Original Article

A comparative study of two different doses of Gabapentin in attenuating the cardiovascular response to direct laryngoscopy and intubation

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Abstract

Introduction: Direct laryngoscopy and endotracheal intubation is an integral part of anaesthesia which offers tremendous safety to administration of general anaesthesia but is associated with hemodynamic changes, due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. **Aims and Objectives:** Tostudy the effect of two different doses of Gabapentin in attenuating the cardiovascular response to direct laryngoscopy and intubation. **Materials and methods:** Prospective, randomized, double blind and placebo controlled clinical study involving90 patients of kidwai memorial institute of oncology,Banglore visiting pre anaesthesia clinic scheduled for elective surgery under GA with ASA I and ASA II was designed after approval from institute ethics committee. Statistical analysis was done by Analysis of variance (ANOVA) to find the significance of study.Student t test (paired) has been used to find the significance within the same group. **Result:** Laryngoscopy and intubation caused a significant increase in heart rate and blood pressure in controlled group. Gabapentin can be used to attenuate pressor response to laryngoscopy and intubation. Gabapentin 800mg and 400mg attenuated the pressor response to laryngoscopy and intubation. SBP, DBP, MAP and HR were all attenuated by Gabapentin in comparison to control group. Gabapentin 800mg is more effective than 400mg for attenuation of pressor response to laryngoscopy and intubation (Statistically significant $p<0.05$) **Conclusion:** SBP, DBP, MAP and HR were all attenuated by Gabapentin in comparison to control group. Gabapentin 800mg is more effective than 400mg for attenuation of pressor response to laryngoscopy and intubation.

Key Words: Gabapentin, cardiovascular response to direct laryngoscopy and intubation.

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INTRODUCTION

Direct laryngoscopy and endotracheal intubation is an integral part of anaesthesia which offers tremendous safety to administration of general anaesthesiabut is associated with hemodynamic changes, due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation[1].This increased sympatho-adrenal activity may result in hypertension, tachycardia and arrhythmias. This increase in blood pressure and heart rate are usually transient, variable and unpredictable.[1,2] Transitory hypertension and tachycardia are probably of no consequence in healthy individuals but either or both may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular diseases[3,4]. The complications resulting from these hemodynamic responses from laryngoscopy and intubation include left ventricular dysfunction, hypertensive crisis, cardiac dysrhythmias, myocardial ischemia and cerebral hemorrhage[3]. Thus, it is a critical event and potential problem in anesthesia and surgery.

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Cautious precautions should be taken to attenuate such responses in critically ill patients.

Several techniques have been proposed to attenuate this pressor response following laryngoscopy and intubation, such as deepening of anaesthesia, use of i.vlignocaine,[5,6,7,8] adrenergic blockers,[6,9] calcium channel blockers[10]and other methods like nerve blocks11, Topical anaesthesia with lignocaine as spray[5,12,13]or nebulisation[14,15,16,17]. Each technique has variable effectiveness and some have undesirable side effects, so that no single technique has gained popularity. Gabapentin is a structural analogue of gamma-amino butyric acid, which wasintroduced in 1994 as an antiepileptic drug, particularly for partial seizures later proved to be effective in neuropathic pain. More recently it has been studied to treat acute post-operative pain[18,19,20,21]. While doing these studies, it was observed that it attenuates pre-operative anxiety and stress response to intubation[22,23]. Recently many reports have indicated that gabapentin may have a place in attenuation of cardiovascular response following laryngoscopy and intubation[23]. As the use of gabapentin in perioperative setting is becoming more frequent, more studies are needed to know the efficacy of this drug for attenuation of cardiovascular response to laryngoscopy and intubation. The present study was designed as double blind randomized control study to investigate the effect of different doses of gabapentin on changes in heart rate and blood pressure observed during laryngoscopy and tracheal intubation.

MATERIALS AND METHODS

Prospective, randomized, double blind and placebo controlled clinical study was designed involving 90 patients of Kidwai Memorial Institute of Oncology ,Bangalore visiting pre anaesthesia clinic aged between 17yrs to 65yrsscheduled for elective surgeryunder GA with ASA I and ASA II after approval from institute ethics committee and Consent from patients. Anticipated difficult intubation, more than one attempt of laryngoscopy and intubation, duration of laryngoscopy more than 45 sec andpatients allergic to Gabapentin excluded from the study. A common standard anaesthetic regimen was followed for all patient which included fasting for six hours prior to surgery and pre medication in the form of Tab Diazepam10mg and Tab Ranitidine 300mg the night before surgery. Patients are randomly allocated into three groups of 30 each.

GROUP I: The patients received Cap placebo with sips of water one hour prior to procedure.

GROUP II: The patients received Cap Gabapentin 400mg with sips of water one hour prior to procedure.

GROUP III: The patients in this group received Cap Gabapentin 800mg with sips of water one hour prior to surgery. Anaesthesia was maintained with O2: N2O (40:60), Halothane0.5% and an intermediate acting non depolarizing muscle relaxant Vecuronium bromide 0.1mg/kg. The Power analysis was performed with 5% levels of significance on way Model using the SYSTAT 12.0, the sample size of 30 is sufficient enough to provide the study power of 90.0%.

Statistical software: The Statistical software namely SAS 9.0, SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Descriptive statistical analysis has been carried out. Significance is assessed at 5 % level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three groups of patients. Post Hoc Tukey test has been used to find the significance for pair wise comparison between two groups. Student t test (paired) has been used to find the significance within the same group.

RESULT

Table 1: Comparison of Heart rate (bpm) between three groups Study

Study points	Group I	Group II	Group III	P value	
Baseline	80.93±8.63	84.63±12.34	82.63±6.82	F= 1.130;	p=0.328
Post induction	88.27±7.96	93.07±12.8	82.13±7.05	F= 9.765;	p<0.001**
1 min after Laryngoscopy	100.80±8.77	101.20±13.33	87.83±5.67	F= 18.154;	p<0.001**
3 min after Laryngoscopy	107.67±8.83	103.93±14.49	89.53±5.53	F= 25.910;	p<0.001**
5 min after Laryngoscopy	109.83±7.79	103.60±13.8	89.30±5.96	F= 34.802;	p<0.001**
10 min after Laryngoscopy	108.90±9.18	100.53±14.37	86.37±6.03	F= 35.685;	p<0.001**
15 min after Laryngoscopy	104.83±9.07	95.33±14.4	83.53±6.14	F= 31.308;	p<0.001**
P value (Baseline vs. 15 min after Laryngoscopy)	<0.001**	<0.001**	0.437	-	

The HR in group III was lowest as compared to group I and II for all readings. In group III the HR was noted maximum at 3 min interval and returned to baseline by 15 min. In group I and II the maximum response was at 5 min and 3 min respectively and the response did not return to baseline at 15 mins. The baseline HR between all the 3 groups was comparable .The post induction fall in HR in group III was highly significant as compared with group II, and moderate significant as compared to group I. Post intubation at interval of 1 min, 3 min, 5 min

10min and 15 min after laryngoscopy the data between group I and group III, group II and group III was strongly significant, but that between group I and II was moderately significant at interval of 5 min and strongly significant at 10 min and 15 min. In Gabapentin 800mg (group III), the mean HR was significantly lower at all intervals as compared to group II and group I.

Table 2: Comparison of Systolic BP (mm Hg) between three groups of patients

Study points	Group I	Group II	Group III	P value	
Baseline	124.6±11.52	120.87±24.76	123.93±11.76	F= 0.404;	p=0.669
Post induction	119.53±11.01	118.20±11.55	120.07±19.81	F=0.129;	p=0.880
1 min after Laryngoscopy	136.13±9.17	132.47±10.81	126.27±10.26	F= 7.308;	p=0.001**
3 min after Laryngoscopy	140.60±8.93	133.90±10.98	128.4±10.28	F= 10.976;	p<0.001**
5 min after Laryngoscopy	144.00±8.87	136.37±11.75	128.87±10.33	F= 15.941;	p<0.001**
10 min after Laryngoscopy	144.20±9.04	134.73±10.85	124.97±9.56	F= 28.629;	p<0.001**
15 min after Laryngoscopy	140.73±8.84	130.33±11.29	123.4±10.21	F= 22.098;	p<0.001**
P value (Baseline vs. 15 min after Laryngoscopy)	<0.001**	0.035*	0.459	-	

The SBP values recorded at all intervals were lower in group III as compared with group I and II. The maximum response was noted at 5 min interval in group III andgroup II, at 10 min in group I. The values came back to baseline at 15 min interval ingroup III but the values did not return to baseline in group I and II even after 15 mins.The base line mean systolic blood pressure in all the three groups was comparable.Post induction value of mean systolic blood pressure fell in all the three groups. Theintergroup statistics was insignificant. Post intubation at 1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy there was strong significance between group I and III, suggestive significance between group II and group III at 1 min and 3 min interval and moderate significance at 5 minand 15 min. Between group I and II there was moderate significance at 3 min and 5min interval and strongly significance at 10 min and 15 min interval. At 15 min interval after intubation the mean SBP was highly significant in group Iand moderate significance in group II when compared with their baseline values.

Table 3: Comparison of Diastolic BP (mm Hg) between three groups of patients

Study points	Group I	Group II	Group III	P value
Baseline	79.00±6.94	78.87±6.96	77.13±6.64	F= 0.694;p=0.503
Post induction	76.33±6.71	75.47±6.28	72.67±5.64	F= 2.844;p=0.064+
1 min after Laryngoscopy	88.33±6.22	85.17±5.55	79.87±5.68	F= 16.201;p<0.001**
3 min after Laryngoscopy	91.60±6.42	86.27±4.42	81.13±5.6	F= 26.770;p<0.001**
5 min after Laryngoscopy	93.13±5.84	86.53±4.58	80.33±6.26	F= 39.121;p<0.001**
10 min after Laryngoscopy	92.53±6.19	84.27±5.22	78.87±6.45	F= 39.803;p<0.001**
15 min after Laryngoscopy	88.67±5.47	81.3±5.48	76.87±6.03	F= 33.23;p<0.001**
P value (Baseline vs. 15 min after Laryngoscopy)	<0.001**	0.058+	0.738	-

The DBP in group III was lowest as compared to group I and II at all intervals. Ingroup III the DBP was noted maximum at 1min interval and at 5 min interval in groupI and II. The response in group III returned to baseline by 15 min but the response ingroup I and II did not return to baseline.The baseline mean diastolic pressure in all the three groups was comparable. The postinduction mean DBP decreased in all the three groups, but the fall was more so ingroup III.Post intubation at1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy there was strong significance between group I and III and group II and III. But there was suggestive significance between group I and II at 1 min and strong significance at the rest intervals. At 15 min interval the mean DBP of group III was nearer to baseline, but there was suggestive significance in group II and high significance in group I.

Table 4: Comparison of Mean Arterial BP (mm Hg) between three groups of patients

Study points	Group I	Group II	Group III	P value
Baseline	94.20±8.22	92.77±11.68	92.73±7.75	F= 0.239; p=0.788
Post induction	90.77±7.62	89.70±6.94	88.47±8.63	F= 0.660; p=0.520
1 min after Laryngoscopy	104.30±6.75	100.93±6.73	95.40±6.67	F= 13.434; p<0.001**
3 min after Laryngoscopy	107.90±6.76	102.20±6.08	96.93±6.6	F= 21.456; p<0.001**
5 min after Laryngoscopy	110.07±6.05	103.17±6.53	96.53±7.04	F= 32.013; p<0.001**
10 min after Laryngoscopy	109.73±6.4	101.03±6.62	94.20±6.39	F= 43.417; p<0.001**
15 min after Laryngoscopy	106.07±5.73	97.63±6.88	92.37±6.91	F= 33.618; p<0.001**
P value (Baseline vs 15 min after Laryngoscopy)	<0.001**	0.020*	0.590	-

The MAP values in group III were lowest as compared to group I and II at all intervals. In group III the MAP was noted maximum at 1min interval and in group I and II the maximum response was at 5 min interval. The values returned to baseline by 15 min in group III, but in group I and II values did not return to baseline. The baseline mean arterial pressure (MAP) in all the three groups was comparable. The post induction mean MAP decreased in all the three groups. The intergroup statistics was insignificant. Post-intubation at 1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy the mean MAP was strongly significant between group I and III and group II and III. But there was no significance at 1 min between group I and II, but at the subsequent readings it was strongly significant. The mean MAP at 15 min interval in group III was comparable with the baseline while in group I it was strongly significant and in group II moderately significant.

DISCUSSION

Endotracheal intubation is an integral part of anaesthesiologists contribution to patient care. Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure and arrhythmias. These physiological changes are well tolerated by healthy individuals, however these changes may be detrimental or even fatal in patients with coronary artery disease, hypertension cerebrovascular disease, intracranial aneurysms valvular heart disease[3,24]. As today more and more patients with cardiovascular disorders are presenting themselves for surgery anaesthesiologists are in search of safest and the most efficient drug which can prevent cardiovascular response to the laryngoscopy and tracheal intubation. Many drugs and methods have been recommended and used till date but none of them has evolved as the drug of choice yet.

Gabapentin, a structural analogue of gamma amino butyric acid, was originally introduced as antiepileptic drug was shown to be effective in management of neuropathic pain and in the perioperative setting as an analgesic. Recently the effect of gabapentin on the pressor response to laryngoscopy and intubation has been tested in some studies but with different dose regimens and conflicting results. In the present study we have compared the effect of 400mg and 800mg oral gabapentin on pressor response to direct laryngoscopy and intubation. Ninety patients belonging to ASA I and II status were randomly allocated in to 3 groups of 30 each. In Group I the patients received placebo as control, Group II patients received 400mg of oral gabapentin and Group III received 800mg gabapentin one hour before surgery. We observed in our study that the values in group III were significantly lower (P<0.001) as compared to group I and II at all intervals for all the hemodynamic variables(HR, SBP, DBP and MAP) .The maximum response was noted at 3 min and 5 min intervals after laryngoscopy .The values in group III (800mg gabapentin) returned to baseline by 15 min where as in group I and II the values were more even after 10 mins. The results in our study is comparable with results obtained in studies conducted by Fassoulaki *et al*[25]. In study done by Fassoulaki *et al*[25] they found that gabapentin 1600mg given orally in 4 divided doses every 6 hours the day before surgery attenuated the hypertensive but not the tachycardic response to laryngoscopy and tracheal intubation. The SBP was significantly lower in the gabapentin group versus the control group at 0, 1, 3, 5 and 10 min after intubation. DBP was also lower in the gabapentin group at 0, 1, 3 and 10 min after intubation. In our study patients receiving placebo and 400mg gabapentin showed significant increase in heart rate, SBP and DBP associated with tracheal intubationompared to baseline levels and 800mg gabapentin group. Post intubation at 1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy there was strong significance between placebo and 800mg gabapentin group, suggestive significance between 400mg gabapentin and 800mg gabapentin group at 1 min and 3 min interval and moderate significance at 5 min and 15 min. Between placebo and 400mg gabapentin group there was moderate significance at 3 min and 5 min interval and strongly significance at 10 min and 15 min interval. Mean DBP decreased in all the three groups, but the fall was more so in 800mg gabapentin group. Post intubation at1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy there was strong significance between placebo and 800mg gabapentin and 400mg. But there was suggestive significance between placebo and 400mg gabapentin group at 1 min and strong significance at the rest intervals. At 15 min interval the mean DBP of 800mg gabapentin was nearer to baseline, but there was suggestive significance in 400mg gabapentin group and high significance in placebo group. Contrary to this study we also observed significantly lower MAP and Heart rate. But in study done by Fassoulaki *et al*[25], heart rate did not differ between the two groups at any time and also not commented on MAP. Memis *et al*[23] studied the effect of Gabapentin on mean arterial pressure and heart rate on induction of anaesthesia and tracheal intubation. Patients receiving placebo and 400mg Gabapentin showed a significant increase in blood pressure and heart rate associated with tracheal intubation compared to baseline levels and from patients receiving 800mg gabapentin. There was a significant decrease in heart rate and mean arterial pressure in the group receiving 800mg gabapentin

1, 3, 5 and 10min after intubation compared to placebo group and 400mg gabapentin group. Our results were similar to this study however they did not comment on SBP and DBP. We observed heart rate in gabapentin 800mg group was significantly lower at all intervals compared to 400mg group and placebo. Between placebo and 400mg gabapentin group heart rate was moderately significant at interval of 5 min and strongly significant at 10 min and 15 min. MAP at Post intubation 1 min, 3 min, 5 min, 10 min and 15 min after laryngoscopy was strongly significant between placebo and 800mg gabapentin group. But there was no significance at 1 min between placebo and 400mg gabapentin group, but at the subsequent readings it was strongly significant. The mean MAP at 15 min interval in 800mg gabapentin was comparable with the baseline while in placebo itwas strongly significant and in 400mg gabapentin group moderately significant. It has been shown that arterial pressure and heart rate responses are greater when the duration of laryngoscopy exceeds 30 sec. The above 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. The anaesthetic agents have an important impact on attenuation of pressor response to laryngoscopy and intubation. In one study sevoflurane and nitrous oxide were used for induction and in another study propofol and atracurium were used. We used thiopentone sodium and succinyl choline. KOC *et al*[26] studied the effect of gabapentin, dexamethasone and their combination in patient undergoing varicocele surgery. They found that heart rate and mean arterial pressure values are 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 values were significantly low as compared with placebo in patients pretreated with gabapentin. They attributed the smooth muscle relaxation property of dexamethasone for the effectiveness in the suppression of laryngoscopic response. Though the results were comparable with our study in terms of decrease in MAP and HR values, we did not use any adjuvant with gabapentin. 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 ca2+ flux in muscle cells with consequent inhibition of smooth muscle contraction might explain the effectiveness of gabapentin in attenuation of pressor response to laryngoscopy. Thus it may act in a manner similar to ca2+ channel blockers.Limitations of our study is that we did not measure the stress mediators, i.e. endogenous plasma catecholamines or cortisol and we didn't score sedation. Though measurement of endogenous catecholamines would give useful information, scoringsedation before induction of anaesthesia would interfere with the double blinding of the study. In conclusion gabapentin attenuates the pressor response associated with laryngoscopy and tracheal intubation. Further studies are needed to know the dose - response relationship of gabapentin during laryngoscopy and tracheal intubation.

CONCLUSION

SBP, DBP, MAP and HR were all attenuated by Gabapentin in comparison to control group. Gabapentin 800mg is more effective than 400mg for attenuation of pressor response to laryngoscopy and intubation.

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