GABA-Ergic Premedication and Hemodynamic Stability during Induction Laryngoscopy Phase of General Anesthesia

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Abstract: *introduction:* Gabapentin is a second generation anticonvulsant that is effective in the treatment of chronic neuropathic pain. Recent data suggests its perioperative administration for attenuation of the hemodynamic response to laryngoscopy and intubation. The aim of this study was to compare Oral Gabapentin premedication with no premedication in patients undergoing rigid laryngoscopy and endotracheal intubation for General Anaesthesia in terms of mean heart rate and mean arterial pressure.

Methods: This was a randomized controlled trial conducted at Anesthesia Department Holy Family Hospital Rawalpindi. Total 100 patients were included in the study and randomly divided into 2 groups. In Group-A patients were given 800 mg Gabapentin orally and in Group-B patients were not given Gabapentin orally. Baseline parameters (including heart rate, Mean Arterial Pressure MAP) were recorded 1 hr. before surgery. Drug selected for given patient was given orally with a sip of water. After 1 hr. Data was collected on a standardized Performa and analyzed on SPSS 16 version.

Results: Mean hear rate in Group-A patients at 1st, 3rd, 5th and at 10th minute was 96.22±11.96, 91.84±11.28, 84.66±10.98 and 82.10±11.47 respectively. While in Group-B mean heart rate in Group-B patients at 1st, 3rd, 5th and at 10th minute was 105.70±11.95, 100.42±11.58, 92.18±10.56 and 88.40±9.61 respectively. It was observed that at 1st , 3rd , 5th and at 10th minute mean heart rate was statistically different in both treatment groups. Mean arterial pressure in Group-A patients at 1st, 3rd, 5th and at 10th minute was 103.68±6.55, 100.42±5.63, 96.54±5.72 and 95.04±5.86 respectively. While in Group-B mean arterial pressure in Group-B patients at 1st, 3rd, 5th and at 10th minute was 112.40±6.93, 106.60±5.98, 100.90±5.95 and 99.16±5.69 respectively. It was observed that at 1st, 3rd, 5th and at 10th minute mean arterial pressure was statistically different in both treatment groups.

Conclusion: 800 mg oral gabapentin given 1 hour before undergoing rigid laryngoscopy and endotracheal intubation for general anesthesia significantly affects mean heart rate and mean arterial pressure at 1st, 3rd, 5th and at 10th minute.

Keywords: Oral gabapentin, Premedication, Attenuation, Hemodynamic response, Laryngoscopy, Tracheal intubation.

INTRODUCTION

Airway management via laryngoscopy and tracheal intubation is one of most important components of general anaesthesia [1]. Laryngoscopy and tracheal intubation result in hemodynamic pressor response via sympathetic stimulation [2]. This may lead to hypertension tachycardia dysrhythmias and in extreme cases may lead to myocardial ischemia, infarction and cerebral hemorrhage [1, 3-5].

This pressor response has shown to be associated with increased perioperative morbidity and mortality in patients with cerebrovascular and cardiovascular diseases. Various techniques have been developed to attenuate this hemodynamic pressor response. These include deepening of anaesthesia, omitting anticholinergic premedication, lignocaine spray, intravenous lignocaine, calcium channel blockers, high dose opioids, nitroglycerine ointment, alpha blocker, beta blocker and oral clonidine premedication [1, 2, 4-6]. Gabapentin is an antiepileptic drug. It acts on central nervous system by decreasing synthesis of neurotransmitter glutamate and also by binding to voltage gated calcium channels. Gabapentin has antiallodynic and antihyperalgesic properties and is effective in treating neuropathic pain, post herpetic neuralgia, complex regional pain syndrome type1, malignancy pain and headaches. Studies have shown gabapentin to be beneficial in reducing post-operative pain scores and opioid requirement, prevention of postoperative nausea and vomiting, preoperative anxiolysis and reduction of postoperative delirium. It's most recent studies have shown it to be effective in attenuating the pressor response of laryngoscopy [1, 2, 6-9].

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Fassoulaki et el. showed gabapentin to be effective in stabilizing blood pressure only but has no effect on controlling heart rate upon intubation (P=0.001 for systolic blood pressure at 0,1,3,5 and 10 min respectively as compared to P=0.269 for heart rate) [5].

Memiş *et al*. [8] has shown it to be effective in controlling both heart rate and blood pressure upon intubation.

So the basic aim of our study is to evaluate the effect of gabapentin premedication on both heart rate and blood pressure upon laryngoscopy and intubation so that gabapentin may be used, in our population, as routine premedication for suppression of hemodynamic responses to laryngoscopy and intubation during general anaesthesia for elective surgeries.

METHODS

This randomized control trial study was conducted at Holy Family Hospital, Rawalpindi for a period of 6 months from Jan 2016 to June 2016. A total of 100 patients were recruited in the study. Sample size = n = 50 patients in each group. Sampling was done by using lottery method.

SAMPLING SELECTION

Inclusion Criteria

- ASA–I (normal healthy patient), II (mild systemic disease with no functional limitation).
- Age: Adults, 20-60 years.
- Any Elective surgery involving only General Anesthesia.

Exclusion Criteria

- Emergency procedures.
- ASA grade III and IV patients with history of compromised renal status, cardiac disease (low cardiac output states), hypertension, COPD and asthma, diabetes
- Anticipated difficulty in intubation (Mallampatti Grade 3 and 4)
- Hypersensitivity to any drug used,
- GI disturbance which hinders enteric absorption to oral medicine
- Pregnancy.

Sampling Technique

Non probability consecutive sampling

Duration

6 months after approval of synopsis from 1-11-2013 to 31-04-2014.

Data Collection

After approval from hospital ethical committee, 100 patients were recruited according to selection criteria and written informed consent was taken. Patients were randomly divided in group A and B by lottery method.

Group A Receive 800 mg Gabapentin orally.

Group B did not receive Gabapentin.

Baseline parameters (including heart rate, Mean Arterial Pressure MAP) were recorded 1 hr. before surgery. Drug selected for given patient was given orally with a sip of water. After 1 hr. patient were taken to operation theatre. Intravascular access with two 18G cannulas was established. Standard monitoring including Electrocardiography, pulse oximeter, noninvasive blood pressure was attached. Each group received lactated ringer solution. Patients were pre-oxygenated for 3 minutes via face mask and General anesthesia was administered with 0.1-0.2 mg/kg Nalbuphine, followed by 2mg/kg Propofol, 1-2mg/Kg suxamethonium or 0.5 mg/kg Atracurium for induction and intubation respectively. After intubation, anesthesia was maintained with 60% Nitrous oxide, 40% Oxygen and 1.0 - 1.2% Isoflorane. Injection Atracurium 1/5th of the induction dose was repeated every 25-30 minutes to maintain muscle relaxation. Intubation was performed by experienced anesthetist using standard Macintosh laryngoscope. Vitals parameters including HR and MAP recorded at 1 3 5 10 minutes after intubation by anesthesiologist, not knowing the premedication received by the patient, on the Performa.

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 and decrease in heart rate below45 beats/min was treated by incremental doses of ephedrine 4mg IV and atropine 0.3mg IV respectively and were excluded from study.

Data Analysis

Data was collected on a standardized Performa and analyzed on SPSS 16 version. Continuous variables like age, weight, heart rate and Mean Arterial Pressure MAP (1 3 5 and 10 min post induction) was expressed as mean ± S.D. Categorical variables like gender was expressed as frequencies and percentages. Independent sample t-test was used to compare mean heart rates and mean arterial pressure in two groups. A p-value <0.05 was considered statistically significant. Effect modifier like age, gender and weight were controlled by stratification.

RESULT

A total of 100 patients were included in the study. Each group contained 50 patients. Mean age of patients in Group-A and in Group-B was 31.91±9.72 and 31.82±9.53 years. Minimum age in Group-A and in Group-B was 20 years and maximum age of patients in both treatment groups was 57 and 58 years respectively. Mean weight of patients in Group-A and in Group-B was 64.72±12.28 and 64.54±11.29 Kg.

In Group-A 21 patients were male and 29 patients were females while in Group-B 21 patients were male and 29 patients were female. In both treatments group's number of male and female patients was same.

Table 1: Age (Years) Distribution of Patients in Treatment Groups

	Group-A	Group-B	Total
N	50	50	100
Mean	31.92	31.82	31.87
SD	9.72	9.53	9.58
Minimum	20.00	20.00	20
Maximum	57.00	58.00	58

Group-A= Gabapentin Orally
Group-B= Gabapentin orally was not given

Table 2: Weight (KG) of Patients in Treatment Groups

	Group-A	Group-B	Total
N	50	50	100
Mean	64.72	64.54	64.63
SD	12.28	11.29	11.74
Minimum	45.00	45.00	45
Maximum	96.00	86.00	96

Mean hear rate in Group-A patients at 1st, 3rd, 5th and at 10th minute was 96.22±11.96, 91.84±11.28, 84.66±10.98 and 82.10±11.47 respectively. While in Group-B mean heart rate in Group-B patients at 1st, 3rd, 5th and at 10th minute was 105.70±11.95, 100.42±11.58, 92.18±10.56 and 88.40±9.61 respectively. It was observed that at 1st, 3rd, 5th and at 10th minute mean heart rate was statistically different in both treatment groups. In Group-A patients mean heart rate was low as compared to that of Group-B patients.

Mean arterial pressure in Group-A patients at 1st, 3rd, 5th and at 10th minute was 103.68±6.55, 100.42±5.63, 96.54±5.72 and 95.04±5.86 respectively. While in Group-B mean arterial pressure in Group-B patients at 1st, 3rd, 5th and at 10th minute was 112.40±6.93, 106.60±5.98, 100.90±5.95 and 99.16±5.69 respectively. It was observed that at 1st, 3rd, 5th and at 10th minute mean arterial pressure was statistically different in both treatment groups. In Group-A patients mean arterial pressure was low as compared to that of Group-B patients.

Table 3; Heart Rate in Treatment Groups at 1ST, 3RD, 5TH and 10TH Minute

	Group	Mean ± SD	p-value
Heart Rat-1st Minute	*Group-A*	96.22± 11.96	0.000
	Group-B	105.70± 11.95	
Heart Rate-3rd Minute	*Group-A*	91.84± 11.28	0.000
	Group-B	100.42± 11.58	
Heart Rate-5th Minute	*Group-A*	84.66± 10.98	0.001
	Group-B	92.18±10.56	
Heart Rate-10th Minute	*Group-A*	82.10±11.47	0.004
	Group-B	88.40±9.61	

Table 4: Mean Arterial Pressure in Treatment Groups at 1ST, 3RD, 5TH and 10TH Minute

	Group	Mean ± SD	p-value
Mean Arterial Pressure -1st Minute	*Group-A*	103.68±6.55	0.000
	Group-B	112.40±6.93	
Mean Arterial Pressure -3rd Minute	*Group-A*	100.42±5.63	0.000
	Group-B	106.60±5.89	
Mean Arterial Pressure -5th Minute	*Group-A*	96.54±5.72	0.000
	Group-B	100.90±5.95	
Mean Arterial Pressure -10th Minute	*Group-A*	95.04±5.86	0.001
	Group-B	99.16±5.69	

Heart rate was stratified to see any changes in relation to gender of the patients. It was observed that at 1st, 3rd, 5th and at 10th minute among male significant difference was observed in heart rate in both treatment groups. In Group-A male patient's heart rate was less as compared to that of Group-B patients. Similarly heart rate was observed for female patients at 1st, 3rd, 5th and at 10th minute. At 1st and 3rd minute mean heart rate was statistically different in both treatment groups while at 5th and at 10th minute mean heart rate was statistically same in both treatment groups.

Mean arterial pressure was stratified to see any changes in relation to gender of the patients. It was observed that at 1st, 3rd, 5th and at 10th minute among male & female patients significant difference was observed in mean arterial pressure in both treatment groups. In Group-A among male & female patients mean arterial pressure was less as compared to that of Group-B patients at 1st, 3rd, 5th and at 10th minute respectively.

Table 5: Post Stratification of Heart Rate in Relation to Gender of Patients

Heart Rate		Male	Female
		Mean ± SD	Mean ± SD
1st Minute	Group-A	96.00±11.38	96.37±12.55
	Group-B	108.38±11.59	103.75±12.03
p-value		0.001	0.026
3rd Minute	Group-A	91.33±10.52	92.20±11.97
	Group-B	102.71±11.41	98.75±11.62
p-value		0.002	0.039
5th Minute	Group-A	84.09±11.13	85.06±11.04
	Group-B	95.57±10.29	89.72±10.23
p-value		0.001	0.102
10th Minute	Group-A	81.95±11.24	82.20±11.83
	Group-B	91.38±9.40	86.24±9.33
p-value		0.005	0.155

Heart rate in both treatment groups was stratified in relation to the age of patients. It was observed that in Group-A patients heart rate was statistically different in age groups at 1st, 3rd, 5th and at 10th minute respectively. But in Group-B patients heart rate was not statistically significant in relation to the age of the patients at 1st, 3rd, 5th and at 10th minute respectively. It was also observed that increasing heart rate trend was seen in patients in Group-A with the increase in age. Mean arterial pressure in both treatment groups was observed in relation to the age stratification. On the basis of age stratification it was observed that in both treatment groups no statistically significant difference was present for mean arterial pressure at 1st, 3rd, 5th and at 10th minute.

Table 6: Post Stratification of Mean Arterial Pressure in Relation to Gender of Patients

Mean Arterial Pressure		Male	Female
		Mean ± SD	Mean ± SD
1st Minute	Group-A	102.28±6.52	104.68±6.50
	Group-B	114.19±6.76	111.10±6.87
p-value		0.000	0.001
3rd Minute	Group-A	99.14±5.34	101.34±5.75
	Group-B	107.33±5.57	106.06±6.15
p-value		0.000	0.004
5th Minute	Group-A	95.00±5.48	97.65±5.72
	Group-B	100.71±6.43	101.03±5.70
p-value		0.004	0.028
10th Minute	Group-A	93.33±5.39	96.27±5.96
	Group-B	98.80±6.26	99.41±5.34
p-value		0.004	0.039

DISCUSSION

Tracheal intubation is a noxious stimulus, tending to provoke a marked sympathetic response manifested as tachycardia and hypertension which is potentially deleterious in some patients. Various agents effectively attenuate this response, including anaesthetics, analgesics, adrenergic blocking agents and vasodilators. This has been a fertile area for clinical investigation, spawning numerous studies of the various techniques which might be expected to modify the haemodynamic response to intubation. Some patients unquestionably require careful haemodynamic control during induction of anaesthesia and intubation. Even a transient hyperdynamic response may cause serious complication in patients with symptomatic aortic aneurysm, recent myocardial infarction, cerebral aneurysm, or intracranial hypertension. Gabapentin, a structural analogue of γ-aminobutyric acid, is used primarily for the treatment of seizures, neuropathic pain, and hot flushes. There are, however, some concerns regarding the quality of the research about its use to treat migraines, bipolar disorders, acquired pendular nystagmus, menopausal symptoms, spasticity in multiple sclerosis and uraemic pruritus. Recently, gabapentin has been found to be effective in reducing

Table 7: Post Stratification of Heart Rate in Relation to Age of Patients

			20-30	31-40	41-50	>50	p-value
	Time	Group	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Heart Rate	1st	A	92.61±9.67	96.30±11.75	102.62±13.56	110.00± 15.62	0.029
		B	105.65±12.63	103.66±11.65	108.71±10.93	108.00±14.14	0.842
	3rd	A	87.80±8.56	93.00±11.29	98.62±12.98	103.66±15.30	0.017
		B	100.00±12.10	98.91±12.01	103.42±9.58	105.00±14.14	0.806
	5th	A	80.46±8.12	88.23±11.37	89.37±14.47	93.00±10.81	0.033
		B	91.20±9.88	90.08±12.43	98.42±10.14	97.00±4.24	0.317
	10th	A	77.769±8.81	86.53±11.75	86.00±15.09	90.00±10.00	0.040
		B	87.37±9.09	86.33±10.15	95.42±10.30	91.00±1.41	0.190

Table 8: Post Stratification of Mean Arterial Pressure in Relation to Age of Patients

			20-30	31-40	41-50	>50	p-value
	Time	Group	Mean± SD	Mean± SD	Mean ± SD	Mean± SD	
MAP	1st	A	101.92±6.22	104.46± 6.56	106.25±6.25	108.66± 8.08	0.170
		B	113.58±7.01	109.58±5.99	113.00±8.46	110.00±0.00	0.382
	3rd	A	98.53±5.24	101.61±5.65	103.25±5.57	104.00±5.29	0.077
		B	107.27±5.64	104.33±5.59	107.71±7.91	106.50±2.12	0.505
	5th	A	95.03±5.62	97.69±5.75	98.62±5.95	99.00±4.58	0.274
		B	100.89±5.67	99.25±4.73	104.28±8.84	99.00±1.41	0.344
	10th	A	93.42± 6.13	96.69±5.08	96.75±6.04	97.33±4.16	0.249
		B	99.06±5.47	97.91±4.67	102.57±7.97	96.00±2.82	0.301

the noxious stimuli to laryngoscopy and intubation, thereby attenuating the hemodynamic response. Gabapentin acts by decreasing the synthesis of neurotransmitter glutamate and by binding to α-2δ subunit of voltage dependent calcium channel. Action similar to calcium channel blockers may be responsible for blunting hemodynamic response to laryngoscopy and intubation [10, 11].

In our study mean arterial pressure and heart rate was significantly reduced in Group-A patients who were given 800 mg Gabapentin orally as compared to those patients who were not given Gabapentin.

Vida Ayatollahi *et al* in his study evaluated the effect of 800 mg oral gabapentin on the haemodynamic variables during microlaryngoscopic surgery. They concluded that 800 mg oral gabapentin given 90 min before a procedure attenuates the rise of diastolic blood pressure and mean arterial blood pressure in the first 15 min after microlaryngoscopy surgery, but has no effect on systolic blood pressure or heart rate [12].

CONCLUSIONS

Premedication with Gabapentin in a dose of 800 mg orally given 1 hour before induction causes significant reduction in heart rate and mean arterial pressure till 10th minutes after laryngoscopy and endotracheal intubation for General Anaesthesia thus blunting the hemodynamic stress response of laryngoscopy and intubation.

CONFLICT ON INTERESTS

There is no conflict of interests and there is nothing to declare.

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