Research Article

A comparative randomized study to evaluate the effect of gabapentin alone and in combination with labetalol in attenuating the pressor response to direct laryngoscopy and intubation

Shaista Yaqoob, Tantry Tariq Gani, Aabid Hussain Mir, Abida Yousuf, Abdul Waheed Mir, Shahnawaz Khaliq

Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

Correspondence to: Aabid Hussain Mir, E-mail: meeraabid111@gmail.com

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ABSTRACT

Background: Direct laryngoscopy and intubation are associated with the pressor response which leads to increase in blood pressure (BP) and heart rate (HR) which may be tolerated by young healthy individuals but can prove detrimental in elderly and comorbid patients. Hence, some premedication agents are administered to suppress these responses. **Objectives:** In this study, we compared gabapentin and combination of gabapentin and labetalol with a placebo group to study their effect on attenuation of these pressor responses. **Materials and Methods:** A total of 90 patients belonging to American Society of Anesthesiologists Class I and II were divided into three Groups A, B, and C of 30 patients each. 1 h before induction of anesthesia patients in Group A received gabapentin 800 mg and in Group B received 400 mg of gabapentin plus 50 mg of labetalol orally, while patients in Group C did not receive any drug and acted as control. Mean arterial pressure (MAP) and HR were recorded in all the three groups at baseline and at 0, 1, 3, 5, and 10 min after tracheal intubation. **Results:** Demographic characteristics were comparable in all the three groups. The baseline HR and MAP were also comparable in all the three groups and were statistically insignificant ($P > 0.05$). However, after tracheal intubation, there was significant increase in HR and MAP in the control Group (C), whereas in Group A and B the response was attenuated and was statistically significant ($P = 0.05$). Among the two study groups, BP was better attenuated by gabapentin, whereas the combination of gabapentin and labetalol abolishes HR response better. **Conclusion:** We conclude gabapentin alone and in combination with labetalol attenuates the hemodynamic response to laryngoscopy and intubation.

KEY WORDS: Laryngoscopy; Intubation; Gabapentin; Labetalol; Pressor Response

INTRODUCTION

An ideal anesthetic regimen consists of premedication agents which allay the anxiety and stress of the patient, stabilize the hemodynamics, decrease the secretions, and attenuate any pressor or stress responses associated with the use of techniques in delivering of standard general anesthesia. Laryngoscopy and endotracheal intubation are associated with pressor response which is recorded as tachycardia and increase in systemic arterial pressure. This increase is due to autonomic responses as a result of stimulation of upper respiratory tract. The majority of these stimuli arise from stimulation of supraglottic region by tissue tension induced by laryngoscopy. Placement of endotracheal tube and inflation of cuff in subglottic region produces a smaller additional response.[1] In 1940, Brace first established hemodynamic variation with laryngoscopy, irrespective of type of laryngoscopy blade used.[2] Direct laryngoscopy and

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intubation causes afferent vagal stimulation and efferent vagal sympathetic-adrenal response, this causes increase in blood pressure (BP), heart rate (HR), and cardiac arrhythmias. In some patients, these changes constitute pressor response which is transient, variable, and unpredictable. Usually, these changes are well tolerated by healthy individuals. However, these changes may be fatal in patients with hypertension, coronary artery disease, intracranial hypertension, and aneurysm.[3] Basically laryngoscopy and intubation violates patient's protective airway reflexes and leads to physiological changes involving various systems of body. The reflex changes in cardiovascular system are more marked and lead to average increase in BP by 20–40% and increase in HR by 20%.[4] Increase in HR, BP, and dysrhythmias is due to the activation of proprioceptors by laryngoscopy at base of tongue and this leads to increase in catecholamine concentration in plasma. Subsequent intubation stimulates the receptors in trachea and larynx which leads to in hemodynamic and epinephrine response.[5] Complications of pressor response include myocardial ischemia, cardiac failure, intracranial hemorrhage, and increase in intracranial and intraocular pressure. Age may be an important factor influencing cardiovascular response to tracheal intubation. Laryngoscopy and tracheal intubation in elderly and middle-aged patients leads to exaggerated increase in systolic BP as compared to young patients. However, diastolic pressure and HR increase more in middle-aged group. The greater increase in HR in middle-aged group may be related to receptor hypersensitivity or due to variation in balance between sympathetic and parasympathetic outflow. The lesser chronotropic response in elderly may be due to loss of sensitivity of cardiac beta-adrenergic stimulation in spite of high noradrenaline levels.[6]

Keeping in view, the frequency with which pressor response is observed during direct laryngoscopy and intubation various drugs and techniques have been utilized to blunt this response with variable degree of success. These techniques include deepening of anesthesia, newer techniques and instruments for laryngoscopy and intubation (lightwand, styletoscope, and flexible fiberoptic endoscope),[7-9] omitting cholinergic premedication, and pre-treatment with vasodilators such as nitroglycerine, beta-blockers, calcium channel blockers, clonidine, and opioids with variable results.[10-14] Earlier studies compared the effectiveness of various newer techniques for laryngoscopy and various individual drugs on the suppression of pressor response. The administration of premedication agents has been found to suppress the pressor response effectively in multiple studies. However, a gold standard technique or premedication regime has not been devised yet. Hence, in our study, we had an objective to compare individual drug with combination of drugs and control group in an attempt to find out an ideal drug combination for the laryngoscopic stress response suppression. We compared orally administered gabapentin and gabapentin-labetalol combination with control group for attenuation of pressor response to laryngoscopy and endotracheal intubation.

Labetalol was introduced in 1976 as α and β receptor antagonist for control of arterial BP and HR. Scott *et al*.[15] concluded in his study that labetalol effectively decreases BP unaccompanied by tachycardia. Chung *et al*.[16] demonstrated that intermediate dose of labetalol blunts HR response to laryngoscopy and intubation in healthy patients but has minimal effect on BP. Roelofse *et al*.[17] found labetalol 1 mg/kg more effective when compared with acebutolol 0.25 mg/kg and lidocaine 2 mg/kg for attenuation of pressor response. Singh *et al*.[18] found labetalol 0.25 mg/kg more effective than esmolol 0.5 mg/kg for attenuation of pressor response when given to patient 1 h before intubation. Gabapentin is a relatively new drug, which was introduced as antiepileptic but proved to be effective in controlling neuropathic pain. The drug is well tolerated with limited side effects, as compared with older antiepileptics such as carbamazepine. More recently, gabapentin has been used in randomized controlled trials to treat acute post-operative pain and to reduce the post-operative opioid requirements.[19,20] Recently, studies have generated interest in use of gabapentin for attenuation of pressor response to laryngoscopy and intubation.[21] 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 calcium 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.[22] It does not support the increase in catecholamine concentration in response to tracheal intubation.[23] Labetalol lowers systemic BP by decreasing systemic vascular resistance, α_1 blockade, whereas reflex tachycardia triggered by vasodilatation is attenuated by simultaneous β-blockade. Cardiac output remains unchanged. Vasodilatation is also mediated by β_2 agonistic activity.

In this study, we aimed to find out the better premedication agent between gabapentin and gabapentin-labetalol combinations for attenuation of stress response to laryngoscopy and endotracheal intubation.

MATERIALS AND METHODS

This study was carried out in the department of anesthesiology and intensive care at a tertiary care hospital in north India for 2 years after obtaining clearance from the Institutional Ethical Committee and written informed consent from the patients involved in the study. Our study was conducted on 90 patients of American Society of Anesthesiologists (ASA) Grade I and II between the age group of 18 and 65 years of either sex, undergoing elective surgery under general anesthesia with endotracheal intubation. A preanesthetic checkup was done 1 day before surgery that included detailed history, thorough clinical examination and relevant clinical investigations. Patients with anticipated difficult airway,

ASA Grade III or greater, age >65 years, history of any comorbidities, patients on drugs were excluded from the study. Patients were premedicated with tablet alprazolam 0.25 mg and tablet omeprazole 40 mg on night before surgery. Patients were randomly allocated into one of the three Groups A, B, and C with 30 patients in each group. 1 h before induction of anesthesia patients in Group A received gabapentin 800 mg and in Group B received 400 mg of gabapentin plus 50 mg of labetalol orally, while patients in Group C did not receive any drug and acted as control. In the operating room, intravenous line was secured and standard monitoring as electrocardiogram, non-invasive BP, and pulse oximeter was attached to the patient. After 3 min of preoxygenation, anesthesia was induced with propofol 2.5 mg/kg body weight over 30 s and injection rocuronium 0.6 mg/kg body weight. All intubations were performed by experienced anesthesiologist. The duration of laryngoscopy and intubation was limited to minimum possible time being similar in all patients. Depending on the type and duration of surgery, all the patients were maintained with 50% oxygen, 50% nitrous oxide, <1% isoflurane, and rocuronium 0.15 mg/kg as intermittent boluses. Parameters such as HR, systolic BP, diastolic BP, and mean arterial pressure (MAP) were recorded before intubation and at 0, 1, 3, 5, and 10 min after intubation. At the end of the surgery, neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01 mg/kg before extubation.

The data were analyzed with the help of computer software SPSS. 12. 0. Microsoft Excel for windows and presented as mean and standard deviations. The baseline characteristics evaluated to ascertain comparability among groups were assessed by repeated measures ANOVA. Appropriate tests were used to evaluate statistically significant difference among different groups. $P < 0.05$ was considered as statistically significant unless specified otherwise. All analysis was done as intention to treat biases.

RESULTS

The demographic characteristics were comparable in all the three groups and were statistically insignificant [Table 1].

The baseline mean HR of Group A was 84.23 ± 6.34 and of Group B was 85.47 ± 8.63 and that of Group C was 87.03 ± 9.89 and was comparable in all the three groups ($P > 0.05$). However, after the induction, HR in all the three Groups A, B, and C dropped to 77.63 ± 7.43, 78.03 ± 8.23, and 79.53 ± 8.57, respectively, and when compared with baseline values were statistically significant with $P < 0.05$ [Table 2]. There was a significant increase in HR after laryngoscopy and endotracheal intubation in control group and HR remained elevated above baseline up to 5 min after endotracheal intubation. Although there was an initial increase in HR in Group A and Group B at 0 min after laryngoscopy and intubation, it returned toward baseline at rest of study stages and even remained below baseline at 5 and 10 min after intubation. Intergroup comparison revealed a lower HR in Group B at most of the study stages. There was a statistically significant decrease in HR in Group B followed by Group A and then by Group C [Table 2].

Table 1: Comparison of age and weight in three groups

Group	Age (in years)	Weight (in kg)
Group A	36.63±11.17	54.62±5.15
Group B	39.03±10.16	5813±5.43
Group C	36.03±7.23	55.93±4.95
	P=0.774	*P*=0.445

Values are expressed as mean±SD, $P<0.05$=significant,
SD: Standard deviation

The baseline MAP of Group A was 86.89 ± 8.15 and Group B was 89.27 ± 8.08 and Group C was 90.43 ± 11.10. All the three groups were comparable and difference was statistically insignificant ($P > 0.05$). All the three groups had a drop in MAP on induction as shown in Table 3 and the comparison with baseline MAP was statistically significant ($P = 0.000$). In control group (Group C), increase in MAP was seen after induction of anesthesia and it remained significantly higher than baseline at all study stages. In Group A, MAP remained below baseline value at all study stages. In Group B, a significant increase in MAP above baseline was seen at 0 and 1 min after laryngoscopy and intubation, however, at subsequent stages MAP was comparable to baseline. Intergroup comparison shows a lower value of MAP in Group A at most of study stages and was statistically significant as compared to Group B and C with $P < 0.05$ [Table 3].

DISCUSSION

Laryngoscopy and intubation are mandatory for most patients undergoing surgeries in general anesthesia. Direct laryngoscopy and intubation cause afferent vagal stimulation and efferent sympathetic-adrenal response, this causes increase in BP, HR, and cardiac arrhythmias in some patients, these changes constitute pressor response which is transient, variable, and unpredictable. Hence, various techniques and drugs such as opioids, beta-blockers, calcium channel blockers, nitroglycerine, gabapentin, and clonidine were used to suppress the pressor response in various studies with variable results.

The present study was undertaken to study the effects of gabapentin 800 mg and labetalol 50 mg + gabapentin 400 mg combination on attenuation of pressor response to laryngoscopy and endotracheal intubation and compared it with the control group in three groups of 30 patients each. The age ($P = 0.774$) and weight ($P = 0.445$) were comparable in three groups and were statistically insignificant. Baseline HR was also comparable in three groups. The pre-intubation HR of

Table 2: Significance of HR changes in the groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C	
	Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*
Before induction	84.23±6.34		85.47±8.63		87.03±9.89	
Before intubation	77.63±7.43	0.001	78.03±8.23	0.002	79.53±8.57	0.002
After intubation (min)						
0	90.27±7.15	0.002	88.80±6.33	0.009	104.87±11.17	0.000
1	88.10±6.94	0.032	87.60±5.97	0.275	102.27±10.27	0.000
3	85.40±6.68	0.490	79.17±5.71	0.275	96.60±10.17	0.001
5	81.13±6.23	0.066	72.83±4.47	0.002	92.90±9.70	0.027
10	78.53±4.23	0.000	72.83±6.31	0.000	84.20±8.96	0.254

Values are expressed as mean±SD, $P<0.05$=significant, SD: Standard deviation, HR: Heart rate

Table 3: Significance of MAP changes in three groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C	
	Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*
Before induction	86.89±8.15		89.27±8.08		90.43±11.10	
Before intubation	81.20±9.35	0.000	82.09±8.11	0.000	80.09±10.91	0.000
After laryngoscopy and intubation (min)						
0	84.56±7.95	0.307	92.8±9.70	0.000	120.26±11.42	0.000
1	83.9±6.32	0.000	91.78±8.46	0.000	118.09±11.90	0.000
3	79.09±6.49	0.000	91.7±6.90	0.061	116.06±11.06	0.000
5	75.39±6.35	0.000	90.23±506	0.081	112±12.44	0.000
10	74.08±5.58	0.000	89.67±6.01	0.651	109±10.64	0.001

Values are expressed as mean±SD, $P<0.05$=significant, SD: Standard deviation

Group A (gabapentin) was 77.63 ± 7.43, Group B (gabapentin + labetalol) was 78.03 ± 8.23, and Group C (control) was 79.53 ± 8.57 and was again comparable; however, 0 min post-intubation HR rose in all the three groups to 90.27 ± 7.15, 88.80 ± 6.33, and 104.87 ± 11.17, respectively. Rise in HR was maximum in control group as compared to other two groups and was statistically significant ($P < 0.05$). Similarly at 1, 3, 5, and 10 min, there was statistically significant rise in HR in control group as compared to gabapentin and gabapentin + labetalol group [Table 2]. Comparing gabapentin and gabapentin + labetalol group, the later had lesser HR and hence better attenuation at 3, 5, and 10 min. Comparing the MAP, the pre-intubation value in Group A (gabapentin) was 81.20 ± 9.35, Group B (gabapentin + labetalol) was 82.09 ± 8.11, and Group C (control) was 80.09 ± 10.91 and was comparable. These values raised to 84.56 ± 7.95, 92.8 ± 9.70, and 120.20 ± 11.42 in three groups, respectively. The increase in control group was statistically significant ($P = 0.000$). Comparing at 1, 3, 5, and 10 min, the control group had statistically significant increase in MAP than gabapentin and gabapentin + labetalol group. When Group A and Group B are compared, Group B had increase values of MAP than Group A at 1, 3, 5, and 10 min and were statistically significant [Table 3], which indicated that gabapentin attenuated rise in MAP better than gabapentin + labetalol combination.

Hence, we observed that both gabapentin 800 mg and gabapentin 400 mg + labetalol 50 mg attenuate pressor response to direct laryngoscopy and intubation, but gabapentin 800 blunts the increase in arterial BP better than gabapentin 400 mg + labetalol 50 mg while the combination of gabapentin and labetalol blunts increase in HR better than gabapentin alone. Our observations are in accordance with Memis *et al*.[21] who reported complete attenuation of reflex increase in HR and MAP after laryngoscopy and intubation with 800 mg gabapentin when given 1 h before surgery. Fassoulaki *et al*.[24] reported that gabapentin attenuated increase in BP but not the tachycardia response to laryngoscopy and intubation. Our study results are also similar to Kong and Irwin[20] who concluded pre-operative gabapentin is efficacious for not only post-operative analgesia, post-operative nausea, and vomiting but also for the attenuation of pressor response. Ali *et al*.[23] observed pre-operative administration of gabapentin significant attenuates pressor response and our study was in accordance to his study. Montazeri *et al*.[25] observed similar results with 800 mg gabapentin, especially on systolic, diastolic, and MAPs. Singh *et al*.[18] found labetalol 0.25 mg/kg more effective than esmolol 0.5 mg/kg for the attenuation of pressor response when given to patient 1 h before intubation. Chung *et al*.[16] demonstrated that intermediate dose of labetalol blunts HR response to laryngoscopy and intubation in healthy patients but has minimal effect on BP, and in our study, the combination of labetalol and gabapentin blunted HR response better than gabapentin alone. Our results corresponded to most of the earlier studies conducted on these drugs, however, more studies need to be done to find

out the appropriate dosage regimen in combination which will attenuate the increase in both MAP and HR effectively.

Our study suggested a dose combination of gabapentin and labetalol which can be used as a premedication for suppression of stress response to laryngoscopy and endotracheal intubation safely and effectively. The limitation of our study was that it was not blinded which might have added to observers bias. Furthermore, different patients have unique pharmacokinetic and pharmacodynamic profile which may have led to altered responses.

CONCLUSION

We concluded that gabapentin 800 mg and gabapentin 400 mg + labetalol 50 mg attenuate pressor response to direct laryngoscopy and intubation. However, gabapentin 800 blunts the increase in arterial BP better than gabapentin 400 mg + labetalol 50 mg, and HR is better controlled by gabapentin + labetalol combination than gabapentin alone.

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