Gabapentin attenuates the pressor response to direct laryngoscopy and tracheal intubation

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Background. Laryngoscopy and tracheal intubation increase blood pressure and heart rate (HR). The aim of the present study was to investigate the effect of gabapentin when given before operation on the haemodynamic responses to laryngoscopy and intubation.

Methods. Forty-six patients undergoing abdominal hysterectomy for benign disease were randomly allocated to receive gabapentin 1600 mg or placebo capsules at 6 hourly intervals starting the day (noon) before surgery. Anaesthesia was induced with propofol and cis-atracurium. Systolic, diastolic arterial blood pressures (SAP, DAP) and heart rate (HR) were recorded before and after the anaesthetic and 0, 1, 3, 5 and 10 min after tracheal intubation.

Results. SAP was significantly lower in the gabapentin vs the control group 0, 1, 3, 5 and 10 min after intubation [128 (27) vs 165 (41), P = 0.001, 121 (14) vs 148 (29), P = 0.0001, 115 (13) vs 134 (24), P = 0.002, 111 (12) vs 126 (19), P = 0.004 and 108 (12) vs 124 (17), P = 0.001 respectively]. DAP also was lower in the gabapentin group 0, 1, 3, and 10 min after intubation [81 (18) vs 104 (19), P = 0.0001, 77 (9) vs 91 (16), P = 0.001, 71 (10) vs 84 (13), P = 0.001 and 67 (10) vs 79 (12), P = 0.004]. HR did not differ between the two groups at any time [82 (11) vs 83 (15), 79 (10) vs 80 (12), 86 (17) vs 92 (10), 82 (11) vs 88 (10), 81 (12) vs 81 (11), 77 (13) vs 79 (13), and 75 (15) vs 78 (12)].

Conclusion. Gabapentin, under the present study design attenuates the pressor response but not the tachycardia associated with laryngoscopy and tracheal intubation.

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Laryngoscopy and intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmias and even, myocardial ischaemia¹ and increased circulating catecholamines.² Several techniques have been proposed to prevent or attenuate the haemodynamic responses following laryngoscopy and intubation, such as deepening of anaesthesia,¹ omitting cholinergic premedication,⁴ pretreatment with vasodilators such as nitroglycerin,⁴ beta-blockers,⁵ calcium channel blockers⁶ and opioids.⁷–⁹ The most recent studies aiming at controlling or attenuating the haemodynamic response to intubation and laryngoscopy focused on the effect of remifentanil at different dosing regimens.¹⁰–¹²

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 postoperative pain and to reduce the postoperative opioid requirements.¹³–¹⁷ While performing these studies with gabapentin, we noticed that some patients were haemodynamically stable.

The present study was designed as double-blind randomized controlled trial to investigate the effect of gabapentin on the changes in blood pressure and heart rate (HR) observed during laryngoscopy and tracheal intubation.

Methods

Subjects

After obtaining approval from the Hospital Ethics Committee and patients' informed consent, 46 patients undergoing abdominal hysterectomy for benign disease were allocated randomly to the gabapentin or the control group. Exclusion criteria included anticipated difficult...
intubation, ASA physical status III or greater, hiatus hernia and gastro-oesophageal reflux, patients with body weight more than 20% of the ideal body weight, age more than 59 yr, and consumption of antihypertensive drugs, sedatives, hypnotics, antidepressants, drugs with effect on the nervous system, except those determined by the study protocol.

Randomization and treatment

Sixty opaque envelopes containing the code odds or even numbers for the Athina or Foivos groups, respectively, were prepared and sealed. Gabapentin 400 mg or placebo capsules were kept in vases labelled as Athina and Foivos (the mascots of the Olympic Games, Athens 2004), respectively. After opening an envelope the day before surgery patients were randomized to the Athina or to the Foivos group accordingly and treated with the capsules from the vase labelled as Athina or Foivos, respectively. Gabapentin 400 mg or placebo capsules were administered at noon, 18 h, and 24 h the day before surgery and at 6 AM, the morning of surgery. Envelope labelling, placebo capsules, vaso filling and group allocation were done by an anaesthetist who was not aware of the study protocol and did not participate in the study. The same anaesthetist distributed the capsules to the patients according to the group allocation and the instructions of administration. Placebo capsules were prepared after meticulous emptying of the gabapentin capsules and filled with thin sugar.

Anaesthetic technique

Patients were treated with omeprazol 40 mg per os the night before surgery. In the operating room a 16 G catheter was inserted in a peripheral vein and a Ringer lactate solution was started. All patients received i.v. of metoclopramide 10 mg 10 min before induction of anaesthesia. Standard monitoring, consisting of inspired oxygen concentration, ECG, pulse oximetry, HR, and non-invasive blood pressure, was used. Intra-operatively, the inspired and end-tidal concentrations of carbon dioxide, oxygen, and inhalational anaesthetics and side-stream spirometry were monitored (S/5™ Anesthesia Monitor, GE Healthcare, Helsinki, Finland).

After 3 min of preoxygenation anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\) and \textit{cis}-atracurium 0.15 mg kg\(^{-1}\) to facilitate tracheal intubation. Systolic, diastolic arterial blood pressure (SAP and DAP) and HR were recorded before and after administration of the i.v. anaesthetic, immediately after intubation and cuff inflation and 1, 3, 5 and 10 min after. All intubations were performed by an experienced anaesthetist (A.F.), the duration of laryngoscopy and intubation limited to the minimum possible time and being similar to all patients. However, we did not record the duration of each intubation. Regarding difficulty, the grade of the view during laryngoscopy was I according to the Cormack–Lehane classification.

Study population size

Preliminary sample size estimation based on initial pilot observations indicated that approximately 20–23 patients should be included in each group, in order to ensure power 0.80 for detecting clinically meaningful reductions in HR and SAP by 10–20%. Alpha error was assumed to be 0.05. Estimated standard deviations were approximately 11 and 20 for HR and SAP, respectively. Sample size estimation was performed using the following software available on-line: (i) Power Calculator (UCLA Department of Statistics, calculators.stat.ucla.edu/powercalc/) and (ii) Java applets for power and sample size (provided by Professor R.V. Lenth, Department of Statistics and Actuarial Science, University of Iowa, www.stat.uiowa.edu/~rlenth/power).

Statistics

Patients’ characteristics between the two groups were compared with Student’s \(t\)-test for unpaired observations. ANOVA with repeated measures was used to compare the changes in SAP, the DAP and HR values. Individual inter-group comparisons, where appropriate, were done using Scheffe’s test.

\(P<0.05\) was considered statistically significant. The statistical package SPSS® 10.0 (SPSS® Inc., Chicago, IL, USA) was used.

Results

Similar patient characteristics were found in both groups (Table 1). One patient in the control group presented bronchospasm during induction of anaesthesia and was excluded from further data collection except for the patient characteristics. One patient in the gabapentin group received atropine 8 min after intubation attributable to bradycardia (<40 bpm) and data collection was limited up to 5 min after intubation.

SAP differed with regard to group \((P=0.003)\) and with regard to time \((P=0.0001)\). Inter-group comparisons for each time point showed significantly higher SAPs at 0, 1, 3, 5 and 10 min after tracheal intubation in the control group \((P<0.001, P=0.0001, P=0.002, P=0.004\) and \(P=0.001\), respectively) (Table 2).

DAP values differed with regard to group \((P=0.01)\) and with regard to time \((P=0.0001)\). Inter-group comparisons showed significantly higher DAPs immediately and 1, 3, and 10 min after laryngoscopy and tracheal intubation in

| Table 1 Patient characteristics in each group of patients. Values are mean (range or sd) |
|--------------------------------------|-----------------|-----------------|
| **Gabapentin**                      | **Control**     |
| Age (yr)                             | 41 (24–53)      | 43 (31–38)      |
| Body weight (kg)                     | 63 (9)          | 63 (7)          |
| Height (cm)                          | 162 (5)         | 163 (6)         |


Control

Table 3

DAP before and after i.v. anaesthetics, and immediately (0 min), 1, 3, 5 and 10 min after tracheal intubation and cuff inflation in the gabapentin and the control group. Values are mean (sd) and 95% CI. ANOVA with regard to group: F=10.018, df=1, P=0.003. ANOVA with regard to time: F=22.470, df=3.374 P=0.0001. *P<0.0001 vs the control, †P<0.0001 vs the control, ‡P<0.002 vs the control, and §P<0.004 vs the control.

<table>
<thead>
<tr>
<th>Group</th>
<th>Before i.v. anaesthetic</th>
<th>After i.v. anaesthetic</th>
<th>0 min</th>
<th>1 min</th>
<th>3 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (n=22)</td>
<td>135 (17)</td>
<td>114 (15)</td>
<td>128 (27)</td>
<td>121 (14)</td>
<td>115 (13)</td>
<td>111 (12)</td>
<td>108 (12)</td>
</tr>
<tr>
<td>Control (n=22)</td>
<td>138 (23)</td>
<td>110 (16)</td>
<td>165 (41)</td>
<td>148 (29)</td>
<td>134 (24)</td>
<td>126 (19)</td>
<td>124 (17)</td>
</tr>
<tr>
<td>95% CI</td>
<td>−15.78 to 9.33</td>
<td>−4.944 to 13.580</td>
<td>−57.578 to −15.877</td>
<td>−40.738 to −13.081</td>
<td>−31.639 to −7.815</td>
<td>−24.171 to 5.011</td>
<td>−24.148 to −6.397</td>
</tr>
</tbody>
</table>

the control group when compared with the gabapentin treated group (P=0.0001, P=0.001, P=0.001 and P=0.004, respectively) (Table 3).

HR did not differ with regard to group (P=0.269) but differed with regard to time (P=0.0001) (Table 4).

Discussion

Our results showed that gabapentin attenuated the pressor response to tracheal intubation, as SAP and DAP, but not HR were significantly lower in the gabapentin vs the control group.

The cardiovascular responses to laryngoscopy and tracheal intubation are well known and linked with increases in catecholamine blood levels. Shribman and colleagues found that laryngoscopy alone or followed by tracheal intubation increases arterial pressure and catecholamine levels while intubation significantly increases HR. Barak and colleagues reported that the stress response to tracheal intubation is comparable when using direct laryngoscopy or fibreoptic bronchoscope. These investigators did not find a correlation between the haemodynamic changes and catecholamine levels.

Several techniques have been proposed to attenuate such responses. Tachycardia and rhythm disturbances as a result of intubation were attenuated by omitting atropine as premedicant. Nitroglycerin administered intranasally attenuated the hypertensive response to laryngoscopy and intubation but tachycardia was observed in both the nitroglycerin and the control group. Also, i.v. lidocaine prevented the increase in mean arterial blood pressure but had no effect on the HRs.

Beta-blockers and calcium channel blockers have also been used successfully to prevent the haemodynamic responses to tracheal intubation. Drugs with rapid onset and short duration of action similar to the beta-blocker esmolol and the opioid remifentanil are particularly useful for the induction-intubation period. The most recent studies regarding prevention of haemodynamic changes after laryngoscopy and tracheal intubation investigate the effect of remifentanil, an opioid with very rapid onset and very short time of action.

Remifentanil 1 µg kg⁻¹ followed by 0.5 µg kg⁻¹ min⁻¹ attenuated the pressor response to intubation but was associated with bradycardia and/or hypotension. Other workers found that remifentanil 0.5 µg kg⁻¹ did not prevent...
hypertension and tachycardia during rapid sequence induction. However, remifentanil 1 μg kg⁻¹ was effective while 1.25 μg kg⁻¹ in some patients caused hypotension. Finally, Hall and colleagues reported that 0.5 μg kg⁻¹ over 30 s followed by infusion of 0.25 μg kg⁻¹ min⁻¹ was associated with slight changes in haemodynamic responses after laryngoscopy and orotracheal intubation.

When assessing techniques to ameliorate the cardiovascular responses to intubation the drugs used to induce anaesthesia may influence the results. We induced anaesthesia with propofol, which produces bradycardia. Thus tachycardia resulting from intubation may have been attenuated by propofol in both groups covering such a possible effect of gabapentin on the HR. Omission of opioids during induction of anaesthesia in patients ASA I and II should not be a concern. Besides, propofol produces hypotension more than thipental and bradycardia, which may compensate in part the cardiovascular changes attributable to laryngoscopy and tracheal intubation.

We did not measure stress mediators such as endogenous plasma catecholamines or cortisone, and we did not score sedation. These can be considered as limitations of the study. Though measurements of endogenous catecholamines would give useful information, scoring sedation before induction of anaesthesia would interfere with the double-blinding of the study.

As we pretreat our patients with four doses of gabapentin as adjuvant to prevent acute and chronic postoperative pain we investigated whether the same pretreatment regime may attenuate the cardiovascular response to intubation and laryngoscopy. Gabapentin originally introduced as antiepileptic, is effective in neuropathic pain and most recently has been evaluated as analgesic, anti-hyperalgesic, or both, perioperatively. However, only few data in the literature are available regarding the effect of gabapentin on the cardiovascular system. Gabapentin administered intrathrocally or intraperitonally in the rats did not change significantly the haemodynamics during the following 60 min when compared with the baseline values. In humans, 1200 mg of gabapentin administered 1 h before surgery had no effect on the mean blood pressure and HR at 0–24 h after operation. Other studies investigating the analgesic effect of gabapentin after operation did not assess its effect on the cardiovascular system. In our study SAP, DAP and HR baseline values did not differ significantly between the controls and the patients pretreated with gabapentin. None of the patients exhibited hypotension before induction of anaesthesia. After induction but before intubation four patients in the control group and three patients in the gabapentin group had SAP below 100 mm Hg (99, 83, 88, 75 mm Hg and 97, 95 and 92 mm Hg, respectively). So none of the patients in the gabapentin group exhibited severe hypotension as compared with the control group. According to the study protocol during the induction period we should administer ephedrine if SAP remained less than 80 mm Hg 1 min after intubation. However, none of our patients needed active treatment for hypotension during the study period.

We studied patients up to 59 yr as elderly patients take more often drugs such as antidepressants, hypnotics and antihypertensives. Older patients also exhibit increased sensitivity to drugs and the cardiovascular effects of gabapentin are not studied extensively. Aged patients should comprise a different group with doses of gabapentin probably adjusted to age.

The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. The drug inhibits membrane voltage-gated calcium channels, thus acting in a manner similar to calcium channel blockers. To our knowledge no randomized controlled trial has as primary aim the cardiovascular effects of gabapentin. As gabapentin is recently used as adjuvant for acute postoperative pain studies on its haemodynamic effects will be more than welcome. Also, patients who are treated with the drug before operation will benefit from its effect on the pressor response to laryngoscopy and tracheal intubation.

In conclusion, pretreatment with gabapentin under the dose given and the present study design attenuates the pressor response to laryngoscopy and intubation of the trachea. It has no effect on the changes in HR. As the use of gabapentin in the peri-operative setting is becoming more frequent more studies focusing on its cardiovascular effects and its effect on stress mediators are needed.

Acknowledgement
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References


