A Comparison of Different Doses of Gabapentin to Attenuate the Haemodynamic Response to Laryngoscopy and Tracheal Intubation in Normotensive Patients

Usha Bafna, Vipin K Goyal, Ashish Garg

ABSTRACT

Background: Laryngoscopy and intubation evokes a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure & arrhythmias. We conducted a study to compare the effect of different doses of gabapentin on hemodynamics associated with laryngoscopy and intubation.

Patients & Methods: Ninety normotensive patients (ASA I and II) between 20-60 years undergoing elective surgery requiring intubation were randomly allocated into three groups of 30 patients each. Group I received oral placebo, Group II received 600 mg of gabapentin and Group III received 1000 mg of gabapentin, with sip of water 1 h prior to surgery in the operation theatre. Patients were premedicated with Glycopyrrrolate, midazolam and fentanyl and induction was done with thiopentone sodium and succinylcholine. Heart rate, systolic, diastolic and mean arterial pressure were recorded at baseline, 0, 1, 3, 5 and 10 min after intubation.

Results: MAP and HR were significantly increased in patients receiving placebo and 600 mg gabapentin after laryngoscopy and intubation compared to baseline value and Group III. Significant decrease in MAP was seen just after intubation, 1, 3, 5 and 10 min after (P < 0.001, P < 0.001, P < 0.05, P < 0.05 and P < 0.05 respectively) in Group III compared to Groups I and II. HR was significantly decreased within 10 min of intubation (P<0.001)) in Group III compared to Groups I and II.

Conclusion: Gabapentin 1000 mg given 1 h before operation significantly attenuated the haemodynamic response to laryngoscopy and intubation in normotensive patients.

KEYWORDS: Gabapentin; Laryngoscopy; Intubation; Haemodynamic Response

Endotracheal intubation is an integral part of anaesthesiologist’s contribution to patient care. Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in Heart rate, Blood pressure & arrhythmias. Deepening of Anaesthesia, lidocaine spray, sodium nitroprusside, opioids, α blockers, I.V lignocaine, nitroglycerine ointment and oral clonidine have traditionally been used as preoperative medication to eliminate or to suppress the stress response to laryngoscopy and intubation.

Gabapentin, is 1-aminomethyl cyclohexane acetic acid, is used as an anticonvulsant drug. It prevents partial seizures and generalized tonic-clonic seizures both in add-on and monotherapy.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but is does not modify GABA or GABAB radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin has an alternative mechanism of action in CNS, it acts by decreasing the synthesis of neurotransmitter glutamate and by binding to the alpha 2 delta subunits of voltage dependent calcium channels.

In literature, we found that there is paucity of work evaluating the haemodynamic effect of gabapentin on laryngoscopy and tracheal intubation. For this reason, we planned a study design to evaluate and compare the efficacy of different doses of gabapentin in attenuating the hemodynamic responses related to laryngoscopy and tracheal intubation.

PATIENTS & METHODS

Following approval from the Institutional Ethical Committee, we obtained written informed consent of the patients. This prospective, randomized and double blind study was carried out on ninety normotensive patients (ASA I and II) between age 20-60 yrs undergoing elective surgery under general anaesthesia with endotracheal intubation. All patients were thoroughly examined. Routine investigation were carried out in all the patients including Hb, complete blood count, serum urea and creatinine, blood sugar, urine examination, chest x-ray and ECG. Exclusion criteria were ASA grade III and IV, anaemia, compromised renal status, cardiac disease, hypertension, COPD and asthma, diabetes, anticipated difficulty in intubation (Mallampatti Grade 3 and...
GP III - received 1000 mg of gabapentin
GP II - received 600 mg of gabapentin
GP I - received Placebo

According to chit in box method, randomly allocated in three groups of 30 patients each.

Midazolam 0.05 mg kg\(^{-1}\) started. All patients were uniformly premedicated with atropine (0.3 mg IV).

Baseline vital parameters of patients (Pulse rate, SBP, DBP and MAP) were recorded 1 hour (h) prior to entering in the operation theatre. Mean arterial pressure (MAP) was calculated by formula MAP = (SBP+2XDBP)/3. Drug selected for the study was given with sip of water by a different anaesthesiologist not involved in the study. After 1 h patients were taken to the operation theatre. Intravenous line was secured with 20G i.v canula and ringer lactate infusion was started. All patients were uniformly premedicated with Midazolam 0.05 mg kg\(^{-1}\), Glycopyrrolate 0.004 mg kg\(^{-1}\) and Fentanyl 1 mcg kg\(^{-1}\) IV. After preoxygenation with 100% O\(_2\) for 3 minutes anaesthesia was induced with thiopentone (5mg kg\(^{-1}\)) and atracurium (0.5 mg kg\(^{-1}\)). Patients were intubated with appropriate size cuffed endotracheal tube and anaesthesia was maintained with Isoflurane, 60% N\(_2\)O in oxygen and atracurium 0.1 mg kg\(^{-1}\) maintenance dose. All intubations were performed by an experienced anaesthesiologist, the duration of laryngoscopy and intubation limited to the minimum possible time in all the patients. Patients in whom duration of laryngoscopy was more than 30 seconds were removed from the study.

Vital parameters (HR, SBP, DBP, MAP and ECG) of patients were recorded at 0, 1, 3, 5 and 10 min after intubation using multipara monitor. At the end of surgery residual neuromuscular blockage was reversed with Neostigmine 0.05 mg kg\(^{-1}\) and Glycopyrrolate 0.01 mg kg\(^{-1}\) IV. Patients were extubated after adequate reversal. A decrease in mean arterial pressure greater than 30% below the preanaesthetic baseline value was treated by incremental doses of ephedrine 4mg IV. Decrease in heart rate below 45 beats/min was treated with incremental doses of atropine 0.3mg IV.

**Sample Size and Statistics**

After the initial pilot observations, it was decided that a 20% of difference should be the minimum detectable difference of means in all 3 groups. The standard deviation of residual was also kept same (20% of average difference of all 3 groups) The alpha value was 0.05 and the power (1-\(\alpha\)) of the study was 0.80. Thus, the calculated sample size for each group was 23 patients. Preserving the designing effect it was decided to include 30 patients in each group. Statistical analysis was performed with SPSS, version 15.0, for Windows statistical software package (SPSS inc., Chicago, IL, USA). The normality of the data distributions was evaluated using the Shapiro-Wilk test. Groups were compared for demographic data (age, weight) and hemodynamic parameters (heart rate, blood pressure) by analysis of variance and t-test. Probability was considered to be significant if less than 0.05. Data are represented as mean and standard deviation.

**RESULTS**

The demographic profile of patients in term of age, body weight, male:female ratio were comparable in all three groups (Table 1). There were no significant differences among the three groups (p>0.05).

Cardiovascular responses are shown in Table 2, Figures 1 and 2. The baseline hemodynamic variables (SBP, DBP, MAP and HR) were similar in all the three groups (p>0.05). Figure 1 represents the SBP and DBP of all the three groups at various time intervals. The upper value is the SBP while the lower value is the DBP. MAP (Figure 2) was significantly decreased in Group III after laryngoscopy and tracheal intubation (0 min) when compared to Group I and Group II (P < 0.001). Significant decrease in MAP was seen at 1, 3, 5 and 10 min after intubation (P < 0.05) in Group III compared to Groups I and II. Hemodynamic variables were similar Group I and Group II, but lower in group II c.f. group I (P > 0.05).

Heart rate values (Table 2) were statistically significantly lower in the Group III at 1, 3, 5, and 10 min after intubation than Group II (P< 0.05); when compared with the control group, these values were substantially lower (P< 0.001). Group I and Group II did not differ statistically (P > 0.05).

**Table 1**

| Observation | Group I (n = 30) | Group II (n =30) | Group III (n =30) |
|-------------|-----------------|-----------------|------------------|
| Age (years) | 37.30+11.13     | 41.70+12.56     | 40.03+10.15      |
| Weight (kg) | 57.30 +7.47     | 60.73 +7.05     | 59.40 +8.05      |
| Sex ratio (m/f) | 8.22            | 8.22            | 6.24            |

Values are shown as number (n) of patients or mean _ SD.

* P = 0.05

**Table 2**

| Observation Time | Group I | Group II | Group III |
|-----------------|---------|----------|-----------|
| Base line       | 90.07 ± 7.36 | 91.37 ± 5.89 | 90.73 ± 6.88 |
| 0 min           | 115.93 ± 9.77 | 110.30 ± 10.55 | 89.93 ± 6.73* |
| 1 min           | 110.40 ± 10.71 | 101.10 ± 11.80 | 82.80 ± 7.62* |
| 3 min           | 103.50 ± 10.53 | 94.33 ± 10.61 | 80.03 ± 8.57* |
| 5 min           | 98.57 ± 11.47 | 90.10 ± 9.95 | 79.27 ± 7.79* |
| 10 min          | 93.73 ± 12.15 | 87.20 ± 8.83 | 79.17 ± 7.66* |

*P< 0.001, when compared to group I and P< 0.05 when compared to group II.
though the values were lower in the Group II.

There were no incidences of hypotension, bradycardia, arrhythmias or other ECG changes observed during the study period in any group.

DISCUSSION

Endotracheal intubation is an integral part of anaesthetist's contribution to patient care. Laryngoscopy & Tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in Heart rate, Blood pressure & arrhythmias.

These physiological changes are well tolerated by healthy individuals. However these changes may be detrimental or even fatal in patients with coronary artery disease, hypertension, cerebrovascular disease, intracranial aneurysm, valvular heart disease. The sympathetic response is associated with Acute Left Ventricular Failure, ischaemic ECG changes and ruptured cerebral aneurysm. As today more and more patients with cardiovascular disorders are presenting themselves for surgery, anaesthesiologists are in search of safest and the most efficient drug which can prevent cardiovascular response to the laryngoscopy and tracheal intubation.

Many therapeutic agents and methods have been recommended and used till date but none of them has evolved as the drug of choice yet. Gabapentin, which is second generation anticonvulsant drug, there are recent evidences that preoperative administration of oral gabapentin is efficacious for attenuation of hemodynamic response to laryngoscopy and intubation.

A.Fassoulaki & colleague found that oral gabapentin used as premedication attenuate the hemodynamic response to laryngoscopy & intubation. In their randomized placebo-controlled trial gabapentin-treated patients (1600 mg in four divided doses, at 6 h intervals starting the day before surgery) had significantly lower systolic (p<0.004) and diastolic arterial pressure (p<0.004) during the first 10 min after endotracheal intubation when compared with placebo. Nevertheless, gabapentin had no effect on heart rate changes. None of the patients in the gabapentin group exhibited severe hypotension when compared with the control group. Memis D and colleague found that patients receiving 800 mg of gabapentin 1 h before surgery had significantly decreased mean arterial pressure and heart rate during the first 10 min after endotracheal intubation compared with either 400 mg gabapentin or placebo (p<0.05). Serhat Koc and colleague also observed the same response.

In this study, oral gabapentin 1000 mg given 1 h prior to operation resulted in significant decreases in MAP and HR during study period (p<0.05). This effect was found to be dose dependent. Although attenuation of the haemodynamic response to laryngoscopy and intubation were statistically significant in normotensive patients, however its use in hypertensive patients needs further evaluation. There were no incidences of hypotension, bradycardia, arrhythmias or other ECG changes observed during the study period.

We did not measure stress mediators such as endogenous plasma catecholamines or cortisol, 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 doubleblinding of the study.

Overall, it appears that preoperative gabapentin blunts the hypertensive response to intubation. However, the effects may be dose-dependent. The mechanism by which gabapentin attenuate the pressure response to laryngoscopy and intubation is not fully known. One of the proposed mechanisms is by inhibition of membrane voltage gated...
calcium channels, thus acting in a manner similar to calcium channel blockers. Other is by decreasing the synthesis of neurotransmitter glutamate. There is, as yet, no data, on the possible role of gabapentin in the attenuation of other aspects of the stress response to surgery.

Gabapentin is effective in the treatment of chronic neuropathic pain; however, little is known about its mechanism of action. It binds with high affinity to Ca2+ channel alpha2delta subunits that are expressed in dorsal root ganglia. Hussain and colleague found that pre-emptive gabapentin reduces postoperative pain and morphine requirement following surgery. 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.

It is concluded that pre-treatment with oral gabapentin 1000 mg, 1 h prior to induction of anaesthesia is a safe and effective method to attenuate the haemodynamic response to laryngoscopy and intubation.

REFERENCES
1. King BD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anaesthesia. Anesthesiology 1951; 12: 556-66.
2. Stoelting R.K, Peterson C. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 1977; 47: 381.
3. Stoelting R.K. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 1979; 58: 116-119.
4. Dahlgren N., Messeter K. Treatment of stress response to laryngoscopy and intubation with fentanyl. Anaesthesia 1981; 36: 1022-6.
5. Black T.E, Kay B, Healy and T.L.J. Reducing the hemodynamic responses to laryngoscopy and intubation. A comparison of alfentanil with fentanyl. Anaesthesia 1984; 39: 883-887.
6. Coleman A.J. and Jordan C: Cardiovascular responses to anaesthesia influence of beta adrenoceptor blockade with metoprolol. Anaesthesia 1980; 35: 972-8.
7. Vucevic M, Purdy G.M, Ellis F.R. Esmolol hydrochloride for management of cardiovascular stress response to laryngoscopy and tracheal intubation. Br J Anaesth1992; 68: 529-30.
8. James F. Hamill, Robert F. Lidocaine before endotracheal intubation: Intravenous or Laryngotracheal? Anesthesiology 1981; 55: 578-581.
9. Elkayam, Uri and Wilbert, S. Aronow. Glyceryl trinitrate (Nitroglycerine) ointment and isosorbide dinitrate: review of their pharmacological properties and therapeutic use. Drugs 1982; 23: 165.
10. Dipak L, Raval, Malini K, Mehta. Oral clonidine pre medication for attenuation of haemodynamic response to laryngoscopy and intubation. Indian J Anaesth 2002; 46 (2): 124-129.
11. Andrews J, Chadwick D, Bates D. Gabapentin in partial epilepsy. Lancet 1990; 335: 1114-1117.
12. Surgery.G.K. Gabapentin Monotherapy: An 8-day double blind, dose controlled multicentre study in hospitalized patients with refractory complex partial and secondarily generalized seizures. Neurology 1997; 49: 739-745.
13. Su. Transport of gabapentin a amino acid transporter; a comparative study in astrocytes synaptosomes and CHO cells. Neurochem 1995; 64: 2125-2131.
14. Patel. Placebo controlled study of gabapentin treatment of panic disorder. Pain 2001; 90: 217-226.
15. Gee NS, Brown JP, Dissanayake VU. The novel anticonvulsant drug,gabapentin, binds to alpha 2 delta subunit of calcium channel. J Biol Chem 1996; 271: 5768-76.
16. Fox E.J, Sklar G.S, Hill C.H, Villanueva R, King B.D. Complications related to the pressure response to endotracheal intubation. Anesthesiology 1977; 47: 524-5.
17. Prys-roberts C, Greene L.T, Meloche R, Forex P. Studies of anaesthesia in relation to hypertension. II: Hemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1971; 43:531.
18. A Fassoulaki, A Melemeni, A Paraskeva and G Petropoulos. Gabapentin attenuates the pressure response to direct laryngoscopy and tracheal intubation. Br J Anaesth 2006; 96 (6) : 769-773
19. Memis D, Turan A, Karamanlioglu B, Seker S, Ture M. Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol 2006; 23 (8) : 686-90
20. Serhat KOC, Dilek Memis, Necdet Sut. The preoperative use of gabapentin, dexamethasone and their combination in vericocele surgery: A randomised controlled trial. Anesth Analg 2007; 105: 1137-1142.
21. Kong VK, Irwin MG Gabapentin: a multimodal perioperative drug? Br J Anaesth 2007; 99(6): 775-86
22. Mich PM, Horne WA. "Alternative splicing of the Ca2+ channel beta4 subunit confers specificity for gabapentin inhibition of Cav2.1 trafficking". Mol Pharmacol 2008; 74(3): 904-12.
23. Hussain Al-Mujadi, Abdul Rahman, Mario Gueorguiev. Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. Can J Anaesth 2006; 53:3; 268-273.