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Comparison of Two Different Doses of Oral Gabapentin for Attenuation of Hemodynamic Response to Laryngoscopy and Intubation: A Prospective Randomized Double Blind Study

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Abstract

Introduction: Laryngoscopy and endotracheal intubation causes transient circulatory changes and are marked by tachycardia, hypertension and sometimes cardiac arrhythmias. *Aims and Objective*: This study was designed to compare the effectiveness of oral Gabapentin in two different doses of 800mg and 1200mg on hemodynamic response during laryngoscopy and endotracheal intubation. *Method*: After hospital ethics committee permission,100 patients of either sex, 18-60 years, ASA grade one, weighing 40-70 kg posted for elective surgery under general anaesthesiawere included. Group Areceived 800 mg of Gabapentin and Group B received 1200 mg of Gabapentin orally two hours prior to surgery randomly. The allocation sequence was in sealed opaque envelopes. After 90 seconds of injection Rocuronium, endotracheal intubation was performed by an anaesthetist of the level of senior resident. For each patient heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded before induction of anaesthesia, after induction of anaesthesia, immediately after endotracheal intubation at 0,1,3,5 and 10 minutes. Statistical analysis was summarized as mean and standard deviation. *Results*: In Group A, mean heart rate and arterial pressure increased at 0, 1, 3, 5 and 10 minutes of laryngoscopy and intubation while in Group B there was no significant change. When two groups were compared, the difference between the mean heart rate and mean arterial pressure after was statistically significant ($p < 0.001$). When the mean heart rate and arterial blood pressure after intubation was compared with pre induction, an increasing trend was seen in Group A at 0,1,3, 5,10 min of intubation.($p < 0.001$). In Group B, the change in the mean heart rate at 0 min after intubation was significant ($p = 0.027$) and change in the mean arterial pressure after intubation at 1 min ($p = 0.029$) , 3 min ($p = 0.021$) and 10 min ($p = 0.014$) was significant. *Conclusion*: Oral Gabapentin 1200 mg when given two hours prior to surgery was better in attenuating the pressor response to laryngoscopy and intubation as compared to oral Gabapentin 800 mg.

Keywords: Oral Gabapentin; Laryngoscopy; Intubation; Pressor Response.

Introduction

Laryngoscopy and endotracheal intubation are integral parts of anaesthesiology. Reid and Brace (1940) were first to recognize that cardiovascular stability may be affected by laryngoscopy and endotracheal intubation [1]. The circulatory changes are mediated by reflex sympathetic discharge due to epilaryngeal and laryngopharyngeal stimulation and are marked by tachycardia, hypertension and cardiac arrhythmias. These are usuallytransient, unpredictable and variable. Young, healthy and normotensive patients tolerate these changes well. But in patients with hypertension, heart disease, coronary artery disease, the pressor response can result in increase in cardiac workload leading to morbidity and mortality.

A variety of drugs have been used to control this hemodynamic response such as Sodium nitroprusside, calcium channel blockers, IV Lignocaine or Lignocaine topical spray, opioids like Fentanyl, Remifentanil & beta blockers like Esmolol,

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Metoprolol etc.Recently Gabapentin has proved as an efficient multimodal perioperative drug in the field of anaesthesia [2,3,4].

Gabapentin is a structural analogue of gamma butyric acid. It is used as an anticonvulsant drug. In addition it has been shown to be effective in diabetic neuropathy [5], neuropathic pain [6,7], post herpetic neuralgia [8] and reflex sympathetic dystrophy [8,9]. Pre-treatment with Gabapentin can block the development of hyperalgesia. Gabapentin has a selective effect on the nociceptive process involving central sensitization [5]. Studies have shown that preoperative Gabapentin decreased pain scores in early postoperative period and postoperative opioid consumption in surgical patients [11,12].

While performing these studies with Gabapentin, authors noticed that some patients were hemodynamically stable. Gabapentin has been shown to block voltage gated calcium currents and calcium efflux from the muscle cells, a mechanism similar to calcium channel blockers which may cause consequent inhibition of smooth muscle relaxation. This might explain the effectiveness of Gabapentin in stable hemodynamics [13]. This double blind randomized study was designed to evaluate and compare the effectiveness of oral Gabapentin in two different doses of 800mg and 1200mg on hemodynamic changes during laryngoscopy and endotracheal intubation.

Materials and Methods

After obtaining hospital ethics committee permission and written informed consent, 100 patients of either sex, having age group 18-60 years, American Society of Anesthesiology grade one, weighing 40-70 kg posted for elective surgery under general anaesthesia, lasting for less than three hours were included. Patients with history of hypertension, diabetes and liver disease, acute or chronic renal disease, neurological disease, pregnant patients, psychiatric disorders, patients on antihypertensive drugs, sedatives, hypnotics, antidepressants, beta blockers, calcium channel blockers were excluded.

Patients were randomly allocated into two groups by computer generated random number tables. Group Areceived 800 mg of Gabapentin (2 capsules of 400 mg) and Group B received 1200 mg of Gabapentin (3 capsules of 400 mg) orally two hours prior to surgery with sips of water. The allocation sequence was in sealed opaque envelopes which were opened just before administration of the drug. Personnel involved in the patient management and data collection were not aware of the group assignment. No other premedicationwas given. Before shifting to the operating room, the patients were assessed for any side effects of Gabapentin.

One day prior to surgery, all the patients were subjected to preanaesthesiacheckup and were thoroughly investigated. They were kept nil by mouth 8 hours prior to the surgery. On arrival to the operating room a 20 G intravenous catheter was inserted into a peripheral vein and a crystalloid infusion was started. Routine monitoring included five lead ECG, non-invasive blood pressure, pulse oximetry and end tidal CO2 monitoring.

Patients were pre medicated with injection Glycopyrrolate 0.2 mg, injection Midazolam 1 mg and injection Fentanyl 2 mcg/kg. After 3 minutes of pre oxygenation, general anaesthesia was induced with injection Propofol 2 mg/kg and injection Rocuronium 0.9 mg/kg. After 90 seconds, endotracheal intubation was performed by an anaesthetist of the level of senior resident to limit the duration of intubation. Patients who were not intubated in more than two attempts or within 30 seconds were excluded. The lungs were mechanically ventilated on Datex-Ohmeda S/5 Avance workstation andmaintained onSevoflurane 1.2-2% and intermittant doses of injection Rocuronium.

For each patient heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded before induction of anaesthesia (baseline), after induction of anaesthesia, immediately after endotracheal intubation at 0,1,3,5 and 10 minutes.The study period ended at this monitoring level.

At the end of surgery, injection Ondansetron 4 mg was given and residual neuromuscular blockade was reversed with injection Neostigmine 0.05 mg/kg and injection Glycopyrrolate 0.01 mg/kg. Patients were extubated after adequate reversal.

A decrease in mean arterial pressure greater than 30% below the pre anaesthetic baseline value was treated by incremental doses of InjectionEphidrene 3 mg and volume replacement. Decrease in the heart rate 20 % below the baseline value was treated with incremental doses of injection Glycopyrrolate 0.2 mg. The data was collected by an observer who blinded to the patient groups.

Based on pilot study it was found that 15% difference had been the minimum detectable difference in the mean of heart rate and blood

pressure between the study groups to ensure 80% power of calculation and 95% confidence interval, so the calculated sample size was found to be 50 in each group.Statistical analysis was summarized as mean and standard deviation. P value of < 0.05 was considered as significant.For detail analysis, Chi-Square test, Student- t test, ANOVA, repeated measure ANOVA and mixed model ANOVA were used to calculate the p value and to establish correlation between study groups.

Results

The groups were similar with respect to demographic variables. One patient from Group A and two patients from Group B were excluded due to prolong duration of laryngoscopy. The baselinemeanheart rate and blood pressurewere comparable among groups (Graph 1).

In Group A, mean heart rate and arterial pressure increased at 0, 1, 3, 5 and 10 minutes of laryngoscopy and intubation while in Group B there was no significant change in the heart rate and blood pressure throughout the study period (Graph 1 and 4). When two groups were compared, the difference between the mean heart rate and mean arterial pressure after intubation was statistically significant ($p < 0.001$). None of the patients developed severe bradycardia or hypotension requiring treatment during the study period.

When the mean heart rate and arterial blood pressure after intubation was compared with pre induction, an increasing trend was seen in Group A at 0,1, 3, 5 , 10 min of intubation .This change was statistically highly significant ($p <0.001$).

In Group B, the change in the mean heart rate at 0 min after intubation was significant ($p = 0.027$), but was not significant at 1 min ($p = 0.17$), 3 min ($p = 0.53$), 5 min ($p = 0.2$) and 10 min ($p = 0.25$). The mean arterial pressuresignificantly decreased after induction ($p <0.001$). The change in the mean arterial pressure after intubation at 1 min ($p = 0.029$),3 min ($p = 0.021$) and 10 min ($p = 0.014$) was significant and at 0 min ($p = 0.069$) and 5 min ($p = 0.059$) was not significant (Graph 1,2,3,4).

Thus overall Group B was better in attenuation of increase in mean heart rate and arterial pressure after laryngoscopy and endotracheal intubation.

Table 1: Demographic data

	Group A(n=49)	Group B(n=48)
Age (yrs)	49±3	50±3
Sex (M:F)	28:22	30:18
Height (cm)	160±3	161±2
Weight(kg)	59.4 ± 2.2	60.4 ± 2.1

All values are expressed as mean ± standard deviation or number of patients.

Table 2: Side effects

Side effects	Group A	Group B
Fatigue	0	1
	0.0%	2.0%
Blurred vision	1	2
	2.0%	4.0%
Dizziness	1	3
	2.0%	6.0%
Drowsiness	2	5
	4.0%	10.0%
Dryness of mouth	2	5
	4.0%	10.0%
Headache	5	10
	10.0%	20.0%
Nausea	5	10
	10.0%	20.0%
Vomiting	2	3
	4.0%	6.0%
Nil	32	11
	64.0%	22.0%

Discussion

The present study compared the efficacy of oral gabapentin 800 mg and 1200mg on hemodynamic changes during laryngoscopy and endotracheal intubation. In Group A, mean heart rate increased at 0 min, 1min, 3 min, 5 min and 10 min of laryngoscopy and intubation while in Group B there was no significant change in the heart rate throughout the study period ($p<0.001$). In the previous studies various doses ranging from 400 mg to 1600 mg of Gabapentin have been used and most of the studies have found that doses more than 800 mg are effective in attenuation of pressor response. Perioperative use of various inducing agents, opioids and muscle relaxants also influence changes in heart rate and blood pressure.

Amani A. Ali et al compared the effects of tablet Gabapentin for hemodynamic stability with oral placebo (Group I), 800 mg of Gabapentin (Group II) or 1200 mg of Gabapentin (Group III) 2 hours prior to surgery. They concluded that HR was significantly lower in Group II (Gabapentin 800) and Group III (Gabapentin 1200) than in Group I (the control group) at 1, 5, and 10 min after intubation with no significant difference between groups II and III [14]. Fasssoulaki A et al studied the role of oral Gabapentin 1600 mg (400 mg tablets given 6 hourly when started one day prior to surgery) to attenuate response to endotracheal intubation and reported thatgabapentin 800 mg, but not 400 mg, was effective in preventing theincrease in HR and BP after tracheal intubation [15]. In another study, Kaya et alreported that gabapentin 800 mg given 2 hours prior to surgery prevented the laryngoscopy response and found that mean diastolic blood pressure was significantly lower in the Gabapentin versus the control group at 0,1,3,5 and 10 minutes after intubation [16].

There was a significant fall in the mean arterial pressure after induction in both the groups followed by significant rise in the mean arterial pressure after laryngoscopy and endotracheal intubation in Group A. But in Group B,there was statistically significant fall in the mean arterial pressure as compare to Group A after laryngoscopy andendotracheal intubation at 1, 3, 10 minutes ($p < 0.05$). Thus a better control of mean arterial pressure was observed in Group B than in Group A ($p< 0.001$). None of the patient developed severe bradycardia or hypotension during the study period.

Memis et alcompared the effect of 400 mg and 800 mggabapentin on hemodynamic response and found that increase in MAP after tracheal intubation but not the HR [17]. Bafna et alfound that gabapentin 1000 mg given before operation significantly attenuated the hemodynamic response to laryngoscopy and intubation, whereas gabapentin 600 mg had no effect [18]. V.R.R Chariet al studied the efficacy of same doses in 90 patients and reported that there was no attenuation of the mean pulse rate and blood pressure by any of the groups [19].

The technique or drug of choice for attenuation of pressor response depends on the necessity and duration of operation, choice of anesthesia technique, route of administration, and medical condition of the patient. In search of a better agent for attenuation of pressor response, authors have compared Gabapentin with Ramifentanyl, beta blockers, clonidine, nitroglycerineetc [20,21]. Marashi S M et alcompared the effect of Clonidine 0.2mg and Gabapentin 900 mg for attenuation of pressor response following laryngoscopy and tracheal intubation in 75 patients. They concluded that both Clonidine and Gabapentin have effective role in blunting pressor response after laryngoscopy, more so with Gabapentin [22].

We observed various side effects such as 33fatigue, blurred vision, dizziness, drowsiness, headache, nausea, vomiting and dryness of mouth. The overall side effects were significantly more in Group B.Probably because of high dose of Gabapentin. Koç S et al in 2007 investigated the effects of Gabapentin and Dexamethasone given together or separately 1 h before the start of surgery in randomlydivided four double-blind groups: Group C (control) received placebo, group G (Gabapentin) received 800 mg Gabapentin, group D (Dexamethasone) received 8 mg Dexamethasone, group GD (Gabapentin plus Dexamethasone) received both 800 mg Gabapentin and 8 mg Dexamethasone IV 1 hour before the start of surgery [23]. They concluded that Gabapentin and Dexamethasone administered together prevented postoperative nausea and vomiting better than individual administration of each drug.

We did not measure levels of catecholamine or cortisol and did not score sedation or analgesia pre as well as postoperatively. These can be considered as limitations of our study.

Conclusion

We concluded that oral Gabapentin 1200 mg when given two hours prior to surgery was better in attenuating the pressor response to laryngoscopy

and intubation as compared to oral Gabapentin in the dose of 800 mg. Oral Gabapentin is easy to administer, cost effective in perioperative settings.

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