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ORAL CLONIDINE VERSUS GABAPENTIN FOR ATTENUATION OF HAEMODYNAMIC SURGE DURING ENDOTRACHEAL INTUBATION

Anaesthesiology

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ABSTRACT

Objectives: 1.To compare the efficacy of oral clonidine 100 microgram and oral gabapentin 400 milligram for the attenuation of hemodynamic response to laryngoscopy and tracheal intubation under general anaesthesia by measuring pulse rate and blood pressure at specific intervals. 2. To find out the adverse effects after administration of study drugs. Materials and methods: 62 patients of ASA I receiving General Anaesthesia were randomised into two groups, Group C (n=31) received oral clonidine 100 mcg .Group G (n=31) received oral gabapentin 400mg two hours before intubation. **Results:** Clonidine prevented rise in Heart rate, Systolic, Diastolic and Mean Blood Pressure significantly throughout the first 15 minutes following laryngoscopy as compared to gabapentin group. **Conclusion:** oral clonidine 100mcg is a better premedicant than oral gabapentin 400mg in attenuating the hemodynamic responses to laryngoscopy and intubation. Adverse effects are minimal in both groups.

KEYWORDS

Clonidine, Gabapentin, laryngoscopy, intubation surge

INTRODUCTION:

Laryngoscopy and endotracheal intubation is the traditional method of securing the airway for administration of general anaesthesia .The influence of airway manipulation on heart rate and blood pressure were recognized more than 50 years ago[1].It is now well established that laryngoscopy and endotracheal intubation invariably cause hemodynamic changes associated with increase heart rate, increase blood pressure and occasional disturbance in cardiac rhythm[2, 3]. These hemodynamic changes arise as a form of sympathoadrenal reflex and due to release of norepinephrine and to a lesser extent epinephrine [4].

In normotensive subjects these hemodynamic changes are short lived [5] and probably of little significance. However hemodynamic alteration are hazardous in patient with hypertension, myocardial insufficiency or cerebrovascular disease [6]. In patient with coronary artery disease it may lead to myocardial ischemia and dysrhythmia because tachycardia and hypertension associated with laryngoscopy and endotracheal intubation may result in an increase in myocardial oxygen demand and demand for increase coronary flow. In hypertensive patients these exaggerated response may lead to left ventricular failure, pulmonary oedema and congestive cardiac failure. In patient with intracranial aneurysm or dissecting aneurysm of the aorta, the increase in blood pressure may cause rupture of vessels with life threatening consequences.

So, effective attenuation of sympathoadrenal stress response is an important goal in anaesthesiology. Various pharmacological methods have been tried to limit the pressor response following the insertion of endotracheal tube [7]. The success rate is variable with different methods because each methods has its own merits and demerits.
In several trials, drugs like opioids, lidocaine, nitrates, calcium channel blockers, alpha-2adrenergic agonists, beta blockers or magnesium have been used orally or parenterally to obtund this sympathoadrenal responses.

Pre-anaesthetic medication forms an integral part of anaesthetic management. Alpha-2 adrenorecepter agonist have been used as premedication because of their beneficial properties in anaesthesia. Many studies have shown clonidine, a selective alpha 2 agonist with sedative and analgesic effects, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation by reducing plasma level of epinephrine and norepinephrine[8].

Gabapentin, a structural analogue of inhibitory neurotransmitter gamma amino butyric acid (GABA) but it is not functionally related to it. It selectively binds to alpha 2 subunit of voltage dependent calcium channel which results in decreased synthesis of glutamate, an excitatory neurotransmitter in CNS. It is also used as an anticonvulsant and anxiolytic drug. Pre-treatment with gabapentin can prevent development of hyperalgesia. Also gabapentin has a selective effect on the nociceptive process relating central sensitization [9].

The present study was designed to compare any possible attenuation of hemodynamic response of laryngoscopy and tracheal intubation by the preoperative administration of oral clonidine 100 mcg and oral gabapentin 400 mg.

Materials and Methods:

A randomised double blind prospective study was carried out in Medical College, Kolkata, West Bengal, India.

1. Study population: Patients of either sex, aged between 18 and 60 years, ASA physical status I, posted for elective surgery under general anaesthesia with tracheal intubation.

2. Study period: 12 months, January to December 2016

Sample size:

This study was designed primarily to detect the difference in the hemodynamic stress response (primary end point of the study), i.e. pulse rate, SBP and MAP among the two different groups during laryngoscopy and tracheal intubation under general anaesthesia. There were approximately 8 consecutive measurements of the primary end point in the study subjects (before pre-medication, immediately before induction, immediately after tracheal intubation, and every 3 minutes thereafter for 15 min). To detect a 15% (0.15) difference in the hemodynamic stress response among the two groups using ANOVA (repeated measures, within factors), we studied 62 participants (31 participants in each group) to be able to reject the null hypothesis that the hemodynamic responses in the groups are equal with probability (power) 95% (0.95). The Type I error probability associated with this test of this null hypothesis is 0.05. [Sample Size calculated using G*Power Version 3.1.9.2, 2014. Copyright © 1992-2014 by Franz Faul, Universität Kiel, Germany]

Study technique:

Sixty two (62) patients, belonging to ASA-I, scheduled for elective surgery under general anaesthesia were randomly assigned in 1:1 ratio into two groups depending on the drug given with the help of a computer generated table of random numbers.

- Group C: received oral clonidine 100 mcg tablet with 50 mL of water, 2 hours before the anticipated starting time of surgery.
- Group G: received oral gabapentin 400 mg capsule with 50 mL of water, 2 hours before the anticipated starting time of surgery.

All the patients were fasted as per ASA guideline and pre medicated with oral alprazolam 0.25 mg tablet and oral pantoprazole 40 mg tablet on the night before surgery.

General anaesthesia technique:

Every patient was pre-medicated with of glycopyrolate 0.04 mcg/kg IV, approximately 5 minutes before induction of anaesthesia. On spontaneous ventilation, pre-oxygenation was done with 100% oxygen for 3 minutes, and general anaesthesia was induced with propofol 2 mg/kg IV administered over 20 seconds. Tracheal intubation was facilitated with succinylcholine 1 mg per kg IV. General anaesthesia were maintained with 1% isoflurane and 40% oxygen in nitrous oxide. Surgical muscle relaxation were maintained with loading bolus of 0.3 mg per kg atracurium IV and 0.1 mg/kg IV at 30 minutes intervals. Intraoperative analgesia was provided by tramadol 3 mg/kg IV and paracetamol 20 mg/kg intravenous infusion. Ringer lactate solution 500 mL IV initially over 30 min, followed by 100 mL/h IV through till the end of surgery were infused to replace fasting fluid deficits and hourly maintenance fluid therapy. At the end of surgery, Isoflurane was turned off and each patient was clinically assessed for spontaneous return of neuromuscular function. Residual neuromuscular blockade was reversed with neostigmine 50 mcg/kg plus glycopyrolate 10 mcg/kg IV given slowly over 3 minutes. The hemodynamic parameters (pulse rate, systolic and mean blood pressure) were recorded at specific intervals, i.e. before pre-medication, immediately before induction, immediately after tracheal intubation, and every 3 minutes thereafter for 15 min. The time taken for completion of laryngoscopy and tracheal intubation were measured and recorded for each patient.

Analysis of data:

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3 which is a trademark of the Centers for Disease Control and Prevention (CDC).

Using this software, basic cross-tabulation and frequency distributions were prepared. x^2 test was used to test the association between different study variables under study. Corrected x^2 test was used in case of any one of cell frequency was found less than 5 in the bivariate frequency distribution. Test of proportion (Z-test) was used to test the significant difference between two proportions. T-test was used to test the significant difference between means. $p<0.05$ was considered statistically significant. ANOVA (repeated measure, within factors) will be used to compare pulse rate, SBP, MAP measured at specified intervals in the two study groups. Incidence of adverse effects in each group will be expressed as percentage.

RESULTS:

Table-1: Comparison of demographic parameters of the patients of the two group

Demographic Parameters	Group-C (mean±s.d.) (n=31)	Group-G (mean±s.d.) (n=31)	Test Statistic	p-value
Age (in years)	33.42±7.85	35.19±8.83	t60=0.83	0.41 NS
Gender (Male: Female)	16:15	16:15	= 0.01	0.99 NS
Weight (in kg)	61.84±7.98	63.42±6.84	t60=0.84	0.40 NS
Height (in cm)	159.81±8.86	160.71±6.08	t60=0.46	0.64 NS
BMI (in kg/m2)	24.29±3.18	24.53±1.96	t60=0.35	0.72 NS

All the patients in both the groups were with ASA Class-I.

The patients of the two groups were matched for all demographic parameters by age, gender, weight, height and BMI

Table-2: Comparison of heart rate (HR) per minute at different time of the two groups

Time Interval	Group-C (mean±s.d.) (n=31)	Group-G (mean±s.d.) (n=31)	Test Statistic (t60)	p-value
Before Premedication	89.23±9.45	89.65±9.01	0.17	0.85 NS
Immediately Before Induction	87.16±5.41	88.23±5.90	0.74	0.46 NS
Immediately After Tracheal Intubation	92.71±9.55	107.94±4.70	7.96	<0.001*
3 Minute After Intubation	88.55±8.19	103.97±4.69	9.09	<0.001*
6 Minute After Intubation	87.61±7.50	98.29±3.73	7.09	<0.001*
9 Minute After Intubation	85.97±8.22	96.90±3.72	6.74	<0.001*
12 Minute After Intubation	83.65±5.67	94.10±3.17	8.96	<0.001*
15 Minute After Intubation	84.35±7.68	93.19±3.80	5.74	<0.001*

NS – Statistically Not Significant * Statistically Significant

T-test showed that the mean heart rate of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.0001$).Table-3: Comparison of SBP (mmHg) at different time of the two groups

Time Interval	Group-C (mean±s.d.) (n=31)	Group-G (mean±s.d.) (n=31)	Test Statistic (t60)	p-value
Before Premedication	123.61±12.65	127.87±8.92	1.53	0.13 NS
Immediately Before Induction	120.00±8.84	123.58±7.19	1.74	0.08 NS
Immediately After Tracheal Intubation	122.29±8.43	157.61±4.54	20.52	<0.001*
3 Minute After Intubation	116.19±9.79	154.32±5.09	19.23	<0.001*
6 Minute After Intubation	120.10±9.49	147.48±4.50	14.51	<0.001*
9 Minute After Intubation	123.74±8.85	137.55±4.84	7.62	<0.001*
12 Minute After Intubation	121.81±10.59	129.58±3.95	3.82	<0.001*
15 Minute After Intubation	121.10±9.42	127.90±4.94	3.56	<0.001*

NS – Statistically Not Significant * Statistically Significant

T-test showed that the mean SBP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.0001$).

Table-4: Comparison of DBP (mmHg) at different time of the two groups

Time Interval	Group-C (mean±s.d.) (n=31)	Group-G (mean±s.d.) (n=31)	Test Statistic (t60)	p-value
Before Premedication	77.89±13.21	81.47±5.54	1.39	0.16 NS
Immediately Before Induction	80.81±12.60	83.81±10.28	1.02	0.31 NS
Immediately After Tracheal Intubation	81.02±11.28	99.02±3.52	8.47	<0.001*
3 Minute After Intubation	76.56±13.15	83.73±3.90	2.90	0.005*
6 Minute After Intubation	79.74±13.72	78.48±5.87	0.46	0.64 NS
9 Minute After Intubation	82.27±12.00	81.08±8.14	0.28	0.78 NS
12 Minute After Intubation	79.42±12.17	80.18±8.92	2.90	0.005*
15 Minute After Intubation	72.81±13.89	78.65±8.36	2.01	0.049*

NS – Statistically Not Significant *Statistically Significant

T-test showed that the mean DBP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.01$) except after 6 minutes and 9 minutes.

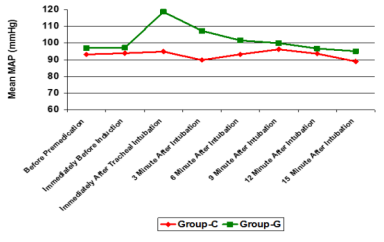
Table-5: Comparison of mean arterial pressure (MAP) (mmHg) at different time of the two groups

Time Interval	Group-C (mean±s.d.) (n=31)	Group-G (mean±s.d.) (n=31)	Test Statistic (t60)	p-value
Before Premedication	93.13±9.65	96.94±4.62	1.92	0.06 NS
Immediately Before Induction	93.87±10.31	97.06±8.35	1.34	0.18 NS
Immediately After Tracheal Intubation	94.77±9.03	118.55±2.68	14.04	<0.001*
3 Minute After Intubation	89.77±10.88	107.26±2.79	8.66	<0.001*
6 Minute After Intubation	93.19±10.97	101.48±4.57	3.88	<0.001*
9 Minute After Intubation	96.10±9.56	99.90±5.83	1.89	0.063 NS
12 Minute After Intubation	93.55±10.43	96.65±6.75	1.38	0.17 NS
15 Minute After Intubation	88.90±11.46	95.06±6.38	2.61	0.011*

NS – Statistically Not Significant * Statistically Significant

T-test showed that the mean MAP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.01$) except after 9 minutes and 12 minutes.

Figure 1: Comparison of mean arterial pressure (MAP) (mmHg) at different time of the two groups



Adverse Effects:

Table-6: Comparison of peri-operative adverse effects

Adverse Effect	Group-C (n=31)	Group-G (n=31)	Z-value	p-value
Hypotension	2 (6.5%)	3(9.7%)	0.82	0.41 NS
Hypertension	0 (0.0%)	0(0.0%)	0.01	0.99 NS
Bradycardia	2 (6.5%)	0(0.0%)	2.59	<0.001*
Nausea	0 (0.0%)	4(12.9%)	3.71	<0.001*
Sedation	3(9.7%)	4(12.9%)	0.71	0.47 NS

* - Statistically Significant NS – Statistically Not Significant

There was no incidence of hypertension in both the groups.
Proportion of patients with bradycardia was significantly higher in Group-C ($p<0.01$).

Proportion of patients with nausea was significantly higher in Group-G ($p<0.001$).

Though all other complications were higher in Group-G as compared to Group-C test of proportion showed that there was no significant difference in the proportions. ($p>0.05$)Discussion:

Several studies have been proposed to attenuate the haemodynamic responses during laryngoscopy and intubation. Tachycardia and rhythm disturbances as a result of intubation were attenuated by omitting atropine as premedication [10]. Nitro-glycerine administration intranasal attenuate the hypertensive response to laryngoscopy and intubation but tachycardia was observed in both the nitro-glycerine and the control group [11].Also IV lidocaine prevented the increase in mean arterial blood pressure but had no effects on the HR [12]. Beta blockers and calcium channel blockers have also been used successfully to prevent the haemodynamic responses to tracheal intubation. Drug with rapid onset and short duration of action similar to beta blocker esmolol and opioid remifentanyl are particularly useful for the intubation period.

The most recent studies regarding prevention of haemodynamic changes after laryngoscopy and tracheal intubation investigate the effects of remifentanyl 1 -5 mcg/kg followed by 0.5mcg/kg/min attenuated the pressure response to intubation but was associated with bradycardia and/or hypotension. [13].

Several studies revealed the use of oral clonidine [8, 14, 15] on attenuation of haemodynamic response to laryngoscopy and tracheal intubation. The possible mechanism of attenuating these response is its ability to decrease central sympathetic outflow as clonidine is a centrally acting selective partial alpha 2 adrenergic agonist.

Gabapentin is a known anticonvulsant drug with widespread effects on pain. Its efficacy on attenuating hemodynamic responses following laryngoscopy was revealed by Fassoulaki and colleagues in 2006. Kayan and colleague in 2008 demonstrated that gabapentin attenuate MAP following laryngoscopy and intubation. [16]

The randomised double blind study was undertaken to compare the usefulness of oral clonidine 100 mcg and oral gabapentin 400 mg given as premedicant.

Both Gabapentin and Clonidine are used as anti-anxiety and have sedative effect [17]. So, patients on psychoactive drugs were excluded in this study to avoid synergistic or added effect of these drugs in post-operative period.

The most significant factors influencing cardiovascular responses in this study are the duration of laryngoscopy during intubation [18]. In this study duration of laryngoscopy and intubation were limited to less than 30 seconds.

Clonidine had a better effect than gabapentin in controlling heart rate after intubation. The mean heart rate of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.0001$).

Clonidine prevented the increase in SBP significantly throughout the first 15 minutes following laryngoscopy as compared to the gabapentin group. T-test showed that the mean SBP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.0001$).

D. Memis et al [19] –used various doses of gabapentin for blunting the response occurring for laryngoscopy and intubation. In their study, two different doses of gabapentin (400mg and 800mg) was given one hour prior to intubation and found that 800mg gabapentin is more effective in suppressing the pressor response comparatively with significant decrease in heart rate and blood pressure. In our study we used lower dose of oral gabapentin (400 mg).

This finding is similar to the study done by Saikat Majumdar et al. in 2015 where they compared 200 mcg clonidine and 800 mg gabapentin. Preoperative sedation between two groups were similar but clonidine attenuated HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) more significantly before induction, during Laryngoscopy and Intubation, 1, 3, and 5 min, following laryngoscopy and intubation, while comparing with gabapentin. But gabapentin-reduced HR, BP, (SBP, DBP, MBP) significantly more at 7 and 10 min after Laryngoscopy and Intubation in comparison to clonidine, [20]

Probably the increased dose of both clonidine (200mcg) and gabapentin(800mg) attenuate the haemodynamic response to laryngoscopy and intubation better than the doses of both drugs we studied .This is a limitation of our study.

The DBP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.01$) except after 6 minutes and 9 minutes.

The mean MAP of the patients of Group-G was significantly higher than that of Group-C for all the time intervals after intubations ($p<0.01$) except after 9 minutes and 12 minutes.

Serum catecholamine are the most important markers to assess the sympathoadrenal stress response. But in this study we could not measure its level in every patient due to scarcity of the resources.

Conclusion and Future Scope:

This prospective randomised double blind study showed that clonidine 100 mcg dose attenuate haemodynamic stress response in term of Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Arterial Pressure better than gabapentin 400 mg dose. A few patients in both the groups presented with minor perioperative complications (e.g. nausea, post-operative bradycardia, dizziness) which were mild in nature. But incidence of post-operative bradycardia was more with oral Clonidine and nausea is more with oral gabapentin and it was statistically significant.

So from these observations we can conclude that oral clonidine 100mcg is a better agent than oral gabapentin 400mg in attenuating the hemodynamic responses to laryngoscopy and intubation. Adverse effects are minimal in both groups.

Further research works are required in search of a suitable premedicant for attenuation of laryngoscopy and intubation surge having no side effects.

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Nil

Conflict of interest:

There are no conflicts of interest.

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