Evaluation of gabapentin in attenuating pressor response to direct laryngoscopy and tracheal intubation

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ABSTRACT

Background: To evaluate effect of gabapentin in attenuation of haemodynamic responses to direct laryngoscopy and tracheal intubation.

Methods: Hundred patients undergoing elective surgery were randomly allocated to two groups of 50 patients each. Patients in group A received gabapentin 800 mg and patients in group B received placebo capsules the night before and on the morning of surgery. Anaesthesia was induced with propofol and vecuronium. Systolic, diastolic, mean arterial blood pressures (SAP, DAP, MAP) and heart rate (HR) were recorded before and after the induction of anesthesia and 0, 1, 3, 5 and 10 min after tracheal intubation.

Results: SAP was significantly lower in the gabapentin as compared to the control group 0, 1, 3, 5 and 10 min after intubation [121 vs 135 (P<0.001), 117 vs 132 (P<0.001), 112 vs 124 (P<0.001), 110 vs 118 (P<0.05) and 107 vs 112 (P<0.05) respectively]. DAP also was lower in the gabapentin group 0, 1, 3, and 5 min after intubation [77 vs 87 (P<0.001), 74 vs 84 (P<0.001), 70 vs 78 (P<0.001) and 68 vs 74 (P<0.05)]. MAP also was lower in the gabapentin group 0, 1, 3, and 5 min after intubation [92 vs 103 (P<0.001), 88 vs 100 (P<0.001), 84 vs 93 (P<0.001) and 82 vs 88 (P<0.05)]. HR also was lower in the gabapentin group 0, 1 and 3 min after intubation [90 vs 98 (P<0.05), 88 vs 95 (P<0.001) and 84 vs 90 (P<0.05)].

Conclusion: Gabapentin, under the present study design attenuates the pressor response associated with laryngoscopy and tracheal intubation but tachycardiac response is not completely eliminated.

Introduction

Endotracheal intubation is commonly performed as a part of general anaesthesia technique. This, however, is a noxious stimulus and during light plane of general anaesthesia, direct laryngoscopy and intubation are capable of producing marked circulatory effects characterised by a sudden increase in arterial pressure, increase in heart rate and rhythm.[1] Such transient cardiovascular changes are well tolerated in healthy individuals but are of great concern in susceptible individuals particularly those with systemic hypertension, coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm and recent myocardial infarction. In such patients these transient changes can result in potentially deleterious effects such as myocardial ischaemia (left ventricular failure as a result of increased myocardial oxygen demand) and cerebral haemorrhage.[2,3]

To minimise these potentially harmful responses various methods include laryngoscopy and intubation in a deeper plane of anaesthesia and topical anaesthesia of the upper respiratory tract prior to laryngoscopy with lignocaine.[1,4] Vasodilators like nitroprusside, hydralazine and nitroglycerine have been used to attenuate these responses with varying degree of success.[5-7] Calcium channel blockers, beta blockers and opioids such as alfentanil, fentanyl and remifentanil have also been used in different dosage regimens to control or attenuate hemodynamic responses to laryngoscopy and intubation.[8-12] Each method and drug has variable effectiveness and contradictory results. Moreover, no technique is free of side effects and thus no single method has achieved universal acceptance.

Gabapentin is a relatively new drug. Originally developed as an anticonvulsant, it is effective in controlling neuropathic pain. It has been shown to reverse allodynia and hyperalgesia of many pain models in animal studies.[13] In some randomised controlled trials to treat acute post-operative pain and to reduce post-operative opioid requirements, the authors noticed that some patients receiving gabapentin remained hemodynamically stable.[14] We planned to evaluate gabapentin to attenuate the hypertensive and tachycardiac response to direct laryngoscopy and tracheal intubation in normotensive patients undergoing elective surgery.

Methods

After hospital ethics committee approval a total of 100 patients (20 to 50 years) of either sex belonging to American Society of Anaesthesiologists (ASA) physical status I or II, were allocated randomly to the gabapentin or the placebo group. Patients with a history of hypertension, anticipated difficult intubation, having hiatus hernia or history of gestroesophageal reflux, on dugs which are likely to interfere with cardiovascular variables (e.g. calcium channel blockers and beta-blocker), on antacid therapy preoperatively, obese, pregnant and lactating females were excluded. Group A (n=50) patients received gabapentin 800 mg at 10.00 p.m. the night before surgery and again at 6.00 a.m. on the day of surgery. Group B (n=50) patients received placebo capsules at the same time.

All the patients were premedicated with tablet alprazolam 0.25 mg orally on the night and morning 2 hours before surgery. One hundred opaque coded envelopes bearing serial numbers containing either gabapentin or identical placebo were prepared. Envelope coding and group allocation was done by an anaesthesiologist who was not aware of the study protocol and was not participating in study. The observer was not aware of the drugs given. Upon arrival in the operating room intravenous

access was secured. Monitoring of non invasive blood pressure (NIBP), heart rate, electrocardiogram and arterial oxygen saturation was carried out. A uniform anaesthetic technique was used in both groups. Propofol 2.5 mg/kg and vecuronium bromide 0.1 mg/kg was administered intravenously. Patients were ventilated with 50% N_20 in 50% O_2 and halothane 1 % for three minutes after which laryngoscopy and endotracheal intubation was performed. Then haemodynamic parameters (SAP, DAP, MAP and HR) were recorded just before injecting propofol, just before tracheal intubation, immediately after tracheal intubation and then at 1, 3, 5 and 10 min intervals. Our study ended at this point and surgery was commenced. Maintenance of anaesthesia was carried out using 67% N_20 in 33% 0_2 and halothane 0.5% using controlled ventilation. Intra operative analgesia was provided with 1 mg/kg of pethidine. At the end of surgery residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.1mg/kg intravenously. Data collected was compiled and analysed using chi square test (demographic profile of patients), student't' test and repeated measure ANOVA (hemodynamic parameters).

Results

Demographic profile of the patients in two groups was comparable (Table I).

SAP was significantly lower in gabapentin group as compared with basal values. Inter-group comparisons for each time point showed significantly higher SAPs at 0, 1, 3, 5 and 10 min after tracheal intubation in the control group (P<0.001, P<0.001, P<0.001, P<0.05 and P<0.05, respectively) (Table II).

Table I: Patient characteristic in aach group of patients

	Group A	Group B
Age (yr)	33.34±8.75	34.30±9.06
Body weight(kg)	61.10±8.63	60.26±7.55
Sex (m/f)	24/26	22/28

Table II: Systolic arterial pressure (mmHg) changes compared to basal values at various time intervals (Mean ± SD)

	Gp-A(n=50)			**Gp-B(n=50)**			**P'value (inter group)**
	Mean±S.D.	**'P'value**	**95% C I**	**Mean±S.D.**	**'P'value**	**95% C I**	
Basal T_b	124.54±10.68			120.44±11.74			>0.05**
Just Before Intubation T_{bi}	100.40±10.85	<0.001*	21.8 to 26.4	98.70±10.90	<0.001*	19.6 to 23.8	>0.05**
After intubation							
T_0	121.46±10.27	>0.05*	0.91to5.25	135.30±11.24	<0.001*	-16.7 to -13.0	<0.001**
T_1	117.02±8.90	<0.001*	5.13to9.91	132.06±11.33	<0.001*	-13.9 to -9.3	<0.001**
T_3	112.72±8.99	<0.001*	9.3 to 14.3	124.38±12.92	<0.001*	-6.2 to-1.6	<0.001**
T_5	110.88±10.71	<0.001*	10.5 to 16.7	118.30±11.72	>0.05*	-0.3 to 4.6	<0.05**
T_{10}	107.80±10.97	<0.001*	13.4 to 20.7	112.12±9.95	<0.001*	6.2 to10.4	<0.05**

*p value as compared to basal. ** p value in between groups
95% C I – 95% confidence interval, T0 - just after intubation, T_1 - one min after intubation, T_3 - three min after intubation, T_5 - five min after intubation, T10 – ten min after intubation

Inter-group comparisons showed significantly higher DAPs immediately and 1, 3 and 5 min after laryngoscopy and tracheal intubation in the control group when compared with the gabapentin treated group (P<0.001, P<0.001, P<0.001 and P<0.05 respectively) (Table III).

Table III: Diastolic arterial pressure (mmHg) changes compared to basal values at various time intervals. (Mean±SD)

	Gp-A(n=50)			**Gp-B(n=50)**			**'P'value (inter group)**
	Mean±S.D.	**'P'value**	**95% C I**	**Mean±S.D.**	**'P'value**	**95% C I**	
Basal T_b	76.78±7.62			74.42±8.78			>0.05**
Before Intubation T_{bi}	62.08±7.31	<0.001*	12.7to16.6	60.74±9.20	<0.001*	11.7 to 15.5	>0.05**
After intubation							
T_0	77.96±9.20	>0.05*	-3.0 to 0.7	87.60±9.68	<0.001*	-14.9 to 11.3	<0.001**
T_1	74.48±8.53	>0.05*	0.3 to 4.2	84.32±9.35	<0.001*	-11.7 to 8.0	<0.001**
T_3	70.66±8.54	<0.001*	3.7 to 8.4	78.38±9.24	<0.001*	-5.7 to - 2.1	<0.001**
T_5	68.66±9.47	<0.001*	5.3 to 10.9	74.20±9.16	>0.05*	-1.6 to 2.1	<0.05**
T_{10}	67.30±9.55	<0.001*	6.7 to 12.2	70.04±10.24	<0.001*	2.9 to 5.8	>0.05**

*p value as compared to basal ** p value in between groups

MAP was significantly lower in gabapentin group as compared with basal values. Inter-group comparisons for each time point showed significantly higher MAPs at 0, 1, 3 and 5 min after tracheal intubation in the control group (P<0.001, P<0.001, P<0.001 and P<0.05, respectively) (Table IV).

Table IV: Mean arterial pressure (mmHg) changes compared to basal values at various time intervals (Mean±SD)

	Gp-A(n=50)			Gp-B(n=50)			'P'value (inter group)
	Mean±S.D.	'P'value	95% C I	Mean±S.D.	'P'value	95% C I	
Basal T_b	92.70±7.84			89.76±8.92			>0.05**
Before Intubation T_{bi}	74.85±7.76	<0.001*	15.9to 19.7	73.39±8.46	<0.001*	14.7 to 17.9	>0.05**
After intubation							
T_0	92.46±8.62	>0.05*	-1.4 to 1.9	103.50±9.27	<0.001*	-15.2 to 12.8	<0.001**
T_1	88.66±7.74	<0.001*	2.1 to 5.9	100.23±8.97	<0.001*	-12.1 to -8.7	<0.001**
T_3	84.68±7.81	<0.001*	5.8 to 10.2	93.71±9.13	<0.001*	-5.6 to -2.2	<0.001**
T_5	82.73±9.22	<0.001*	7.1 to 12.7	88.90±8.74	>0.05*	-0.9 to 2.6	<0.05**
T_{10}	80.80±9.38	<0.001*	9.1 to 14.6	84.06±9.04	<0.001*	4.4 to 6.9	>0.05**

* p value as compared to basal ** p value in between groups
95% CI – 95% confidence interval

Inter-group comparisons for each time point showed significantly higher increase in heart rate in control group at 0, 1 and 3 min after tracheal intubation (Table V).

Table V: Heart rate (beats/min) changes compared to basal values at various time intervals (Mean±SD)

	Gp-A(n=50)			Gp-B(n=50)			'P'value (inter group)
	Mean±S.D.	'P'value	95% C I	Mean±S.D.	P'value	95% C I	
Basal T_b	80.60±11.25			80.98±12.67			>0.05**
Before Intubation T_{bi}	75.64±12.11	<0.001*	3.0 to 6.8	72.98±11.90	<0.001*	6.3 to 9.6	>0.05**
After intubation							
T_0	90.40±11.76	<0.001*	-12 to -7.5	98.30±12.85	<0.001*	-19 to -15.2	<0.05**
T_1	88.081±2.35	<0.001*	-9.7 to -5.2	95.14±13.17	<0.001*	-16.2 to -12	<0.05**
T_3	84.50±11.40	<0.001*	-5.9 to -1.8	90.92±14.02	<0.001*	-12.1 to 7.8	<0.05**
T_5	82.62±11.86	>0.05*	-4.1 to 5.1	85.60±12.82	<0.001*	-6.5 to -2.6	>0.05**
T_{10}	77.92±12.52	<0.05*	0.4 to 4.9	78.68±10.75	<0.05*	0.7 to 3.9	>0.05**

* p value as compared to basal. ** p value in between groups
95% CI – 95% confidence interval

Discussion

Our results show that gabapentin attenuates the pressor response to tracheal intubation as systolic blood pressure, diastolic blood pressure and mean arterial pressure are significantly reduced as compared to base line as well as placebo. The heart rate is not significantly attenuated as compared to baseline value; although mean increase in heart rate occurs less with gabapentin as compared with placebo.

Gabapentin originally introduced as antiepileptic, is effective in neuropathic pain and most recently has been evaluated as analgesic, anti-hyperalgesic, or both perioperatively.[15,16] However, only few data are available regarding the effect of gabapentin on the cardiovascular system. Gabapentin administered intrathecally or intraperitoneally in rats did not significantly change the haemodynamics during the following 60 min when compared with the baseline values.[13] In humans 1200 mg of gabapentin administered 1 hr before surgery had no effect on the mean blood pressure and HR at 0-24 hr after operation.[14] Other studies investigating the analgesic effect of gabapentin after surgery did not assess its effect on the cardiovascular system. Memis et al studied the effect of gabapentin on mean arterial pressure and heart rate at induction of anaesthesia and tracheal intubation.[17] Patients receiving placebo and 400 mg gabapentin showed a significant increase in blood pressure and heart rate associated with tracheal intubation compared to baseline levels and from patients receiving 800 mg of gabapentin. There was a significant decrease in heart rate and mean arterial pressure in the group receiving 800 mg gabapentin 1, 3, 5 and 10 min after intubation compared to the placebo group and 400 mg gabapentin group. In a study done by Fassoulaki et al it was observed that SAP was significantly lower in the gabapentin versus the control group 0, 1, 3, 5 and 10 min after intubation. DAP also was lower in the gabapentin group 0, 1, 3 and 10 min after intubation.[18] Heart rate did not differ between the two groups at any time. Koc et al studied the effect of gabapentin, dexamethasone and their combination in patients undergoing varicocele surgery.[19] They found that heart rate and mean arterial pressure values were significantly lower in the group receiving both gabapentin and dexamethasone at 1, 3, 5 and 10 min after intubation than in the group receiving dexamethasone or gabapentin alone. The MAP and HR in gabapentin group were lower than the placebo group. In our study SBP, DBP, MAP and HR values were significantly low as compared with placebo in patients pretreated with gabapentin. None of the patient exhibited hypotension before induction of anaesthesia.

Our reason for studying patients up to 50 years of age was that elderly patients more often take drugs such as antidepressants, hypnotics and antihypertensives. Older patients also exhibit increased sensitivity to drugs and the cardiovascular effects of gabapentin have not been studied extensively.[20] Separate studies are required to study the effect of gabapentin in older age group patients. We did not use any opioid in our patients during induction. It has been commented that omission of an opioid during induction of anaesthesia in ASA I and II patients should not be a concern.[18]

It has been shown that arterial pressure and heart rate responses are greater when the duration of laryngoscopy exceeds 30 sec.[1] The previous studies which studied the effect of gabapentin to attenuate the haemodynamic responses to laryngoscopy and intubation did not comment upon duration of laryngoscopy and intubation. In our study the mean duration of laryngoscopy and intubation did not exceed 14sec. The anaesthetic agents have an important impact on attenuation of the pressor response to laryngoscopy and intubation. In one study sevoflurane, N_2O and O_2 were used and in another propofol and cis-atracurium were used.[17,18] In another study propofol and remifentanil were used.[19] We used propofol and vecuronium. During sevoflurane and N_2O anaesthesia arterial baroreceptor reflexes seems to be depressed.[21] Although systolic blood pressure decreased immediately following intubation in the gabapentin group, the difference was not statistically significant compared to basal value but the difference was statistically highly significant as compared to the placebo group. The blood pressure continued to fall till 10 min after intubation. These results are similar to the study by Fassoulaki et al.[18] The other two studies however did not comment on SBP; instead they commented on MAP only. In our study although a fall in DBP was observed at 1 min after intubation, the difference was statistically insignificant as compared to basal value. As compared to placebo the difference was statistically highly significant. In our study MAP decreased significantly at various time intervals (till 5 min after intubation) in the gabapentin group as compared to placebo. At 10 min although there was fall in MAP blood pressure but the difference was statistically insignificant as compared to placebo. The results are almost similar to the studies by Memis et al and Koc S et al where the fall in MAP was statistically significant till 10 min after intubation[17,19]; the only difference being the insignificant fall at 10 min in our study.

In our study the heart fell significantly ($p<0.001$) in group-A and group-B before intubation as compared to basal value. This might have been due to the effect of propofol which decreases the heart rate. After intubation no decrease in heart rate was observed until after five minutes in both the groups as compared to basal value. However, in the gabapentin group there was less increase in heart rate as compared to the placebo group, indicating that gabapentin did have some effect on attenuation of heart rate as compared with placebo. These changes, although modest, were clinically acceptable in the gabapentin group. In literature the effect of gabapentin on heart rate is inconsistent. Fassoulki et al in their study did not find attenuation of heart rate in the gabapentin group.[18] In another study examining the effect of a single dose gabapentin 400 mg or 800 mg given 1 hr prior to surgery it was seen that patients receiving 800 mg gabapentin had a significant decrease in heart rate during the first 10 min after endotracheal intubation as compared with gabapentin 400mg and placebo[17] ($p<0.05$). Serhat et al commented that significant attenuation of heart rate can be achieved with a combination of dexamethasone 8 mg intravenously and oral gabapentin 800 mg given 1 hr prior to surgery.[19]

Adjuvant used along with gabapentin may have an important role in attenuation of the pressor response to laryngoscopy and intubation. One study has recently examined the role of preoperative gabapentin, dexamethasone and their combination in varicocele surgery.[19] The study showed that a gabapentin (800mg) and dexamethasone (8mg) combination provides significant decrease in MAP and HR values in the first 10 min after induction of anaesthesia than the single drug gabapentin or dexamethasone. They attributed the smooth muscle relaxation property of dexamethasone for the effectiveness in the suppression of laryngoscopic response. We did not use any adjuvant with gabapentin since we gave the drug in divided doses.

The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. Although the molecular targets of gabapentin remain unknown, the inhibition of Ca^{2+} flux in muscle cells with a consequent inhibition of smooth muscle contraction might explain the effectiveness of gabapentin in attenuation of the pressor response to laryngoscopy. Thus it may act in a manner similar to Ca^{2+} channel blockers.[22]

One limitation of our study was that we did not measure the stress mediators, i.e. endogenous plasma catecholamines or cortisol. This is controversial in available literature. Some authors have linked pressor response to increase in catecholamine levels, whereas Barak et al did not find a correlation between haemodynamic changes and catecholamine levels.[22] We did not measure sedation scores before induction of anaesthesia as this would have interfered with the double blinding of study.

The most frequently reported side effects of gabapentin are somnolence (20%), dizziness (8%), ataxia (13%) and fatigue (11%). Other side effects are nystagmus, headache, tremor, diplopia and nausea, each less than 10%.[23,24] These are also common side effects of commonly used premedication drugs. Ramsay has commented that the severity of side effects of gabapentin is usually of a minor degree.[24] However, none were observed in our patients.

Although various clinical trials have shown the efficacy of gabapentin in various clinical situations the dose-response relationship has not been studied. Gabapentin has been used preoperatively as a single dose as well as in multiple doses in different clinical settings. Regarding attenuation of pressor response to intubation one author has used gabapentin 1600 mg at 6 hourly intervals whereas others have used 400 mg and 800 mg doses.[17,18] We used gabapentin 1600 mg in two divided doses.

In conclusion gabapentin attenuates the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated. Further studies are needed to elucidate the intubation response attenuation effect of gabapentin in hypertensive patients. **SAJAA**

Conflict of interest: Nil

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