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Original Research Paper

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COMPARISION OF ATTENUATION OF PRESSOR RESPONSES TO DIRECT LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION WITH LABETALOL VERSUS COMBINATION OF GABAPENTIN-LABETALOL

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ABSTRACT

BACKGROUND: Administration of general anaesthesia involves direct laryngoscopy and endotracheal intubation which leads to various physiological stress responses which in turn increases blood pressure and heart rate. These pressor responses may lead to complications in elderly patients and patients with severe systemic diseases. Hence a premedication agent is advocated which can suppress such pressor responses. In this study we compared effect of labetalol and combination of gabapentin-labetalol with a placebo group for attenuation of pressor responses to laryngoscopy and intubation.

METHODS: 60 patients belonging to ASA class I and II were divided into three groups A, B and C. One hour before induction of anaesthesia patients in group A received labetalol 100 mg and in group B received 400 mg of gabapentin plus 50 mg of labetalol orally while patients in group C didn't received any drug and acted as control. Mean arterial pressure (MAP) and heart rate (HR) were recorded in all the three groups at baseline and at 0, 1, 3, 5 and 10 minutes after tracheal intubation.

RESULTS: All the three groups were comparable with regards to demographic characteristics. The baseline HR and MAP was also comparable in all the three groups and was statistically insignificant. However after tracheal intubation there was significant increase in HR and MAP in the control group A and group C whereas in group B the response was attenuated. Among the study groups blood pressure was better attenuated by gabapentin + labetalol combination whereas labetalol alone didn't abolish the pressor response.

CONCLUSION: Gabapentin and Labetalol used in combination attenuate the pressor response to laryngoscopy and intubation but labetalol alone was not able to abolish it.

KEYWORDS : Laryngoscopy, Intubation, Gabapentin, Labetalol, Pressor response.

INTRODUCTION

Administration of general anaesthesia involves direct laryngoscopy and endotracheal intubation to secure the airway and administration of oxygen and inhalational agents. These techniques are associated with stimulation of airway responses and activation of sympathetic-adrenal system which in turn leads to increase in blood pressure and heart rate. These responses may be well compensated by young and healthy individuals but can prove harmful in elderly and patients with severe systemic diseases. These changes may be fatal in patients with hypertension, coronary artery disease, intracranial hypertension and aneurysm.[1] Complications of pressor response include myocardial ischemia, cardiac failure, intracranial hemorrhage and increase in intracranial and intraocular pressure. Techniques to prevent or attenuate this hemodynamic pressor response include deepening of anaesthesia, omitting cholinergic premedication, pre-treatment with vasodilators such as nitroglycerine, beta blockers, calcium channel blockers, clonidine and opioids with variable results.[2,3,4,5,6] So premedication is administered to the patients before the administration of general anaesthesia to suppress these responses. Earlier studies compared the effectiveness of various individual drugs but in present study we will compare individual drug with combination of drugs and control group. We compared orally administered labetalol 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 blood pressure and heart rate. Scott et al [7] concluded in his study that Labetalol effectively decreases blood pressure unaccompanied by tachycardia. Chung K S et al [8] demonstrated that intermediate dose of Labetalol blunts heart rate response to laryngoscopy and intubation in healthy patients but has minimal effect on blood pressure. J.A Roelofse et al [9] found labetalol 1mg/kg more effective when compared with acebutolol 0.25mg/kg and lidocaine 2mg/kg for attenuation of pressor response. Singh SP et al [10] found labetalol 0.25mg/kg more effective than esmolol 0.5mg/kg for attenuation of pressor response when given to patient one hour 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 anti- epileptics such as carbamazepine. More recently gabapentin has been used in randomized controlled trials to treat acute postoperative pain and to reduce the postoperative opioid requirements.[11,12] Recently studies have generated interest in use of gabapentin for attenuation of pressor response to laryngoscopy and intubation.[13]

METHODS

After taking written informed consent from the patients and clearance from the institutional ethical committee, this study was conducted in SVMC and SVRR Govt General Hospital, Thirupathi. This study was conducted on 60 patients belonging to ASA physical class I and II in the age group of 18-65 years of either sex, undergoing elective surgery under general anaesthesia with endotracheal intubation. A pre-anaesthetic check up was done one day prior to surgery that included detailed history, thorough clinical examination and relevant clinical investigations. Patients with anticipated difficult airway, ASA grade III or greater, age greater than 65 years, history of any co-morbidities, patients on drugs were excluded from the study. Patients were premedicated with tablet alprazolam 0.25 mg and tablet omeprazole 40 mg on night prior to surgery. Patients were allocated into one of the three groups A, B and C with twenty patients in each group. One hour before induction of anaesthesia patients in group A received labetalol 100 mg and in group B received 400 mg of gabapentin plus 50 mg of labetalol orally while patients in group C didn't received any drug and acted as control. In the operating room intravenous line was secured and standard monitoring as electrocardiogram (ECG), non invasive blood pressure (NIBP), pulse oximeter were attached to the patient. After 3 minutes of preoxygenation, anaesthesia was induced with Midazolam 0.02mg/kg body weight, Propofol 2mg/kg over 30 seconds and injection Succinyl Choline 2mg/kg body weight. All intubations were performed by experienced anaesthesiologist. The duration of laryngoscopy and intubation was limited to minimum possible time being similar in all patients. Depending upon the type and duration of surgery all the patients were maintained with 50% Oxygen, 50% nitrous oxide, midazolam 0.02mg/kg and Succinyl choline 2mg/kg as intermittent boluses. Parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded before intubation and at 0, 1, 3 ,5 and 10 minutes after intubation. At the end of the surgery neuromuscular blockade was reversed with injection Tramadol 1mg/kg and injection glycopyrolate 0.004mg/kg before

extubation.

The data was analyzed with the help of computer software Epi info statistical software (3.3.2). 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 statistical significant difference among different groups. A p value < 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).

Table 1: Comparison of demographic characteristics in three groups

	Group A (n=20)	Group B (n=20)	Group C (n=20)	p-value
Age	45.03 ± 12.24	44.5± 12.24	45.76± 12.73	0.668
Weight	65.4 ± 7.45	63.9± 7.88	64.66± 8.35	0.400
Male/Female	13/7	12/8	11/9	>0.05
ASA I/II	12/8	13/7	10/10	>0.05

Values are expressed as mean±SD, p-value<0.05 = significant.

The baseline mean heart rate of group A was 83.20±9.38 and of group B was 86.47±7.62 and that of group C was 85.03±11.89 and was comparable in all the three groups with a p-value>0.05 (Table 2). However after the induction HR in all the three groups A, B and C dropped to 78.40±9.19, 78.03±8.23 and 79.53±8.57 respectively and when compared with baseline values were statistically significant with p-value<0.05 (Table 2 and Figure 1 & 2). There was a significant increase in heart rate after laryngoscopy and endotracheal intubation in group A and group C and heart rate remained elevated above baseline up to 5 min after endotracheal intubation. Although there was an initial increase in heart rate in group B at 0 min after laryngoscopy and intubation, it returned towards baseline at rest of study stages and even remained below baseline at 5 and 10 min after intubation. Inter group comparison revealed a lower heart rate in group B at most of the study stages. There was a statistically significant decrease in HR in group B. Group A and group C had minimal decrease in HR at 10 minutes from intubation. (Table 3)

Table 2: Comparison of three groups before induction of Anesthesia

Variable	Group A	Group B	Group C	P-value	Remarks
Heart rate (beats/min.)	83.20±9.38	86.47±7.62	85.03 ±11.89	0.63	N.S
SBP (mmHg)	127.80 ±10.66	129.47 ±7.97	128.43 ±11.18	0.81	N.S
DBP (mmHg)	82.33 ±7.07	82.47±7.26	80.47±8.56	0.34	N.S
MAP (mmHg)	96.77±8.02	89.27±8.08	90.43 ±11.10	0.86	N.S

Values presented as mean ± SD, p-value<0.05=significant

Table 3: Significance of heart rate (HR) changes in the groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C	
	Mean HR ±S.D	P-value	Mean HR ±S.D	p-value	Mean HR ±S.D	p-value
Before induction	85.20±8.38		85.47±8.63		87.03±9.89	
Before intubation	78.40±9.19	0.005	78.03±8.23	0.002	79.53±8.57	0.002
After laryngoscopy and intubation0.009						
0 min	103.80±9.70	0.000	88.80±6.33	0.009	104.87±11.17	0.000
1 min.	100.77±9.45	0.000	87.60±5.97	0.275	102.27±10.27	0.000
3 min	94.60±7.87	0.000	79.17±5.71	0.275	96.60±10.17	0.001
5 min	89.30±7.53	0.045	72.83±4.47	0.002	92.90±9.70	0.027
10 min	84.97±6.47	0.906	72.83±6.31	0.000	84.20±8.96	0.254

p-value<0.05=significant

The baseline mean arterial pressure (MAP) of group A was 96.77±8.02 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-value>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-value=0.000). In group A and group C, increase in MAP was seen after induction of anaesthesia and it remained significantly higher than baseline 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 B at most of study stages and was statistically significant as compared to group A and C with p-values of <0.05 (Table 4).

Table 4: Significance of mean arterial pressure (MAP) changes in the groups before and after laryngoscopy and intubation

Time	Group A		Group B		Group C	
	Mean MAP ± S.D	P-value	Mean MAP ±S.D	p-value	Mean MAP ± S.D	p-value
Before induction	96.77±8.02		89.27±8.08		90.43±11.10	
Before intubation	93.04±1.47	0.000	82.09±8.11	0.000	80.09±10.91	0.000
After laryngoscopy and intubation						
0 min	116.16±9.34	0.000	92.8±9.70	0.000	120.26±11.42	0.000
1 min.	113.21±8.08	0.000	91.78±8.46	0.000	118.09±11.90	0.000
3 min	110.31±4.18	0.000	91.7±6.90	91.7± 6.90	116.06±11.06	0.000
5 min	108.17±3.90	0.000	90.23±5.06	0.081	112±12.44	0.000
10 min	105.25±7.23	0.004	89.67±6.01	0.651	109±10.64	0.001

p-value<0.05=significant

DISCUSSION

The cardiovascular responses to laryngoscopy and tracheal intubation are well known and linked with increasing catecholamine blood levels. Shribman and colleagues found that laryngoscopy alone or followed by tracheal intubation increases arterial pressures and catecholamine levels while intubation significantly increases heart rate. Our results are consistent with its findings, but we did not measure catecholamine levels.

In 1940 Brace first established hemodynamic variation with laryngoscopy.[14] Direct laryngoscopy and intubation causes afferent vagal stimulation and efferent sympathetico-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. Hence various drugs such as opiods, beta blockers, calcium channel blockers, nitroglycerine, gabapentin, clonidine, dexmeditomidine were used to suppress the pressor response in various studies with variable results.

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.[15] It does not support the increase in catecholamine concentration in response to tracheal intubation.[16] Labetalol lowers systemic blood pressure 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.

The present study was undertaken to study the effects of labetalol 100 mg and labetalol 50mg + gabapentin 400mg combination on attenuation of pressor response to laryngoscopy and endotracheal intubation and compared it with control group. We observed that gabapentin 400mg + labetalol 50 mg attenuate pressor response to direct laryngoscopy and intubation, but labetalol 100 mg has a very little effect in blunting the pressor response. Our observation are in accordance with Memis et al[13] who reported complete attenuation of reflex increase in heart rate and MAP after laryngoscopy and intubation with 800mg gabapentin when given one hour before surgery. Fassoulaki et al [17] reported that gabapentin attenuated increase in blood pressure but not the tachycardia response to laryngoscopy and intubation. Our study results are also similar to Kong VKF et al [12] who concluded preoperative gabapentin is efficacious for not only post operative analgesia, post operative nausea and vomiting but also for attenuation of pressor response. Ashgan raouf Ali et al [16] observed preoperative administration of gabapentin significant attenuates pressor response and our study was in accordance to his study. K. Montazeri et al [18] observed similar results with 800 mg gabapentin especially on systolic, diastolic and mean arterial pressures.

Our study differed from Singh SP et al [10] found labetalol 0.25mg/kg more effective than esmolol 0.5mg/kg for attenuation of pressor response when given to patient one hour before intubation, wheras in our study there was no suppression of pressor response. Chung K S et al[8] who demonstrated that an intermediate dose of labetalol blunted the HR response to laryngoscopy and intubation during rapid-sequence induction in healthy patients but had a minimal effect on BP. Our study corresponded to this study as labetalol had minimal effect on MAP but we differed in HR as our study showed minimal effect of labetalol alone on blunting of tachycardia. The difference in above studies could be due to intravenous administration of drug by them and orally by us. Joseph S. Bernsteinet al[19] studied the effect of two intravenous doses of labetalol (0.25 and 0.75 mg/kg) with placebo in partial attenuation of hemodynamic responses to rapid sequence induction and intubation. They found that there is significant rise in heart rate in all the three groups. But there is significantly lower increase of peak heart rates in labetalol group, when compared to placebo (33±2 and 27±3 vs 44±7 beats/minute). Similarly in our study peak heart rates at different intervals were highest in control group followed by labetalol group and then by gabapentin group. The limitation of our study was that it was not blinded which might have added to observers bias. Also different patients have unique pharmacokinetic and pharmacodynamic profile which may have lead to altered responses.

CONCLUSION

We concluded that gabapentin 400mg + labetalol 50 mg given orally attenuates pressor response to direct laryngoscopy and intubation. However, labetalol 100 mg was not able to suppress this response. More studies need to be done in future to standardize the dosage regimens of different drug combinations.

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