Efficacy of Preoperative Oral Gabapentin in Attenuation of Neuro-Endocrine Response to Laryngoscopy and Endotracheal Intubation

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This study was designed to study the efficacy of oral gabapentin premedication in attenuating the cardiovascular responses and catecholamine release to laryngoscopy and endotracheal intubation. Fifty normotensive ASA I patients undergoing elective surgery under general anaesthesia were randomly allocated to one of two equal groups (n = 25 each). Patients were assigned to receive either oral 1200 mg gabapentin (GABA group) or placebo (control group) 2 h before surgery. Anaesthesia was induced with IV propofol 2 mg kg⁻¹ and vecuronium 0.08 mg kg⁻¹ to facilitate tracheal intubation and maintained with 2% sevoflurane and 50% nitrous oxide in oxygen. Laryngoscopy lasting 15 sec was attempted 3 min after administration of propofol and vecuronium. Mean arterial pressure and heart rate were recorded before and after induction of anaesthesia as well as at 1, 2, 3, 4, 5 and 10 min following intubations. Plasma catecholamines were measured before and after induction and at 1 and 5 min after intubation. Patients receiving placebo exhibited significant increase in mean arterial pressure, heart rate and plasma concentrations of catecholamines associated with tracheal intubation compared to baseline. The increase of mean arterial pressure and heart rate was attenuated in patients treated with gabapentin. Gabapentin failed to suppress the increase in catecholamine concentrations in response to tracheal intubation. Preoperative oral gabapentin suppressed the hemodynamic response (MAP and HR) to endotracheal intubation and these effects were not caused by inhibition of the catecholamine response.

Key words: Gabapentin, intubation, stress, response
INTRODUCTION

Laryngoscopy and endotracheal intubation are associated with cardiovascular changes such as hypertension, tachycardia and dysrhythmias and increased circulating catecholamines (Shribman et al., 1987; Kovac, 1996).

These pressor responses may increase perioperative morbidity and mortality, particularly for those patients with cardiovascular or cerebral disease (Thomson, 1989).

A variety of drugs have been used to control this hemodynamic response such as vasodilators, beta blockers, calcium channel blockers and opioids (Kovac, 1996; Maguire et al., 2001; Habib et al., 2002).

Gabapentin is a structural analogue of gamma-aminobutyric acid, which was introduced in 1993 as an antiepileptic drug, particularly for partial seizures (Goa and Sorkin, 1993).

In addition, it has been shown to be effective in neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy (Rosenberg et al., 1997; Backonja et al., 1998; Rowbotham et al., 1998; Melliek and Melliek, 1995).

Furthermore, a growing body of evidence suggests that perioperative administration is efficacious for postoperative analgesia, preoperative anxiolysis and preventing chronic post-surgical pain, postoperative nausea and vomiting and delirium (Ho et al., 2006; Menigaux et al., 2005; Nikolajsen et al., 2006; Pandey et al., 2006; Leung et al., 2006).

Recently, gabapentin was effectively used to attenuate hemodynamic response to laryngoscopy and tracheal intubation (Fassoulaki et al., 2006; Memis et al., 2006; Kaya et al., 2008).

The effect of gabapentin on stress mediators during laryngoscopy and tracheal intubation has not been reported.

The present study was designed as double blinded randomized controlled trial to investigate the effect of preoperative single oral dose of 1200 mg gabapentin on the changes in the blood pressure, heart rate and stress hormones measured during laryngoscopy and tracheal intubation.

MATERIALS AND METHODS

After approval of the Local Ethics Committee, an informed consent was obtained from all patients. Fifty adult patients, 20-40 years of age, ASA physical status I, undergoing elective surgery were studied in Kasr El-Ainy Hospital, from 2007 to 2008. Preoperative assessment included complete blood picture, serum electrolytes, liver function tests, serum creatinine and a 12-lead ECG. Exclusion criteria were known allergy or contraindication to anaesthetics or any drug used, history of cardiovascular disease, renal insufficiency, hepatic impairment, asthma, central nervous system diseases, predicted difficulty in intubation or airway maintenance. Patients who took medications that would influence autonomic or cardiovascular response to laryngoscopy and intubation were also excluded.

The study design was randomized and double blinded. Patients were randomly allocated according to computer-generated randomization to receive either placebo capsules (control group, n = 25) or gabapentin 1200 mg (Neurontin, 400 mg capsule, Pfizer, Goedecke GmbH, Germany) (GABA group, n = 25) 2 h prior to surgery in the operating theater. Patients were not premedicated. The study drugs were prepared by the pharmacy and appropriate code number was assigned. The staff involved in data collection and patient management was unaware of the group assignments.

On arriving to the operating room, crystalloid infusion was started through a 20-G intravenous cannula inserted in an appropriate antecubital vein and a 20-G radial artery Teflon® annula was inserted under local anaesthesia for direct arterial blood pressure measurements and to take blood samples.

Monitoring included five-lead ECG (heart rate [HR] was recorded), direct arterial blood pressure monitoring (mean arterial pressure [MAP] was recorded), pulse oximetry and capnography.

After 3 min of preoxygenation anaesthesia was induced with propofol (2 mg kg⁻¹) and vecuronium 0.08 mg kg⁻¹ to facilitate tracheal intubation and maintained with 2% sevoflurane with fresh gas flow 2 L min⁻¹ (50% N₂O in O₂). Three minutes after induction, when neuromuscular block was achieved, intubation was performed within 15 sec by the same experienced anaesthesiologist using a Macintosh 3 laryngoscope blade and 7.0-8.0 mm endotracheal tube (for women and men, respectively). After tracheal intubation, the lungs were mechanically ventilated to maintain end tidal carbon dioxide CO₂ tension between 30-35 mmHg.

Data from patients in whom intubation required more than 15 sec were excluded. Mean blood pressure (MAP) and heart rate (HR) were recorded as preoperative baseline which is the mean of three resting measurements in the operating room before any instrumentation (baseline), 3 min after administration of IV anaesthetics (post induction), every minutes in the first five post-intubation minutes (PI1-PI5) and at 10 min after intubation (PI10). Ephedrine (3 mg increments) was administered for hypotension (systolic arterial pressure
SAP <100 mmHg, or a decrease of >30% from baseline values for >60 sec) and atropine in 300 μg increments, for bradycardia (HR <45 beats min⁻¹). For hypertension (SAP >200 mmHg or an increase of >30% above baseline for >60 sec), the inspired sevofothane concentration was increased in increments of 0.5%. A dysrhythmia was defined as any ventricular or supraventricular premature beat or any sustained rhythm other than sinus.

Arterial blood samples were drawn before induction (baseline), 3 min after the induction with propofol (post induction), 1 and 5 min after the intubation (P11 and P15). The samples were collected into prechilled tubes containing EDTA-Na and immediately centrifuged at 3000 rpm for 15 min at 4°C. The plasma was stored at -70°C until assayed for catecholamine concentrations. Plasma epinephrine and norepinephrine were separated using a Bio Rad column chromatography (150×4 mm, Part No. GSCD 40512S2504) by isocratic elution with a mixture of 6.9 g sodium phosphate, 37 mg EDTA, 150 mg sodium octane sulfonate, 60 mL acetonitrile, 5 mL of THF and the rest made up to 1000 mL with water in around 20 min and detected by electrochemical detection. The results of epinephrine and nor epinephrine were analyzed and the assay sensitivity was 10.0 pg mL⁻¹ and within non-precision coefficient of variation were 13.5 and 14.2% for nor epinephrine and epinephrine, respectively.

Power calculation suggested that a minimum of 20 patients per group would detect a 15% differences in MAP or HR between groups after intubation (α = 0.05, β = 0.2).

Statistical analysis: Data are expressed as mean (SD). Comparison between the groups was performed using the unpaired student’s t-tests. Intragroup comparisons relative to baseline were performed using repeated measure ANOVA with post Hoc Scheffe’s test if ANOVA results were significant. A p-value of less than 0.05 was considered statistically significant. The statistical package SPSS®10.0 (SPSS ©Inc., Chicago, IL, USA) was used. p- values<0.05 were considered statistically significant.

RESULTS

The two groups were comparable with respect to age, sex, weight, duration and type of surgery (Table 1).

As regards basal and post induction levels, MAP and HR were comparable in the two groups. Direct laryngoscopy and endotracheal intubation produced increase in hemodynamic variables in the two studied groups. MAP and HR in control groups were significantly higher relative to baseline from P11-P15 (p<0.05). During the first 5 post intubation minutes (P11-P15),

Table 1: Demographic characteristics and operative data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group (n=25)</th>
<th>GABA group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29 (4.5)</td>
<td>30 (4.5)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/10</td>
<td>12/13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (1.8)</td>
<td>75 (2.8)</td>
</tr>
<tr>
<td>Surgical procedure (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernioplasty</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>105(20)</td>
<td>105(24)</td>
</tr>
</tbody>
</table>

GABA: Gabapentin. Value are expressed as Mean+SD

Fig. 1: Mean arterial pressure (MAP) changes before and after endotracheal intubation in both groups. Values are means and error bars represent standard deviation. Post induction - 3 min after IV anaesthesia, P11-P110 = 1,2,3,4.5 and 10 min after intubation, respectively. GABA: Gabapentin. *: p<0.05 versus baseline. †: p<0.05 versus control group

Fig. 2: Heart rates (HR) changes before and after endotracheal intubation in both groups. Values are means and error bars represent standard deviation. Post induction - 3 min after IV anaesthesia, P11-P110 = 1,2,3,4.5 and 10 min after intubation, respectively. GABA: Gabapentin. *: p<0.05 versus baseline. †: p<0.05 versus control group
Basal and post induction concentrations of nor-epinephrine and epinephrine were comparable in both groups. Plasma nor-epinephrine concentration significantly increased compared with baseline values 1 min after intubation (p<0.05) in both groups. The degree of increase of nor-epinephrine was significantly greater in gabapentin treated groups than in control group (p<0.05). Five minutes after intubation nor-epinephrine levels decreased in both groups, returned to baseline value in control group while still significantly higher in gabapentin group (p<0.05) (Fig. 3).

Plasma epinephrine concentration also increased significantly 1 min after intubation compared to baseline values (p<0.05) and returned towards baseline 5 min after intubation in both groups with no intergroup differences (Fig. 4).

**DISCUSSION**

The present study demonstrated that a single oral dose of 1200 mg gabapentin given 2 h before surgery attenuated the pressor response to tracheal intubation in adults but the drug did not attenuate the catecholamine response to intubation and even augmented the increase of nor-epinephrine level.

To the best of the researcher’s knowledge, there was no earlier published study in the literature to evaluate the effect of preoperative gabapentin administration on plasma stress mediators’ level during laryngoscopy and intubation.

The objective of the present study was directed to investigate the correlation between the haemodynamic and stress hormone responses to intubation after oral gabapentin administration.

Concerning the haemodynamic effects, patients treated with gabapentin in the present study had attenuated increase in MAP and HR during first 10 min after intubation. Although observed changes in MAP and HR at intubation were statistically significant, they were modest and clinically acceptable.

This result agrees with what was reported by Memis et al. (2006) who determined the effect of single dose of gabapentin 400 or 800 mg, given 1 h before surgery on reducing the cardiovascular response and stated that 800 mg of gabapentin had significantly decreased mean arterial pressure and heart rate during first 10 min after endotracheal intubation.

Another study done by Fassoulaki et al. (2006), demonstrated that gabapentin 1600 mg given in four divided doses, at 6 h intervals starting the day before surgery) attenuated the pressor response but not the tachycardia, associated with laryngoscopy and tracheal intubation. Similar results were also stated by Kayal et al. (2008) who studied the effect of preoperative gabapentin
800 mg, given 2 h before surgery on intraocular pressure (IOP) and haemodynamic changes in response to endotracheal intubation and concluded that pretreatment with gabapentin 800 mg effectively suppressed the increase in intraocular pressure and attenuated the increase in the MAP but not the HR associated with tracheal intubation. Differences between results of the present study and those of Fassoulaki et al. (2006) and Kaya et al. (2008) concerning heart rate changes may be attributed to differences in doses and timing of gabapentin administration.

The mechanism by which gabapentin attenuates the hemodynamic response to laryngoscopy and intubation remains unknown.

A number of mechanisms may be involved in the antinociceptive action of gabapentin (Bertrand et al., 2001). The most likely antinociceptive mechanisms is modulating Ca\(^{2+}\) current by selectively binding to (3H) gabapentin (a radioligand), the a\(_{2}\) \(\gamma\) subunit of voltage-dependent Ca\(^{2+}\) channels (VGCCs) (Fink et al., 2002). The proposed consequence of gabapentin binding to a\(_{2}\) \(\gamma\) subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability (Maneuf et al., 2003).

However, gabapentin inhibits membrane VGCC; it is possible that it may act in a manner similar to calcium channel blockers in controlling the hemodynamic. (Sarantopoulos et al., 2002).

Memis et al. (2006), reported that, the inhibitions of Ca\(^{2+}\) efflux from muscle cells with a consequent inhibition of smooth muscle relaxation might explain the effectiveness of gabapentin in the relaxation of laryngoscopy.

As regards the catecholamine response to intubation, both groups in the present study showed significant increase in plasma concentration of catecholamines during laryngoscopy and tracheal intubation. Gabapentin administration did not affect basal plasma catecholamine (epinephrine and nor-epinephrine) concentrations before intubation, failed to attenuate the catecholamine response to intubation and conversely, enhanced the increase of plasma nor-epinephrine concentration. So, Gabapentin may not affect basal but augment already- stimulated sympathetic activity.

The results of the current study also showed that despite higher plasma concentration of nor-epinephrine in patients receiving gabapentin than in the control group after intubation, the increase in mean arterial pressure and heart rate was lower in gabapentin group during the study period.

These results suggested that, the cardiovascular response to catecholamines may be attenuated by a gabapentin without affecting their secretion as explained by Pilipp et al. (1978) when they reported that, the important determinant of the level of arterial pressure may be plasma nor-epinephrine and reactivity to nor-epinephrine.

In the present study, gabapentin administration showed haemodynamic and catecholamine response similar to calcium channel blockers during laryngoscopy and tracheal intubation. Mikawa et al. (1996) compared between three calcium channel blockades drugs (nicardipine, diltiazem and verapamil) for controlling the cardiovascular response to tracheal intubation, concluded that these calcium channel blockers attenuated hypertension but failed to suppress the increase in plasma catecholamine concentration in response to intubation and even nicardipine enhanced the increase.

The similarities between the present study on gabapentin and Mikawa et al. (1996) results may support the opinion that, mechanism of action of gabapentin on controlling pressor response is through Ca\(^{2+}\) channel blockers.

No patient in the present study developed severe hypotension: only one patient in gabapentin group had transient hypotension (MAP <80 mmHg for <1 min), which did not require ephedrine. No incidences of bradycardia, tachycardia, arrhythmia, ST segment alterations, or other echocardiographic changes were observed during the study. There were no differences between the two groups in clinical outcome (e.g., intra- and postoperative morbidity and mortality), possibly because only healthy ASA I patients without cardiovascular or cerebrovascular disease were included in this study.

A single preoperative oral dose of 1200 mg gabapentin given 2 h before induction of anaesthesia, attenuate the pressor response to laryngoscopy and tracheal intubation, and these prophylactic effect were not caused by inhibition of the catecholamine response. The possible role of gabapentin in attenuation of other aspect of stress response to surgery needs further investigation.

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**REFERENCES**


