHg	Baseline	78.00 ± 11.08	84.13 ± 10.61	0.033*
	Pre-intubation	65.17 ± 15.23	70.07 ± 13.82	0.197
	1 min after intubation	67.50 ± 14.78	69.93 ± 14.57	0.523
	3 min after intubation	60.80 ± 8.079	63.03 ± 13.36	0.437
	5 min after intubation	65.53 ± 11.46	69.90 ± 15.03	0.211
	10 min after intubation	77.23 ± 12.33	75.57 ± 13.55	0.620
MAP Mean ± SD mmHg	Baseline	91.63 ± 11.77	98.57 ± 10.94	0.021*
	Pre-intubation	78.80 ± 14.16	83.87 ± 14.89	0.182
	1 min after intubation	81.27 ± 15.99	84.13 ± 16.42	0.496
	3 min after intubation	73.67 ± 7.38	76.17 ± 14.61	0.406
	5 min after intubation	76.80 ± 10.71	83.23 ± 16.14	0.074
	10 min after intubation	90.17 ± 13.38	89.27 ± 15.48	0.810
HR Mean ± SD bpm	Baseline	87.37 ± 16.29	88.17 ± 17.24	0.854
	Pre-intubation	81.17 ± 13.48	81.57 ± 14.27	0.912
	1 min after intubation	84.23 ± 16.07	84.77 ± 16.05	0.898
	3 min after intubation	80.60 ± 12.87	78.13 ± 15.18	0.500
	5 min after intubation	79.87 ± 13.87	79.13 ± 13.63	0.837
	10 min after intubation	78.90 ± 14.56	88.23 ± 16.04	0.022*

*SBP: Systolic blood pressure, G: Gabapentin, P: Placebo, SD: Standard deviation, *: Statistically significant*

The DBP and MAP also decreased significantly before intubation and one, three and five minutes after intubation compared to the baseline. There was a significant decrease in HR before intubation and three and five minutes after intubation compared to the baseline values in group G.

When compared between the two groups, SBP readings in group G were less as compared to that in group P (but statistically non-significant), as shown in figure 1. DBP in group G was less than that in group P with statistical significance at baseline only, as shown in figure 2.

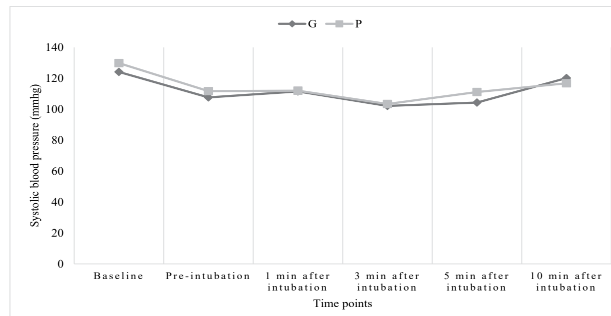

Figure 1: Changes in systolic blood pressure at different time points in two groups (G- Gabapentin, P- Placebo)

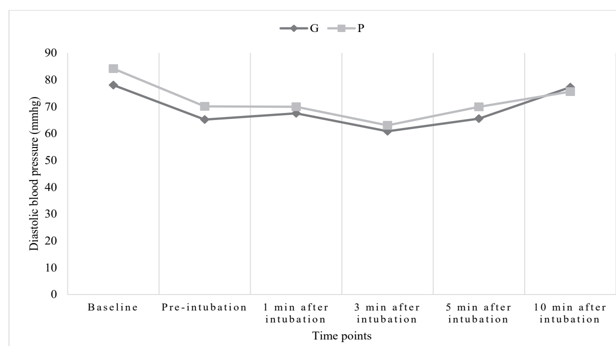

Figure 2: Changes in diastolic blood pressure at different time points in two groups (G- Gabapentin, P- Placebo)

MAP in group G was less than that in group P with statistical significance at baseline only, as shown in figure 3. HR in group G was less compared to group P, with statistical significance, only at 10 minutes after intubation, as shown in figure 4.

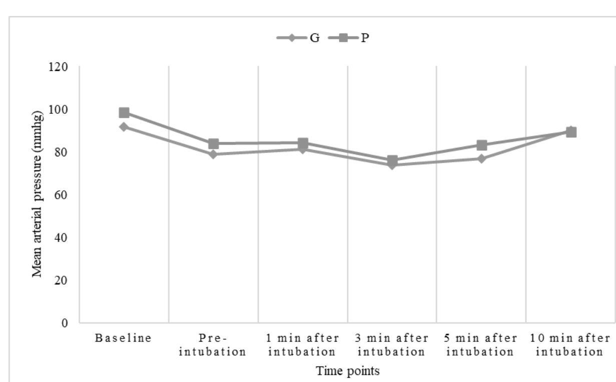

Figure 3: Changes in mean arterial blood pressure at different time points in two groups (G- Gabapentin, P- Placebo)

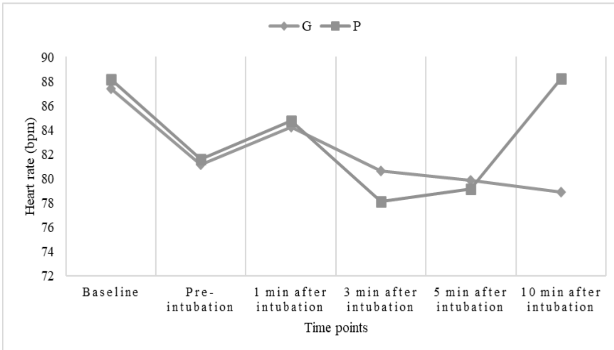

Figure 4: Changes in heart rate at different time points in two groups

The patients in the gabapentin group had a mean age of 34.50 ± 11.20 years while those in the placebo group had a mean age of 40.43 ± 11.08 years. The mean weight of the patients in the gabapentin group was 59 ± 6.77 kg while that of patients in the placebo group was 60.33 ± 7.42 kg. The mean body mass index was 26.03 ± 2.93 kg/m^2 in the gabapentin group and 25.68 ± 2.83 kg/m^2 in the placebo group (Table 2).

Table 2: Demographic characteristics

Variables	Group	N	Mean ± SD	Minimum	Maximum	p-value
Age (years)	G	30	34.50 ± 11.20	16	56	0.044 *
	P	30	40.43 ± 11.08	24	60	
Weight (kg)	G	30	59 ± 6.77	50	75	0.470
	P	30	60.33 ± 7.42	50	73	
Body mass index (kg/m^2)	G	30	26.03 ± 2.93	20.81	33.33	0.643
	P	30	25.68 ± 2.83	21.64	31.53	

*SD: Standard deviation, G: Gabapentin, P: Placebo, *: Statistically significant*

The mean laryngoscopy time was 9.17 ± 2.49 seconds in group G and 9.70 ± 2.03 seconds in group P ($p > 0.05$). Awakening time ranged between 10 and 20 minutes in group G while it ranged between 5 and 20 minutes in group P with a significant difference ($p < 0.05$).

Twenty-nine patients developed somnolence before induction of anaesthesia in the gabapentin group ($p < 0.05$). One patient in group G and four in group P developed bradycardia intra-operatively which was not within 10 minutes of intubation ($p > 0.05$). Two patients in group G also developed hypotension intra-operatively which was not before 10 minutes of intubation ($p > 0.05$). Delayed awakening was observed in none of the patients in the study. No patients developed postoperative nausea and vomiting. Two patients in group G developed dizziness in the post-operative period ($p > 0.05$).

DISCUSSION

Laryngoscopy along with tracheal intubation acts as a noxious stimulus that may provoke a marked sympathetic response in the form of tachycardia, hypertension, and arrhythmia. This can be potentially deleterious in some patients due to which various methods are being used for attenuating this response. Recently, gabapentin was found to be effective for the same.[20] Studies showed that 300-1200 mg oral gabapentin administered 1 hour prior to surgical stimulus significantly reduced pain and postoperative opioid consumption without significant side effects.[21]

In our study, oral gabapentin 900 mg given two hours prior to induction was effective in attenuating the rise in blood pressure and heart rate associated with laryngoscopy and intubation.

When comparing haemodynamic variables within the gabapentin group, there was a significant decrease in SBP just before intubation and one, three, and five minutes after intubation compared to baseline. Similarly, DBP and MAP also decreased significantly before intubation and one, three, and five minutes after intubation compared to the baseline ($p < 0.05$). Furthermore, there was a significant decrease in HR before intubation and three, five, and ten minutes after intubation ($p < 0.05$). Memiş et al. also found that there was a significant decrease in MAP and HR (in patients taking 800 mg gabapentin one hour prior to surgery) one, three, five, and ten minutes after intubation when compared with the baseline levels ($p < 0.05$).[20] This decrease in BP and HR might be elucidated by an indirect effect of gabapentin by reducing pain and anxiety and consequently the accompanying haemodynamic response.

The baseline SBP was comparable between group G and group P. The SBP in group G was lower as compared to group P at baseline, before intubation, one, three, and five minutes after intubation. However, there was no statistically significant difference. The DBP was significantly lower in group G than in group P only at baseline ($p < 0.05$). Fassoulaki et al. observed that SBP was significantly lower in the gabapentin group than in the control group at zero, one, three, five, and ten minutes and DBP at one, and three minutes after intubation.[19] Discrepancy noted in our study compared with theirs can be attributable to the higher dose of gabapentin used in their study (a total of 1600 mg) and higher dose of propofol during induction (2.5 mg/kg).[19]

A comparison of MAP between the two groups in our study showed a significant decrease only at baseline ($p < 0.05$). However, Memiş et al. found a significant decrease in MAP one, three, five, and ten minutes after intubation in the gabapentin group when compared with the control group.[20] This difference between our study and theirs can be attributable to the use of atracurium in their study and vecuronium in our study. ElBaradei S found that atracurium owing to the histamine releasing property caused a fall in MAP, with peak release at one and three minutes of administration of the drug (atracurium 0.5 mg/kg).[21] Kaya et al. also found a significant decrease in MAP in the gabapentin group (800 mg gabapentin given two hours before operation) when compared with the placebo group in the first 10 minutes after intubation.[22]

In our study, there was a significant decrease in HR in group G compared to group P at 10 minutes after intubation ($p < 0.05$). Memiş et al. and Neogi et al. also found a significant decrease in HR after intubation in the gabapentin group when compared with the control group.[20, 23]

When evaluating methods to diminish the cardiovascular response to laryngoscopy and intubation the inducing drugs may influence the results. We used propofol and fentanyl as an inducing agent which could have caused hypotension and bradycardia.

Baseline demographic details compared with gabapentin and placebo group were comparable with respect to weight and body mass index. The mean age of patients in Group G was 34.50 ± 11.20 years and in group, P was 40.43 ± 11.08 years. The reason for including patients up to 60 years of age was that elderly patients exhibit increased sensitivity to drugs and the cardiovascular effects of gabapentin also have not been studied extensively. Serum gabapentin concentrations are found higher in the elderly population than in non-elderly adults who are given the same dose, apparently owing to an aging-related decrease in renal function.[24] There is no significant effect of gender on the metabolism and elimination of gabapentin.[24]

Laryngoscopy and intubation time were kept minimum (<15 seconds) in the study. Arterial pressure and heart rate response were found to be greater when the duration of laryngoscopy and intubation exceeded 30 seconds.[25] In our study, mean laryngoscopy and intubation time were comparable in gabapentin and placebo groups (9.17 ± 2.49 vs 9.70 ± 2.03, $p > 0.05$). This is similar to the finding in the study by Kiran S and Verma D where the mean duration of laryngoscopy and intubation didn't exceed 14 seconds.[25]

Although there were changes in BP and HR in our study, the changes were modest and clinically acceptable. Two patients in group G developed hypotension intra-operatively after the time point of 10 minutes after intubation, which was statistically non-significant when compared with the placebo group ($p > 0.05$). One patient in the gabapentin group and four in the placebo group developed bradycardia. The incidence of hypotension and bradycardia were observed after the time point of 10 minutes after intubation. All the cases that developed hypotension and bradycardia were undergoing laparoscopic cholecystectomy for cholelithiasis. The hypotension might have developed because of increased intra-abdominal pressure during carbon dioxide insufflation.[26] The carbon dioxide insufflation was done after 10 minutes of laryngoscopy and intubation. Furthermore, hypotension might also be because of gabapentin decreasing catecholamine surge following carbon dioxide insufflation. In their study, Shrestha et al. found that gabapentin premedication reduced serum cortisol levels, taken as a stress marker of pneumoperitoneum in laparoscopic cholecystectomy.[27] Bradycardia might have been developed due to vagal-mediated cardiovascular reflex initiated by rapid stretching of the peritoneum after carbon dioxide insufflation.[26] Hypotension was managed with mephentermine 6 mg. Bradycardia was managed with atropine 0.6 mg after stopping carbon dioxide insufflation.

Gabapentin is well tolerated and is free of drug interactions. The adverse effects of gabapentin tend to be CNS related, mild to moderate in severity.[28] A review of adverse events reported by Browne TR among 1748 patients treated in early trials confirmed the good tolerability of this drug.[29] The adverse events seen in that study were somnolence (20.2%), dizziness (17.9%), ataxia (13.2%), fatigue (11.1%), nystagmus (9.3%), headache (8.7%), and tremor (7.2%). Parsons et al. observed that dizziness, somnolence, and peripheral edema were the three most common adverse effects of gabapentin.[30] In our study, 29 patients in the gabapentin group developed somnolence before induction of anaesthesia. Two patients in the gabapentin group developed dizziness in the PACU. None of the patients in the study developed nausea and vomiting and peripheral edema. Overall, there was no severe cardiovascular compromise requiring resuscitation, intensive care unit admission, and mortality in the patients in our study.

CONCLUSIONS

Oral administration of a single dose of 900 mg gabapentin premedication two hours prior to induction of anaesthesia helps attenuate the increase in blood pressure and heart rate following direct laryngoscopy and endotracheal intubation. However, in our study, there is no adequate attenuation of haemodynamic response to laryngoscopy and tracheal intubation with oral gabapentin as compared to a placebo. Besides the significant increase in the frequency of pre-induction somnolence, gabapentin at 900 mg dose has no serious perioperative adverse effects.

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