Original Article

Effect of gabapentin pretreatment on the hemodynamic response to laryngoscopy and tracheal intubation in treated hypertensive patients

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ABSTRACT

Objective: This randomized, double-blind study was conducted to evaluate the effect of gabapentin pretreatment on the hemodynamic response to laryngoscopy and endotracheal intubation (LETI) in treated hypertensive patients undergoing surgery.

Methods: A total of 100 controlled hypertensive patients aged 35–60 years, undergoing elective surgery under general anesthesia with endotracheal intubation, were randomly allocated into three groups. Group 1 patients received placebo at night and 2 hours prior to induction of anesthesia. Group 2 patients received placebo at night and 800 mg gabapentin 2 hours prior to induction of anesthesia. Group 3 patients received 800 mg gabapentin at night and 2 hours prior to induction of anesthesia. Anesthesia was induced with thiopentone, fentanyl, and vecuronium and maintained with isoflurane in oxygen and nitrous oxide. Patients' heart rate (HR), blood pressure (BP), and electrocardiography (ECG) changes were recorded prior to induction, after induction, and at 0 minutes, 1 minute, 3 minutes, 5 minutes, and 10 minutes after intubation. Any episodes of hypotension, bradycardia, tachycardia, hypertension, arrhythmia, and ST-T wave changes were recorded and treated accordingly.

Results: The HR was comparable among groups, with a transient rise just after intubation, followed by a gradual fall thereafter at 3 minutes, 5 minutes, and 10 minutes compared with baseline. A significant increase in BP after intubation was reported in Group 1 but not in Group 2 and Group 3. The mean arterial pressure (MAP) was significantly higher in Group 1 at 0 minute, 1 minute and 3 minutes post-intubation as compared with Group 2 and Group 3 (p = 0.014). Three patients in Group 1, four patients in Group 2, and 10 patients in Group 3 developed hypotension and were treated with ephedrine, whereas five patients in Group 1 and one patient in Group 2 had hypertension after tracheal intubation. There was no significant difference between the groups with respect to the number of patients who received ephedrine boluses and in whom isoflurane had to be increased due to hypertension. No episode of bradycardia, tachycardia, dysrhythmia, or ST-T wave changes was reported.

Conclusion: Gabapentin 800 mg in a single or double dose was equally effective in attenuating the hypertensive response to laryngoscopy and tracheal intubation in treated hypertensive patients.

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1. Introduction

Laryngoscopy and endotracheal intubation (LETI) is accompanied by reflex hemodynamic changes in the form of hypertension, tachycardia, and dysrhythmias. Patients with hypertension, both treated and untreated, are more prone to exaggerated pressor response to LETI than are normotensive patients. Hypertensive patients also have a greater incidence of coexisting coronary artery and cerebrovascular disease. The exaggerated pressor response to LETI in these patients can evoke life-threatening conditions which include myocardial ischemia, pulmonary edema, cardiac failure and cerebral hemorrhage. Various drugs have been used to attenuate the hemodynamic response to LETI in this group of patients like nitroglycerine, verapamil, diltiazem, esmolol, allantoin, and remifentanil with variable success rates.

Gabapentin, a third-generation antiepileptic drug, has been found to be effective for the prevention of LETI response in
normotensive patients. In a study comparing gabapentin with clonidine, Marashi et al. reported that gabapentin was better than clonidine in attenuating the hemodynamic response to LETI. However, there are no reports on the efficacy of gabapentin in attenuating the hemodynamic response to LETI in hypertensive patients. Therefore, this double-blind, randomized study was planned to evaluate the effect of pretreatment with gabapentin on the hemodynamic response to LETI in treated hypertensive patients undergoing elective surgery.

2. Methods

After institutional ethical committee approval and written informed consent, 100 controlled hypertensive patients [blood pressure (BP) < 140/90 mmHg], aged 35–60 years undergoing elective surgery requiring general anesthesia with endotracheal intubation were included in the study. Patients with anticipated difficult intubation, having risk of aspiration (hiatus hernia, gastroesophageal reflux disease), obesity (body mass index > 30 kg/m²) or previous history of myocardial infarction, angina pectoris, congestive heart failure, second and third degree heart blocks, cerebrovascular accident, impaired renal functions, and those receiving sedatives, hypnotics, antidepressants, or antacids were excluded.

Patients were randomly allocated into three groups using a computer generated random number table. Group 1 patients received placebo at night before surgery and 2 hours prior to induction of anesthesia. Group 2 patients received 800 mg gabapentin at night before surgery and 800 mg gabapentin 2 hours prior to induction of anesthesia. Group 3 patients received 800 mg gabapentin at night before surgery and 2 hours prior to induction of anesthesia. The allocation sequence was concealed in sealed opaque envelopes which were opened just before administration of the drug. Placebo capsules were of the same color, shape, and size as that of study drug and contained finely ground sugar. Personnel involved in the patient management and data collection were not aware of the group assignment. Patients received their regular antihypertensive medications 2 hours prior to induction of anesthesia. No other premedication was given. Before shifting to the operating room, the patients were assessed for any side effects of gabapentin such as headache, nausea, somnolence, dizziness, asthenia, and ataxia in the preanesthesia room.

Anesthesia was induced with thiopentone 5 mg/kg and fentanyl 2 μg/kg followed by vecuronium 0.1 mg/kg to facilitate endotracheal intubation and maintained with isoflurane in 60% nitrous oxide and oxygen. Intraoperative monitoring included electrocardiography (ECG), noninvasive BP, pulse oximetry (SpO₂), end-tidal concentration of carbon dioxide, and neuromuscular transmission on a Datex-Ohmeda S/5 Avance work station (Datex-Ohmeda, USA). Laryngoscopy was performed when train of four count reached zero and the trachea was intubated with an appropriate size cuffed endotracheal tube. All intubations were performed by an experienced anesthesiologist and the time taken from the start of laryngoscopy to the cuff inflation was considered as the duration of intubation. If the duration of intubation exceeded 30 seconds or multiple attempts were required for intubation, the patient was excluded from the study.

The patients’ heart rate (HR), BP, and ECG were recorded before induction (baseline), after induction (before intubation), immediately after intubation (time 0), and at 1 minute, 3 minutes, 5 minutes, and 10 minutes after intubation. Any episodes of hypotension, bradycardia, tachycardia, hypertension, arrhythmia, and ST-T wave changes were recorded. ST segment elevation of 1 mm or depression of 0.5 mm at 80 ms after the J point was considered significant. Hypotension [systolic BP (SBP) < 90 mmHg or > 30% decrease from baseline lasting for > 60 seconds] was managed with administration of intravenous fluid or incremental doses of ephedrine 3 mg and bradycardia (HR < 40/min) was treated with atropine. In cases of tachycardia (HR > 130/min or > 30% increase from baseline lasting for > 60 seconds) or hypertension (SBP > 200 mmHg or > 30% increase from baseline lasting for > 60 seconds) the inspired concentration of isoflurane was increased. The patients were followed up for 24 hours postoperatively for any side effects of gabapentin, such as headache, dizziness, and ataxia.

This study was approved by the Hospital Ethics Review Committee PGIMER, Chandigarh, India.

2.1. Statistical analysis

The results of parametric variables were expressed as mean and standard deviation. Nonparametric data were presented as median and interquartile range. One way analysis of variance (ANOVA) was used to analyze the demographic data and hemodynamic variables among groups. The changes in intraoperative HR and BP were compared with the baseline by repeated measures ANOVA followed by the paired t test. The incidence of side effects was compared among groups by using the Pearson’s Chi-square test and Fisher exact test.

3. Results

All patients were intubated successfully. There were a total of 34 patients in Group 1 and Group 3 each, and 32 patients in Group 2. The groups were similar with respect to demographic variables (Table 1). There was no significant difference among groups with respect to the duration of hypertension prior to surgery (p = 0.344). Beta blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and diuretics or their combination were the drugs used for the treatment of hypertension. There was no significant difference between the groups with respect to the distribution of patients consuming different antihypertensive drugs or their combination (p = 0.654) (Table 2).

The baseline HR and mean arterial pressure (MAP) were comparable among groups. There was a significant rise in HR after intubation in all the groups. It returned to normal after 5 minutes with no significant difference between the groups (Figure 1). A significant increase in MAP after intubation was reported in Group 1 but not in Group 2 and Group 3. The MAP values at 3 minutes, 5 minutes, and 10 minutes were significantly lower than baseline in Group 2 and Group 3 with no difference between the two groups (Figure 2). At 0 minutes, 1 minute, and 3 minutes postintubation, the MAP was significantly higher in Group 1 as compared with Group 2 and Group 3 (p = 0.014). After that, there was no difference in MAP among the three groups. Three patients in Group 1, four patients in Group 2, and 10 patients in Group 3 developed

<table>
<thead>
<tr>
<th>Table 1 Demographic data.</th>
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</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Duration of HTN (month)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation or number of patients. Group 1 = placebo group, Group 2 = patients receiving gabapentin 800 mg before induction, and Group 3 = patients receiving gabapentin 800 mg at night and before induction.

F = female; HTN = hypertension; M = male.
Gabapentin for intubation response in hypertensive patients

Table 2
Distribution of patients receiving different antihypertensive drugs.

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Group 1 (n = 34)</th>
<th>Group 2 (n = 32)</th>
<th>Group 3 (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>ARB</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>ACEI</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>CCB</td>
<td>6 (18)</td>
<td>7 (21)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Drug combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>CCB</td>
<td>6 (18)</td>
<td>7 (21)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data presented as number (percentage) of patients. Group 1 = placebo group, Group 2 = patients receiving gabapentin 800 mg before induction, and Group 3 = patients receiving gabapentin 800 mg at night and before induction.

The difference between groups was not significant (p = 0.65).

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta blockers; CCB = calcium channel blockers.

Figure 1. Heart rate (mean value) before and after i.v. anesthetics, and immediately (0 minutes), 1 minute, 3 minutes, 5 minutes, and 10 minutes after tracheal intubation. Group 1 (n = 34) is the placebo group, in Group 2 (n = 32), patients are receiving gabapentin 800 mg before induction, and in Group 3 (n = 34) patients are receiving gabapentin 800 mg at night and before induction. HR = heart rate.

Figure 2. Mean arterial pressure (mean value) before and after i.v. anesthetics, and immediately (0 minute), 1 minute, 3 minutes, 5 minutes, and 10 minutes after tracheal intubation. Group 1 (n = 34) is the placebo group, in Group 2 (n = 32), patients are receiving gabapentin 800 mg before induction, and in Group 3 (n = 34) patients are receiving gabapentin 800 mg at night and before induction. *p < 0.05 between Group 1 and Groups 2 and 3.

Table 3
Intraoperative hemodynamic complications and rescue medication.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 34)</th>
<th>Group 2 (n = 32)</th>
<th>Group 3 (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who required</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>10 (30)</td>
<td>0.05</td>
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<tr>
<td>ephedrine boluses, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ephedrine used, mg</td>
<td>12</td>
<td>15</td>
<td>24</td>
<td>0.19</td>
</tr>
<tr>
<td>Patients who required</td>
<td>5 (15)</td>
<td>1 (3)</td>
<td>0</td>
<td>0.18</td>
</tr>
<tr>
<td>isoflurane increments, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group 1 = placebo group, Group 2 = patients receiving gabapentin 800 mg before induction, and Group 3 = patients receiving gabapentin 800 mg at night and before induction.

4. Discussion

Hypertensive patients undergo eutropic and hypertropic remodeling in the vessels. These patients also have elevated norepinephrine levels and increased sensitivity to catecholamines. Therefore, laryngoscopy and tracheal intubation is associated with exaggerated hemodynamic responses in these patients and can evoke life threatening conditions like myocardial ischemia, congestive heart failure, and cerebrovascular accidents. In the present study, we evaluated the effects of a single morning dose and the two doses of gabapentin 800 mg pretreatment on hemodynamic response to LETI in controlled hypertensive patients. We found that both of the regimens were equally effective in attenuating the hypertensive response to LETI. However, more patients receiving two doses of gabapentin developed hypotension than the other two groups. There was no difference in HR among the three groups.

Various doses of gabapentin have been studied previously to attenuate the hemodynamic response to LETI in normotensive patients. Memis et al compared the effect of 400 mg and 800 mg gabapentin on hemodynamic response to LETI and reported that gabapentin 800 mg, but not 400 mg, was effective in preventing the increase in HR and BP after tracheal intubation. Koc et al also showed that gabapentin 800 mg pretreatment effectively attenuated the hemodynamic response to LETI. In another study, Kaya et al reported that gabapentin 800 mg given 2 hours prior to surgery prevented the increase in MAP after tracheal intubation but not the HR. In a recent study comparing 600 mg and 1000 mg doses of gabapentin, Bafna et al found that gabapentin 1000 mg given before operation significantly attenuated the hemodynamic response to laryngoscopy and intubation, whereas gabapentin 600 mg had no effect. Fassoulaki et al used 1600 mg gabapentin (400 mg/6 hourly) starting the day before surgery and found that it attenuates the pressor response but not the tachycardia associated with LETI. None of the studies evaluated the effect of gabapentin pretreatment on LETI in hypertensive patients. In the present study, we used 800 mg and 1600 mg gabapentin, as 800 mg was the minimum effective dose and 1600 mg was the maximum dose used in the previous studies for normotensive patients. We found significant attenuation of the rise in BP in response to LETI in both groups receiving gabapentin, but there was no effect on the HR. The use of different inducing agents and opioid probably affects the HR. We used fentanyl and vecuronium during induction. Our patients
were also on various antihypertensive medications including beta-blockers, which may also prevent the increase in the HR. Therefore, the maximum rise in HR after intubation was only 17.4% (in the control group) in our study. None of our patients had tachycardia in any group.

The exact mechanism by which gabapentin attenuates the hemodynamic response to LETI is not well understood. However, the possible mechanisms to explain the effects of gabapentin on LETI include vasodilatation by inhibiting the voltage gated calcium channels in vessels, direct action on the muscles of the pharynx causing relaxation, and effects on the descending noradrenergic and spinal alpha-2 adrenergic system.17,18 Gabapentin decreases pain by modulating the sensory impulses through its action on central nociceptive pathways. It is thought that it may also modulate theafferent impulses during noxious stimuli like LETI.19 However, gabapentin did not have any direct cardiovascular effects.

In the present study, there was a significant fall in BP after induction and at 5 minutes and 10 minutes postintubation in all of the groups. However, in no group was the fall in MAP > 25%. Three patients in Group 1, four patients in Group 2 and 10 patients in Group 3 had significant hypotension (SBP < 90 mmHg) which responded to ephedrine. Hypertensive patients show an exaggerated fall in BP on induction of anesthesia, due to altered responsiveness of the microcirculation, which has been seen in various clinical studies.2,6,7 Moreover, the patients in our study were on different antihypertensive medications that could also affect the hemodynamics differently.20

There were no incidences of refractory hypotension or associated ECG changes suggestive of ischemia in any of the patients. Anesthesia was induced with thiopentone and was maintained with isoflurane in our study. It has been shown that thiopentone decreases afterload and causes hypotension, it also decreases left ventricular stroke volume index (LVSWI) and myocardial oxygen consumption, even in patients with coronary artery disease (CAD).21 Isoflurane can also cause hypotension and tachycardia in a concentration of 0.5 to 1 MAC as used in our study. However, it has been safely used in patients with CAD as it decreases myocardial oxygen demand by decreasing afterload and thus improving LVSWI. Isoflurane has also been found to improve diastolic dysfunction in patients with left ventricular hypertrophy and CAD.22 Other factors which are known to alter hemodynamic response, like hypoxia and hypercarbia, were avoided and the duration of laryngoscopy was maintained for < 30 seconds. Hypovolemia was prevented by preloading the patients with 8–10 mL/kg of normal saline.

In conclusion, our results show that the pretreatment with gabapentin 800 mg in single or double doses is equally effective in attenuating the hypertensive response associated with laryngoscopy and tracheal intubation in treated hypertensive patients. However, we did not measure the serum catecholamine levels, which would have suggested whether gabapentin mainly acts by a central mechanism or through a peripheral action. Further studies are required to find out the exact mechanism of action of gabapentin for attenuating LETI.

References