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A Comparative Study of Clonidine and Gabapentin for Attenuating Hemodynamic Responses to Laryngoscopy and Tracheal Intubation

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Abstract: *Laryngoscopy and intubation are associated with stress response changes like tachycardia, hypertension and dysrhythmias. The hemodynamic responses during laryngoscopy and endotracheal intubation should be abolished to balance the myocardial oxygen supply and demand which is a key note in the safe conduct of anaesthesia. Many studies have shown Clonidine , a selective α2 adrenoceptor agonist with sedative and analgesic effects, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation. Gabapentin, is a newer drug being used as an antiepileptic . Recently few studies have shown it to be useful for attenuation of intubation responses. Here we have compared the effects of Clonidine and Gabapentin for attenuating hemodynamic effects on laryngoscopy and intubation. We found that Gabapentin was a better drug compared to clonidine to attenuate the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated. More over incidence of side effects is lower in patients treated with gabapentin.*

Keywords *- Clonidine , Gabapentin, Hemodynamic Response, Intubation.*

I. Introduction

Laryngoscopy followed by tracheal intubation is a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory and other physiological systems. Significant tachycardia, hypertension and dysrhythmias can occur with tracheal intubation [1]. General anaesthesia is the one which is routinely and frequently practiced employing various inhalational and intravenous agents to achieve a state of unconsciousness.

With the loss of consciousness under general anaesthesia, there is a loss of protective airway reflexes such as coughing, loss of airway patency and sometimes loss of a regular breathing pattern due to the effect of anaesthetics. To maintain an open airway and regulate breathing, an endotracheal tube is inserted into the trachea after the patient is unconscious.

The cardiovascular response is directly related to the force and duration of laryngoscopy [2].Many studies have reported that 10%– 18% of the patients develop ischemic ST segment changes during the procedure[3].Though these undesirable changes are transitory in nature and well tolerated in healthy individuals, it may result in potentially deleterious effects in patients with co-morbid conditions like hypertension, raised intracranial pressure or coronary artery disease.

As laryngoscopy followed by endotracheal intubation has become the sine qua non of safe anaesthesia, it has become absolutely necessary to take steps to minimize the adverse cardiovascular effects associated with it.The hemodynamic responses during laryngoscopy and endotracheal intubation should be abolished to balance the myocardial oxygen supply and demand which is a key note in the safe conduct of anaesthesia.

Many studies have shown Clonidine, a selective α2 adrenoceptor agonist with sedative and analgesic effects, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation [4].

Gabapentin is a newer drug being used as an antiepileptic. In addition, it has been shown to be effective in neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy [5]. Furthermore, evidence suggests that perioperative administration is efficacious for postoperative analgesia, preoperative anxiolysis and preventing chronic post-surgical pain, postoperative nausea and vomiting and delirium.Recently, few studies have shown it to be useful for attenuation of intubation responses [6].

At present there are very few studies comparing oral Clonidine and Gabapentin premedication for attenuation of hemodynamic responses following laryngoscopy and intubation. So this study is undertaken to evaluate the efficacy of Gabapentin in attenuating hemodynamic responses to laryngoscopy and intubation and how it fares in comparison with Clonidine.

II. Objectives Of The Study

To assess the efficacy and compare oral Clonidine and oral Gabapentin premedication for the attenuation of hemodynamic responses following laryngoscopy and tracheal intubation and To assess side effects like sedation associated with the drugs.

III. Materials And Methods

The study was conducted at R.L .Jalappa Hospital and Research Centre, Tamaka, Kolar, on patients admitted for elective surgeries under general anaesthesia .

Sixty patients of ASA grade 1 and 2 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for the study.Patients were randomly divided on an alternative basisinto two groups of 30 each.

The study was conducted after obtaining ethical committee clearance and informed written consent was taken from patients in both the groups. The study design was randomized and double blinded.

All patients were examined a day before surgery. All were kept fasting overnight after 10:00pm and received tab. Diazepam 10mg orally and tab. Rantidine 150 mg as premedication on the night before surgery. On the morning of surgery the study medications were given orally with sips of water 2 hour preoperatively by a staff nurse who was not involved in the study. Group "C" received - 200µg clonidine . Group "G" received-900mg gabapentin .

Baseline parameters like pulse rate and systolic blood pressure, diastolic blood pressure, mean blood pressure , oxygen saturation and ECG were recorded, intravenous line were secured and all were given intravenous fluids 5 ml/kg. Temperature and urine output monitoring with an indwelling catheter were initiated in the operation theatre.

The level of sedation was assessed by four point score described by Chernik et al.

Grade 0- patient wide awake. Grade 1-patient is sleeping comfortably but responding to verbal commands.Grade 2-deep sleep but arousable. Grade 3-deep sleep, unarousable.

After 3 mins of pre-oxygenation with 100% oxygen , pre medication was done with 5 µg/kg of i.v glycopyrolate. 2.5µg/kg i.v Fentanyl was given for analgesia. Patient was induced with i.v Thiopentone 5 mg/kg followed by i.v suxamethonium 2 mg/kg for intubation. Care was taken to note that the time taken for laryngoscopy was less than 15 seconds in all the patients. Anaesthesia was maintained with N2O+O2+Isoflurane(0.6-1%). Muscle relaxation was achieved with i.v Vecuronium 0.1mg/kg(loading dose) and 0.02 mg/kg (maintenance dose) later.

The baseline heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was taken as 0 minute value. Thereafter the heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were recorded at 1,3,5 and 10 minutes after endotracheal intubation. Any episode of bradycardia (HR<53) was treated by injection Atropine 0.6mg.

3.1 Inclusion Criteria:

Sixty patients of ASA Grade 1 and 2 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for study.

3.2 Exclusion Criteria

Patients physically dependant on narcotics; with history of drug allergy to clonidine or gabapentin; History of cerebrovascular, neurologic, respiratory, Ischaemic heart disease (history of angina, previous Myocardial Infarction; Renal and hepatic dysfunction.; Head injury cases and patients with difficult airways;Patients with hypertension ,pheochromocytoma and diabetes mellitus;Patients on beta blockers, anti-depressants, anti anxiety, anti convulsant or anti-psychotics.

The study required the following investigations:

Complete haemogram, Bleeding time and clotting time,Random blood sugar,Blood urea and serum creatinine, Serum electrolytes, Urine analysis for sugar, albumin and microscopy, ECG and chest X-ray.

3.3 Statistical Analysis

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements are presented on Mean □ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups

Standard deviation:

Significant figures
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P □ 0.05)
** Strongly significant (P value : P□ 0.01)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables .

IV. Results

Study Design: A randomised prospective Comparative two groups study with 60 patients, randomized in to two groups, 30 in Group G (Gabapentin) and 30 in Group C (Clonidine) was undertaken to study the Hemodynamic Responses To Laryngoscopy And Tracheal Intubation.

Table 1: Age distribution of patients studied

Age in years	Group G		Group C	
	No	%	No	%
18-20	2	6.7	3	10.0
21-30	14	46.7	10	33.3
31-40	9	30.0	9	30.0
41-50	5	16.7	8	26.7
>50	0	0.0	0	0
Total	30	100.0	30	100.0
Mean ± SD	32.37±8.77		34.40±9.84	

Samples are age matched with p= 0.402

Table 2: Gender distribution of patients studied

Gender	Group G		Group C	
	No	%	No	%
Male	14	46.7	9	30.0
Female	16	53.3	21	70.0
Total	30	100.0	30	100.0

Samples are gender matched with p = 0.288

Table 3: Weight (kg) distribution of patients studied

Weight (kg)	Group G		Group C	
	No	%	No	%
40-50	5	16.7	6	20.0
51-60	11	36.7	12	40.0
61-70	11	36.7	7	23.3
71-80	3	10.0	3	10.0
>80	0	0.0	2	6.7
Total	30	100.0	30	100.0
Mean ± SD	59.37±9.46		61.10±11.05	

Weight distribution is statistically similar in two groups with p = 0.517

Table 4: Comparison of heart rate (beats per minute) of two groups of patients studied

Heart rate(bpm)	Group G	Group C	P value
Baseline	85.30±10.72	84.03±10.06	0.639
1 minute	93.93±15.08	89.00±11.69	0.162
3 minutes	89.73±14.05	84.97±9.17	0.125
5 minutes	86.93±10.83	78.73±8.27	0.002**
10 minutes	79.27±9.66	70.87±7.87	<0.001**

\+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value: 0.01<P ≤ 0.05)
** Strongly significant (P value: P≤0.01)

Table 4 : Comparison Of Heart Rate In The Two Groups:

Group G: Gabapentin group showed a mean baseline heart rate and standard deviation of 85.30±10.72. At 1 minute, 3 minute, 5 minute and 10 minute interval the increase in mean heart rate were 93.93±15.08, 89.73±14.05, 86.93±10.83 and 79.27±9.66 respectively.

Table 7: Comparison of Mean Arterial Pressure:

Group G: The baseline mean and standard deviation of mean arterial pressure in group G was 93.49±7.69. The mean arterial pressures were 94.06±8.43, 84.43±8.09, 81.22±9.31 and 82.49±7.30 at 1 minute, 3 minute, 5 minute and 10 minute time intervals respectively (mean arterial pressure fell below the baseline value).

Group C: The baseline mean and standard deviation of mean arterial pressure in group C was 92.26±5.75. The mean arterial pressure were104.74±11.93, 99.37±7.08, 97.41±5.05 and 92.19±4.98 at 1 minute, 3 minute, 5 minute and 10 minute time intervals respectively.

Intergroup Comparison: The mean blood pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval is clinically lesser in Gabapentin group than in the Clonidine group. At all time intervals P<0.001 indicates it is statistically also highly significant. The fall to baseline value in the gabapentin group was at 3rd minute and in Clonidine group at 10th minute and statistically it was significant (P<0.01) indicating Gabapentin group showed earlier recovery to baseline values compared to Clonidine group.

Table 8: Sedation score

Sedation score	Group G		Group C	
	No.	%	No.	%
Score 0	-	-	-	-
Score 1	15	50.0	2	6.66
Score 2	13	43.3	9	30.0
Score 3	2	6.7	19	63.34
Total	30	100.0	30	100.0
Mean ± SD	2.57±0.62		3.73±0.64	

Mean sedation score is significantly less in Group G with P = <0.001**

Table 8 : Comparison Of Sedation Scores:

Group G: In Gabapentin group 50%of the patients had a sedation score of 1 followed by 43.3% with sedation score of 2 and rest 6.7% had a score of 3.

Group C: In Clonidine group 63.34% of the patients had a sedation score of 3 followed by 30.0% with sedation score of 2 and rest 6.66% had a score of 1.

Intergroup Comparison: The mean sedation scores was found to be clinically and statistically more in Clonidine group than Gabapentin group with p value<0.001.

Table 9: Side effects

Side effects	Group G (n=30)		Group C (n=30)	
	No	%	No	%
Nil	26	86.67	13	43.3
Present	4	13.33	17	56.7
Drowsy	2	6.7	15	50.0
dizziness	2	6.6	0	0
Bradycardia	0	0.0	2	6.7
Inference	Incidence of side effects are significantly less in Group G with P<0.001**			

Table 9 : Comparison Of Incidence Of Side Effects:

Group G: In Gabapentin group 13.33%of the patients complained of drowsiness(6.7%) and dizziness(6.6%)whereas rest of them did not report any side effects.

Group C: In Clonidine group 50.0% of the patients complained of drowsiness whereas 6.7% (2patients) had an episode of bradycardia which was treated by injection Atropine 0.6mg.

Intergroup Comparison: The incidence of side effects like drowsiness was seen more in Clonidine group than in Gabapentin group, whereas dizziness was seen only in the Gabapentin group.Two patients had an episode of bradycardia in the clonidine group whereas none of the patients in gabapentin group had bradycardia. Overall the Incidence of side effects are significantly less in Group G with P<0.001**

V. Discussion

Laryngoscopy and endotracheal intubation elicit a reflex cardiovascular response in the form of hypertension and tachycardia in adults. Though well tolerated in healthy adult patients it can have catastrophic consequences in patients with coronary artery disease and cerebrovascular diseases [1].

There is increased release of catecholamines norepinephrine, epinephrine and vasopressin- the result of which is tachycardia and hypertension. It also causes a rise in intracranial pressure. It is very much essential to minimise the hemodynamic response to laryngoscopy and intubation in high risk patients such as patients with history of coronary artery disease, hypertension and cerebrovascular diseases. To achieve this it is important to understand the dynamic interactions between the drugs used, onset of drug effects and the delicate balance between the therapeutic effects of drugs and the effects of the noxious stimuli. One should avoid over treating these responses which are usually short lived and well tolerated by most patients-one ounce of prevention is worth a pound of cure. (Ben franklin)

Premedication forms an integral part of anaesthetic management and some form of premedication is universally administered before any anaesthesia. The ideal premedicant should be effective and pleasant to be taken orally, have analgesic and non emetic properties, should not impair cardiovascular stability or depress respiration, and should effectively alleviate apprehension of the patient. Several techniques have been proposed to attenuate the hemodynamic responses following laryngoscopy and intubation such as deepening of anesthesia, premedication with drugs like lignocaine, nitroglycerine, βblockers[7], Calcium channel blockers and opioids.

In our study we have compared clonidine an α2 adrenergic receptor agonist and an established drug in attenuation of hemodynamic responses to laryngoscopy and intubation with gabapentin which belongs to the class of anticonvulsants and is now being increasingly used not only for neuropathic pain but also for pre and post operative analgesia as well as in control of perioperative stress responses including that of laryngoscopy and intubation.

The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. Although the molecular targets of gabapentin remain unknown, the inhibition of Ca2+ flux in muscle cells with a consequent inhibition of smooth muscle contraction might explain the effectiveness of gabapentin in attenuation of the pressor response to laryngoscopy. Thus it may act in a manner similar to Ca2+channel blockers [13].

The attenuating effect of clonidine on hemodynamic responses to airway manipulation has previously been documented by many studies. Dipak L. Raval and other authors [14], Talebi H and colleagues[15], have documented that orally administered clonidine in preanesthetic period attenuates the stress response to laryngoscopy and intubation.

Our reason for studying patients up to 50 years of age was that elderly patients more often take drugs such as antidepressants, hypnotics and antihypertensives. Older patients also exhibit increased sensitivity to drugs and the cardiovascular effects of gabapentin have not been studied extensively. Separate studies are required to study the effect of gabapentin in older age group patients.

We used gabapentin at a single dose of 900mg as Bafna et al8 used 1000mg, Memis and co workers[11] used 800 mg for attenuation of hemodynamic responses for laryngoscopy and intubation.

Gabapentin's efficacy on attenuating hemodynamic responses following laryngoscopy was revealed by Fassoulaki and colleagues in 2006.10 In their study they administered gabapentin 1600 mg in four divided doses, at 6 h intervals (starting the day before surgery).They showed SAP and DAP significantly were lower in the gabapentin group than in the control group immediately also in 1, 3, 5 and 10 minute after laryngoscopy but HR did not differ between two groups at any of the times.

Memis and colleagues [11] in their randomised study also studied the effect of gabapentin 400mg versus 800mg on mean arterial pressure and heart rate at induction of anaesthesia and tracheal intubation and compared it with a placebo. Their study showed that patients receiving placebo and 400 mg gabapentin showed a significant increase in blood pressure and heart rate associated with tracheal intubation compared to baseline levels and from patients receiving 800 mg of gabapentin. There was a significant decrease in heart rate and mean arterial pressure in the group receiving 800 mg gabapentin 1, 3, 5 and 10 min after intubation compared to the placebo group and 400 mg gabapentin group.

In our study we used gabapentin in a dose of 900mg 120 minutes prior to surgery. Gabapentin was found to effectively attenuate the rise in SBP, DBP and MAP at 1,3,5 and 10 minutes after intubation. This correlates with the studies done by Fassoulaki and colleagues and also Memis et al. But in our study as we have compared Gabapentin with Clonidine (at a dose of 200micrograms) the differences in heart rate responses was not found to be significant at 1 and 3 minutes. In fact clonidine showed better attenuation of heart rate response at 5 and 10 minutes which was statistically significant. But the increase in heart rate in group gabapentin was not much more than the baseline values indicating that it maintains the heart rate closer to baseline than clonidine group in which the heart rate decreased to less than baseline values.

Seyed Mojtaba Marashi and colleagues6 in their study found that the highest rates of heart rate, systolic, diastolic and mean arterial blood pressure were in the placebo group in one minute after laryngoscopy, and the lowest rate were in the gabapentin group at the time of 1, 3, 5 and 10 after laryngoscopy, except that the lowest rate of heart rate in 10 min after laryngoscopy was in clonidine group. They also found that clonidine attenuated heart rate at 10 minutes more better than gabapentin, although at 1 and 5minutes they found no significant difference between the clonidine and gabapentin groups.

Our study also correlates with their study in regards to better control of systolic, diastolic and mean arterial pressures in gabapentin group than clonidine group. We found that clonidine attenuated heart rate response better than gabapentin at both 5 and 10 minutes although at 1 and 3 minutes there was no significant difference between the two groups.. Since we did not have a placebo group so we could not assess the hemodynamic attenuating effects of clonidine and gabapentin in comparison to placebo. The differences in heart rate between their study and ours could have been due to the type of inhalational agent used and its concentration variation.

Kaya and co workers [12]had 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 pre treatment 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.

Kiran S, Verma D [13] in their study compared tab. Gabapentin 800mg and placebo as regards to attenuation of hemodynamic responses following direct laryngoscopy and tracheal intubation. They showed that SBP, DBP and MAP were significantly low as compared with placebo in patients pretreated with gabapentin but the tachycardiac response was not completely eliminated.

Our study correlates well with these studies regarding control of pressor changes to laryngoscopy and intubation by gabapentin. We also did not find gabapentin to attenuate the heart rate changes to laryngoscopy and intubation better than clonidine at 1 and 3 minutes.

In yet another study done by Montazeri K and co workers[9] regarding attenuation of the pressor response to direct laryngoscopy and tracheal Intubation: oral clonidine vs. Oral gabapentin premedication showed that compared with clonidine, Gabapentin significantly reduced DBP,SBP, MAP, and RPP changes for 15 min after endotracheal intubation. Compared with placebo, the incidence of HR, SBP, DBP, and MAP percent increase $\geq$ 20% of baseline values were significantly lower in Group Gabapentin but not so with clonidine group when compared to placebo group.

The difference between their study and our study in regards to attenuation of tachycardiac response by gabapentin (which was found to be present in their study) could be as they did not use any inhalational agent for maintenance of anesthesia after laryngoscopy and instead maintained patients on propofol infusion at 150micrograms/kg. This blunting of tachycardia could be attributed to propofol as it is well known that propofol causes decrease in heart rate more than isoflurane (used in our study) which is an inhalational agent .

Previous studies have shown that arterial pressure and heart rate responses are greater when the duration of laryngoscopy exceeds 30 seconds. The previous studies which studied the effect of gabapentin to attenuate the haemodynamic responses to laryngoscopy and intubation did not comment upon duration of laryngoscopy and intubation. In our study the mean duration of laryngoscopy and intubation did not exceed 15seconds.

The anaesthetic agents also have an important impact on attenuation of the pressor response to laryngoscopy and intubation. In one study propofol and cis-atracurium [10] were used and in another sevoflurane, N2O and O2[11] were used. In yet another study propofol and remifentanil were used. We used Thiopentone and succinylcholine (for intubation) followed by vecuronium, and maintained patients on isoflurane(0.6-1%) and nitrous and oxygen(1:1).

In our study at 1and 3 minutes there was no significant differences between the two groups regarding heart rate changes but at 5 and 10 minutes heart rate response to laryngoscopy and intubation in the clonidine group was clinically lesser than gabapentin group and statistically highly significant. The fall to baseline value in the Gabapentin group was at 5th minute and in Clonidine group at 3rd minute and this indicates Clonidine group showed earlier recovery to baseline values compared to Gabapentin group.

The mean systolic blood pressure, diastolic blood pressure and mean arterial pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval was clinically lesser in Gabapentin group than in the Clonidine group. At 1, 3 and 5 and 10 minutes p value was <0.001, and was statistically highly significant indicating Gabapentin group attenuated the pressor response to laryngoscopy and intubation better compared to group Clonidine.

There are few limitations of this study. Patients with ASA physical status I and II were enrolled in the study, so the results cannot be generalized to the patients with higher ASA status. The study was conducted in a single centre. A multi-centered larger study may be more informative. Another limitation of our study was that we did not measure the stress mediators, i.e. endogenous plasma catecholamines or cortisol values

perioperatively.

The overall various side effects In Gabapentin group was 13.33% out of which drowsiness was in 6.7% and dizziness in 6.6% whereas rest of them did not report any side effects. Whereas in Clonidine group the overall incidence of side effects was 56.7% out of which 50.0% of the patients complained of drowsiness whereas 6.7% (2patients) had an episode of bradycardia which was treated by injection Atropine 0.6mg. Overall the incidence of side effects are significantly less in Group G.

Sedation scores which was measured using four point scale described by Chernik et al showed The mean sedation scores to be clinically and statistically more in Clonidine group than Gabapentin group .A conclusion section must be included and should indicate clearly the advantages, limitations, and possible applications of the paper. Although a conclusion may review the main points of the paper, do not replicate the abstract as the conclusion. A conclusion might elaborate on the importance of the work or suggest applications and extentions.

VI. Conclusion

From our study we conclude that gabapentin is a better drug compared to clonidine to attenuate the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated.

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