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Comparison Between Oral Gabapentin and Oral Clonidine as Premedicant in Obtunding Haemodynamic Response to Laryngoscopy and Endotracheal Intubation

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KEYWORDS

Laryngoscopy,endotracheal intubation, pressor response,haemodynamics ,premedication

ABSTRACT:

Introduction: Effects of laryngoscopy and endotracheal intubation have been studied for more than half a century. Various experiments in this regard have guided modern medical and anaesthesiological practice to safeguard patients undergoing surgery under general anaesthesia. Premedication with drugs to attenuate the sympathoadrenal response caused by this procedure, to facilitate a smooth induction and maintainence of general anaesthesia with minimal hemodynamic alterations have shown good results. Clonidine and Gabapentin are two of such drugs that we considered comparing in our study; both having multiple pharmacological benefits providing effective results.

Objectives: The aim of our study was to compare the efficacy of oral gabapentin versus oral clonidine as premedication with respect to the haemodynamic response during laryngoscopy and endotracheal intubation.

Methods: A prospective randomized double blind study was conducted on a total of 200 patients undergoing elective surgery under general anaesthesia after institutional ethical committee approval and patient informed consent. Randomly assigned into two equal groups of 100 each, Group G received 600mg of oral gabapentin and Group C received 200µg of oral clonidine 90 minutes prior to start of surgery with sips of water. The preoperative sedation and anxiety scores and pulse rate, systolic, diastolic blood pressure and mean arterial pressures, side effects, if any were noted.

Results: Oral Clonidine 0.2mg when compared with oral gabapentin 600 mg caused better attenuation of haemodynamic response to laryngoscopy and tracheal intubation. Clonidine also maintained a significantly lower pulse rate throughout the study period.

Conclusions: 0.2mg clonidine and 600mg gabapentin both proved to be good premedicant drugs for general anaesthesia as well as in maintaining the sedation and anxiety scores. 0.2mg clonidine proved to be statistically better in attenuating the pressor response to laryngoscopy and tracheal intubation.

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1. Introduction

Effects of laryngoscopy and endotracheal intubation have been studied for more than half a century. Various experiments in this regard have guided modern medical and anaesthesiological practice to safeguard patients undergoing surgery under general anaesthesia. Alfred Kirstein[1,2] is known as the pioneer of Direct Laryngoscopy (1895).
Increased tissue tension caused by laryngoscopy followed by intubation is one of the major reasons responsible for the sympathoadrenal responses in the form of tachycardia and hypertension associated with release of catecholamines in the blood.[3]

In patients with no comorbidities, these changes are transient and well tolerated, but adverse response in haemodynamics is observed in patients of older age and systemic comorbidites which include hypertension, cardiac abnormalities and cerebrovascular diseases, this can predispose the patients to develop complications such as ventricular dysrhythmias, myocardial ischaemia, ventricular failure, pulmonary oedema or even cerebrovascular accidents.[4]

Various methods have been used to attenuate the pressor response following laryngoscopy and intubation which include:

1) Opioid analgesics such as remifentanil, alfentanil and fentanyl[5,6,7,8]
2) Beta blockers such as labetolol, esmolol[9]
3) Local anaesthetics through various routes such as administration of intravenous local anaesthetic or application of topical(nebulized) local anaesthesia to airway[10,11]
4) Deepening the plane of anaesthesia
5) Sedatives as premedicant such as midazolam[12]
6) Vasodilators such as nitroglycerine[13,14]
7) Alpha 2 agonists such as dexmedetomidine[15]
8) Decreasing the duration of laryngoscopy and intubation

Multiple factors affect the haemodynamic pressor responses such as intravenous anaesthetic agents, depth of anaesthesia, use of opioid in premedication, inhalational agents and use of airway devices such as supraglottic airway devices.[16] Universally administered before any anaesthesia, premedication[17] forms an integral part in anaesthetic management. A suitable criteria for an ideal premedicant would be a drug that is pleasant to take orally, have properties such as adequate analgesia and prevention of emesis, prevent a depression in the respiratory system and at the same time, maintain the stability of the cardiovascular system with effective alleviation of apprehension.

A structural analogue to Gamma Amino Butyric Acid (GABA), gabapentin[18] has been used in the maintenance of balanced haemodynamics even after stress stimuli such as laryngoscopy and tracheal intubation.[19,20,21] The exact mechanism of attenuating the haemodynamic pressor response to laryngoscopy and intubation is still not clearly understood. It has been observed that, gabapentin, like calcium channel blockers, binds to the α2d subunit of the voltage gated calcium channels (VGCC) resulting in a reduced release of neurotransmitter resulting in reduced neuronal hyperexcitability.[18]
Clonidine[22] acts on both central and peripheral receptors. Centrally, with its action on the alpha-2 receptors of the nucleus of tractus solitarius and on locus ceruleus, clonidine inhibits release of noradrenaline from the sympathetic nerve terminals. There exists documentation for the use of clonidine in general anaesthesia specifically because of its ability to prevent untoward alteration in haemodynamics caused by stimuli including laryngoscopy and intubation.[23,24,25]

This study is thus undertaken to compare the efficacy of oral gabapentin 600mg with oral clonidine 0.2mg in attenuation of haemodynamic response to laryngoscopy and endotracheal intubation as well as to access the sedation score for adult patients undergoing surgery under general anaesthesia.

2. Aims And Objectives

The primary aim of the study was to compare the efficacy of oral gabapentin versus oral clonidine as premedication in the haemodynamic response to laryngoscopy and endotracheal intubation.

The secondary aim of the study is to evaluate the preoperative sedation and anxiety score.

3. Materials And Methods

This prospective, randomized double-blind study was conducted in the Department of Anaesthesiology between October 2018 to March 2020. After the approval of the Institutional Ethics Committee and an informed consent from the patients, a total of 200 patients were enrolled for the study.

Patients that were included were of the age group of 18 to 65 years, classified by the American Society of Anaesthesiologists as ASA I and II scheduled for surgery under general anaesthesia with orotracheal intubation.

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We excluded patients with an anticipated difficult airway, allergy to clonidine or gabapentin, on drugs with contraindication to clonidine or gabapentin such as antihistaminic, barbiturates or on medications known to interact with clonidine and gabapentin such as benzodiazepines, opioids, tricyclic antidepressants and antipsychotics, having disorders of the cardiovascular, hepatic, renal or neuromuscular system, on beta-blockers or calcium channel blockers, pregnant and lactating mothers.

Methodology

The patients posted for surgery were evaluated preoperatively, examined and the preoperative investigations including the complete blood count, renal function tests, 12 lead electrocardiogram, chest radiography and liver function tests were noted.

Sample size calculation was done using G*Power 3.1.9.2 software. Based on previous studies[26,27] with a confidence interval of 95% and calculated power of 80%, the sample size of 200 was derived. Prior to the surgery, the patient was explained about the study, anaesthesia technique and possible effects of the drug and a written informed consent taken. They were kept nil by mouth for 6 hours prior to surgery. Patients were randomly allocated into two equal groups using an online research randomizer (http://www.randomizer.org/)

Based on the randomization, patients in Group G received oral Gabapentin 600 mg (2 capsules, each of 300mg strength)and Group C received oral Clonidine 200 µg (2 capsules, each of 100 µg clonidine tablet crushed and inserted into an identical empty capsule) 90 minutes prior to start of surgery with sips of water.

The baseline vital parameters such as pulse rate/heart rate (P or HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), Sedation Score (assessment based on the Ramsay Sedation Score) and Anxiety Score were noted by an anaesthesiology resident prior to the administration of the study drug. Prepared drugs packets were then given by this resident to the patient according to the group they were allotted to. This resident was not involved in any further aspect of the study. Patient was monitored during this period for any side effects.

Preinduction, on the operation table, after attaching the standard monitoring which included the pulse oximeter, non invasive blood pressure cuff, 12 lead Electrocardiogram, temperature probe, the Pulse rate (P), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP), Sedation and Anxiety Score were noted. Side effects (if any) such as bradycardia, tachycardia or arrhythmias, hypotension, tremors, dizziness, somnolence, dryness of mouth, ataxia were also noted. Both, the anaesthesiologist in the operation theatre and the patient were blinded to the group assignment.

Sedation and Anxiety was assessed using the following:

Ramsay Sedation Score[28]

- Ramsay 1- Anxious and agitated or restless or both
- Ramsay 2 - Cooperative, oriented and tranquil
- Ramsay 3 - Responsive to commands only
- Ramsay 4 - Brisk response to light glabellar tap or loud auditory stimulus
- Ramsay 5 - Sluggish response to light glabellar tap or loud auditory stimulus
- Ramsay 6 - No response to light glabellar tap or loud auditory stimulus

Anxiety Score

- 0-Patient quiet and comfortable
- 1-Patient uneasy
- 2-Patient worried or anxious
- 3-Patient very worried or very upset
- 4-Patient frightened or terrified

An 18 G intravenous cannula was secured and an infusion of crystalloid initiated.The patient received intravenous (IV) ondansetron 0.1mg/kg and intravenous fentanyl 2 µg/kg as premedication. The patient was preoxygenated with 100% oxygen for 3 minutes and induced with intravenous propofol (2-2.5mg/kg) till loss of response to verbal command.

Ventilation was maintained with oxygen and 2% sevoflurane followed by intravenous vecuronium 0.1mg/kg. After 3 minutes, laryngoscopy was done using a MacIntosh Blade of appropriate size and patient was intubated with a standard cuffed endotracheal tube No.7 ID for females and No.8 ID for males by a skilled anaesthesiologist (who was also blinded for the study). Airway was aimed to be secured within a 15 seconds interval and laryngoscopy duration lasting beyond 30 seconds or needing more than a single attempt at intubation were excluded from the study.

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The cuff was inflated and the endotracheal tube connected to the closed circuit. Anaesthesia was maintained with oxygen and nitrous oxide in ratio of 33:66 O_2 in N_2O with sevoflurane 1-2% and intravenous fentanyl 1 µg/kg hourly. Muscle relaxation was maintained with vecuronium bromide 0.02 mg/kg intermittently thereafter. End tidal carbon dioxide ($EtCO_2$) maintained between 35-45 mmHg throughout the surgery. Paracetamol infusion (1gm) was given as part of multimodal analgesia towards the end of surgery. After completion of surgery, IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg was used to reverse the neuromuscular block and patient extubated when adequate spontaneous ventilation was established.

Electrocardiogram (ECG) (lead-II) and heart rate, Saturation (SpO_2), SBP, DBP, MAP were recorded during

- Baseline prior to premedication
- Pre Induction (After 90 minutes of premedication)
- Post induction (After administration of propofol and vecuronium)
- Immediately after laryngoscopy and intubation
- 3 minutes post intubation
- 5 minutes post intubation
- 10 minutes post intubation

Patients were monitored for adverse effect such as bradycardia (a pulse rate less than 20% of the baseline value or heart rate below 50 beats/minute) and hypotension (a decrease in systolic BP more than 30% of the baseline value or less than 90mmHg) were treated with IV glycopyrrolate 0.2mg bolus and intravenous ephedrine 3mg/dose respectively. An increase in blood pressure or heart rate more than 20% baseline was treated by an additional dose of propofol followed by 40µg fentanyl intravenous bolus. Patients were also monitored for dysrhythmias (ventricular, supraventricular premature beats or any deviation from sinus rhythm).

Statistical Analysis

Statistical analysis was performed with SPSS, Version 20.0 from IBM. To compare and find out the statistical difference between the two groups, the following tests were applied:

Independent T Test for intergroup comparison for the following variables:

- Age
- Weight
- Pulse Rate
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Mean Arterial Pressure

The Chi Square Test for comparison of the following categorical variables:

- Sex
- Sedation Score
- Anxiety Score
- Side Effects

A p value of

- >0.05 – considered not significant
- <0.05- considered significant

4. Results

As shown in the above Tables [1,2] and Figure 1, there is no statistical significant difference with respect to the demographic variables namely age, weight and sex and hence was comparable.

From the above results in Table 3, though clonidine appeared to have more sedation and anxiolysis action, there was no significant difference between the clonidine and gabapentin group.

As shown in Table 4, **P0:**Comparison of the BASELINE PULSE between the two groups shows that pulse is higher in Gabapentin group with a t value of -0.363 and is statistically non significant with a p value of 0.717 **P1:** Comparison of the PRE INDUCTION PULSE between the two groups shows that the pulse is higher in gabapentin group with a t value of -1.555 and is statistically non significant with a p value of 0.122 **P2:** Comparison of the IMMEDIATELY AFTER INDUCTION PULSE between the two groups shows that the pulseis higher in gabapentin group with a t value of -2.818 and is statistically significant with a p value of 0.005 **P3:**Comparison of the IMM. AFTER INTUBATION PULSE between the twogroups shows that the pulse is higher in gabapentin group with a t value of -3.155 and is statistically significant with a p value of 0.002 **P4:**Comparison of the AFTER 3 MINUTES PULSE between the two groups shows that thepulse is higher in gabapentin group with a t value of -3.783 and is statistically significant with a p value of <0.001 **P5:** Comparison of the AFTER 5 MINUTES PULSE

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between the two groupsshows that the pulse is higher in gabapentin group with a t value of -3.152 and is statistically significant with a p value of 0.002 **P6:** Comparison of the AFTER 10 MINUTES PULSE between the two groupsshows that thepulse is higher in gabapentin group with a t value of -3.496 and is statistically significant with a p value of 0.001

The intergroup comparison of the pulse rate between Group C (Clonidine) and Group G (Gabapentin) [Table 4 and Figure 2] showed a higher mean pulse rate in Group G compared to Group C with a statistically significant value of p <0.05 at P3,P4,P5,P6.

As per Table 5, **SBP0:** Comparison of the BASELINE SBP between the two groups shows thatthe SBP is higher in gabapentin group with a t value of -0.941 and is statistically non significant with a p value of 0.348 **SBP1:** Comparison of the PRE INDUCTION SBP between the two groupsshows that the SBP is higher in gabapentin group with a t value of -1.796 and is statistically non significant with a p value of 0.074 **SBP2:** Comparison of the IMMEDIATELY AFTER INDUCTION SBP between the two groups shows that the SBP is higher in clonidine group with a t value 0.047 and is statistically non significant with a p value of 0.962 **SBP3:** Comparison of the immediately AFTER INTUBATION SBP between the two groups shows that the SBP is higher in Gabapentin group with a t value of -1.704 and is statistically non significant with a p value of 0.09 **SBP4:**Comparison of the AFTER 3 MINUTES SBP between the two groups shows that AFTER 3 MINUTES SBP is higher in Gabapentin group with a t value of -2.212 and is statistically significant with a p value of 0.028 **SBP5:**Comparison of the AFTER 5 MINUTES SBP between the two groups shows that the SBP is higher in Gabapentin group with a t value of -1.795 and is statistically non significant with a p value of 0.074 **SBP6:**Comparison of the AFTER 10 MINUTES SBP between the two groups shows that the SBP is higher in Gabapentin group with a t value of -1.54 and is statistically non significant with a p value of 0.125

The intergroup comparison for the systolic blood pressure [Table 5 and Figure 3] showed an overall higher mean systolic blood pressure in Group G as compared to Group C with a significant difference p <0.05 at 3 minutes post intubation.

In reference to Table 6, **DBP0:**Comparison of the BASELINE DBP between the two groups shows that the DBP is higher in Clonidine group with a t value of 0 and is statistically non significant with a p value of 1 **DBP1:** Comparison of the PRE INDUCTION DBP between the two groups shows that the DBP is higher in Gabapentin group with a t value of -2.157 and is statistically significant with a p value of 0.032 **DBP2:**Comparison of the IMMEDIATELY AFTER INDUCTION DBP betweenthe two groups shows that the DBP is higher in Gabapentin group with a t value of -1.355 and is statistically non significant with a p value of 0.177 **DBP3:**Comparison of the IMM. AFTER INTUBATION DBP between the twogroups shows that the DBP is higher in Gabapentin group with a t value of -1.296 and is statistically non significant with a p value of 0.196 **DBP4:**Comparison of the AFTER 3 MINUTES DBP between the two groups shows that the DBP is higher in Gabapentin group with a t value of -2.793 and is statistically significant with a p value of 0.006 **DBP5:** Comparison of the AFTER 5 MINUTES DBP between the two groups shows that the DBP is higher in Gabapentin group with a t value of -1.782 and is statistically non significant with a p value of 0.076 **DBP6:**Comparison of the AFTER 10 MINUTES DBP between the two groups shows that the DBP is higher in Gabapentin group with a t value of -1.675 and is statistically non significant with a p value of 0.095

The intergroup comparison of the diastolic blood pressures of Group C with Group G [Table 6 and Figure 3] showed an overall higher mean in Group G with a statistically significant difference with p <0.05 at 3 minutes post intubation.

As shown in Table 7, **MAP0:**Comparison of the BASELINE MAP between the two groups shows that the MAP is higher in Gabapentin group with a t value of -0.457 and is statistically non significant with a p value of 0.648 **MAP1:**Comparison of the PRE INDUCTION MAP between the two groups shows that the MAP is higher in Gabapentin group with a t value of -2.178 and is statistically significant with a p value of 0.031 **MAP2:**Comparison of the IMMEDIATELY AFTER INDUCTION MAP betweenthe two groups shows that the MAP is higher in Gabapentin group with a t value of -0.847 and is statistically non significant with a p value of 0.398 **MAP3:**Comparison of the IMM. AFTER INTUBATION MAP between the two groups shows that the MAP is higher in Gabapentin group with a t value of -1.538 and is statistically non significant with a p value of 0.126 **MAP4:**Comparison of the AFTER 3 MINUTES MAP between the two groups shows that the MAP is higher in Gabapentin group with a t value of -2.724 and is statistically significant with a p value of 0.007 **MAP5:** Comparison of the AFTER 5 MINUTES MAP between the two groups shows that the MAP is higher in

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Gabapentin group with a t value of -1.867 and is statistically non significant with a p value of 0.063 **MAP6:**Comparison of the AFTER 10 MINUTES MAP between the two groups shows that the MAP is higher in Gabapentin group with a t value of -1.725 and is statistically non significant with a p value of 0.086

The intergroup comparison between Group G and Group C [Table 7 and Figure 4] showed an overall higher value of the mean arterial pressure in group G with a significant difference with p value <0.005 at 3 minutes post intubation.

The intergroup comparison for the side effects showed [Figure 5] 4(4%) patients had bradycardia, 2(2%) had bradycardia and hypotension, 6(6%) had only hypotension with only 1(1%) manifesting with tachycardia in Group C (Clonidine). In the Gabapentin group, 1(1%) of patients showed bradycardia, hypotension and a combination of both.

Patients in clonidine group manifested with more side effects compared with the gabapentin group with a Chi Square value of 7.248 and a p value of 0.123 which was not statistically significant.

5. Discussion

In the present study, clonidine attenuated the pressor response to laryngoscopy and intubation better than gabapentin.

Laryngoscopy and tracheal intubation under general anaesthesia[27,29] are well known noxious stimuli which are known to provoke an untoward transient response in multiple systems primarily respiratory and the cardiovascular system. Laryngoscopy and endotracheal intubation[30] evoke prompt physiological response such as autonomic and activate brainstem reflexes which increase the heart rate, blood pressure, plasma catecholamine levels, and may cause dysrhythmias in some cases.

The response to this stimulus is different depending on the age. In children, the mechanism proposed is stimulation via the monosynaptic reflex, resulting in vagal stimulation of the sinoatrial node, leading to bradycardia. On the contrary, in adults, it is a polysynaptic reflex that predominates, wherein the afferent impulses travels via the glossopharyngeal and vagus nerves to the brainstem and spinal cord followed by an efferent sympathetic response resulting in release of norepinephrine from adrenergic nerve terminals, adrenaline from the adrenal glands, and renin–angiotensin system activation, resulting in hypertension and tachycardia. Stimulation of the upper airway reflexes can result in coughing, bronchospasm or even laryngospasm.

In a well compensated healthy adult, haemodynamics are well maintained but can be detrimental in patients with major systemic comorbidities such as myocardial diseases, cerebral or vascular diseases such as aortic or intracerebral aneurysms, major vessel dissection and increase in intracranial pressure (ICP) in altered autoregulation.

Burstein et Al[31], implied that the cardio-accelerator nerve stimulation resulting in increased sympathetic activity was responsible for the electrocardiographic changes predominantly transient sinus tachycardia and less commonly premature ventricular ectopics, prolonged PR intervals, ST segment depression, ventricular arrhythmias, nodal rhythms or sinus bradycardia.

In the present study, 90 minutes prior to surgery, Group C (Clonidine) and Group G (Gabapentin), received 200µg oral clonidine and 600mg oral gabapentin respectively. According to the meta-analysis by B. Doleman et al,[32] gabapentin appeared comparable with clonidine and beta blockers in terms of its haemodynamic effects following intubation.

It has been proposed that gabapentin, like calcium channel blockers, acts on the voltage gated calcium channels resulting in inhibition of calcium influx and nociceptive transmission.[18] Inhibition of release of catecholamines from the adrenal chromaffin cells by gabapentin has also been proposed by an vitro research.[33]

A randomized-controlled trial on women undergoing hysterectomy, has proven that preoperative administration gabapentin can reduce the postoperative levels of catecholamine (both noradrenaline and adrenaline) and cortisol in the body.[34] Fassoulaki A and colleagues[21] concluded that pretreatment with gabapentin adequately attenuates the pressor response to laryngoscopy and tracheal intubation of the trachea with no change on the heart rate. No patient in the study showed severe hypotension requiring resuscitation. Bafna U et al[35] concluded that preoperative gabapentin blunts the hypertensive response to intubation albeit the effects may be dose dependent. Other authors had

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concluded that 600 mg gabapentin administered 2 hours prior to surgery attenuated the pressor response without affecting the heart rate.[36,37] Mishra PR et al[38] pre-treated patients with oral clonidine (0.2mg), gabapentin (800mg) or placebo respectively 90 minutes prior to surgery. The gabapentin group showed dizziness as a side effect. In the study by Shreedhara NS et al,[27] in which they compared 200µg clonidine with 900 mg gabapentin, the incidence of dizziness was 6.6% in the gabapentin group .

We decided to use 600 mg gabapentin to find out if this dose is effective in attenuating the pressor response while lowering the side effects.

Clonidine is an imidazole compound, alpha-adrenergic agonist with selectivity for alpha-2 receptors.[39] Alpha 2 adrenoceptors activation causes a drop in the peripheral sympathetic tone with a rise in reflex bradycardia caused by vagal stimulation. As a premedication administered orally, sedation, hypnosis and anti-sialogogue effect are seen in a dose range of 2 to 4µg/kg.[24] The alpha-2 receptors activation on locus ceruleus and on nucleus of tractus solitarius presynaptically results in decreased sympathetic tonus, with inhibition of release of noradrenaline. By its action on the receptors of the locus ceruleus, sedation is very commonly seen with clonidine use.[40,41] Suppression of release of ATP, norepinephrine and NPY from postganglionic sympathetic nerves by activation of presynaptic α-2 receptors is another mechanism by which clonidine causes a reduction in blood pressure and heart rate.[42]

Carabine UA and colleagues[24] compared 3 doses of clonidine as a preanaesthetic medication (0.1mg , 0.2mg and 0.3mg) 60 to 90 minutes prior to surgery and found that 0.2mg was better for induction of anaesthesia than 0.1mg and had better cardiovascular profile compared to 0.3mg along with significant anxiolysis hence the preferred dose. After oral administration, clonidine achieves a peak plasma concentration within 60 to 90 minutes.[43] From the conclusions drawn from the above studies, we chose clonidine 0.2mg and gabapentin 600mg as the premedicant doses which we administered orally with sips of water 90 minutes prior to surgery.

In this study, patients in the clonidine group were more sedated when compared to patients in gabapentin group but the difference was not of statistical significance. Singhal SK et al[44] found a significantly better sedation score in the clonidine group when compared with gabapentin.

Also, clonidine also provided better anxiolysis but the difference between the clonidine and gabapentin group was not statistically significant. We found that clonidine proved to provide a better control over the pulse rate throughout the study period when compared to gabapentin.This was similar to other studies wherein they found that the clonidine group (200µg) showed significant reduction in heart rate compared to gabapentin group (900 mg).[27,45]

In our study, there was a gradual non significant decrease in SBP from the baseline in both the groups with a slight rise immediately after intubation in both the groups with Group C showing a mean of (107.54 mmHg +/-12.44) and Group G with a mean of (110.7 mmHg +/-13.75) with a (P=0.09) which was not significant. The SBP did not increase above the baseline values.

At 3 minutes post intubation, Group C showed a mean of (101.02 mmHg +/-10.14) and Group G (104.32 mmHg +/-10.94) the difference being of statistical significance. Thereafter there was a gradual drop in SBP in both the groups at 5, 10 minutes after intubation, with a non significant difference between the two. Gabapentin showed an average higher SBP value compared to the clonidine group at every stage.

Similar to our study, Shreedhara NS et al found[27] the systolic blood pressure was better controlled in the clonidine group when compared with gabapentin and placebo group.

As shown in Figure 3, Immediately after intubation, there was a rise in the mean DBP in both the groups, group C (67.36 mmHg+/-8.59) and Group G (69.08 mmHg+-10.11) with a ($p>0.05$) which was not significant. But at 3 minutes after intubation it was noticed that there was a significant difference between the mean DBP of the two groups with Group C (62.16 mmHg+/-8.16) and Group G(65.46 mmHg+/- 8.54) .Thereafter at 5 and 10 minutes, there was a further fall in the DBP in both groups but this was not significant. Gabapentin group showed a consistently higher value compared to the clonidine group. All the measured values in both groups remained consistently lower than that of the baseline.

In the study by Shreedhara NS et al,[27] it was found that the DBP in the clonidine group was significantly lower when compared to placebo but this was not so with gabapentin. At 1, 3, and 5 minutes after intubation, clonidine group showed mean diastolic blood pressures lower than gabapentin group but were not statistically

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significant. The significant difference between clonidine and gabapentin in our study could be due to use of a lesser dose of gabapentin (600mg) compared to above study used Gabapentin 900mg.

In Figure 4, at 3 minutes post intubation, the MAP in the clonidine group was significantly lower than the MAP in the gabapentin group with a P value of (0.007). The overall MAP values of the Gabapentin group were consistently higher compared to the clonidine group.

Our study was comparable with Shreedhara NS et al, who found that at 3 and 5 minutes interval after intubation ,the mean arterial pressure was lower in the clonidine group when compared to gabapentin group. In their study, compared to placebo group, there was a statistically significant reduction in the mean arterial blood pressure in the clonidine group at 3, 5, and 10 minutes. There was also a statistically significant reduction in the mean arterial blood pressure at 3 and 5 minute in the gabapentin as compared to placebo group.

Hossain MS et al[45] found that the mean arterial pressure was significantly attenuated in clonidine group, values of which remained below baseline throughout the study period and did not warrant any active intervention. There was also a fall in MAP in the gabapentin group throughout except at 1 minute following intubation wherein a statistically significant rise in MAP was observed. This is similar to our study except we had a peak rise in MAP at 3 minutes post intubation.

In our study, 4 (4%) of the patients in clonidine group developed bradycardia which did not require the use of atropine. 2 patients (2%) developed bradycardia with hypotension, 6 patients (6%) developed only hypotension whereas in the gabapentin group only 1 patient (1%) developed bradycardia, 1 patient (1%) developed bradycardia with hypotension and 1 patient (1%) developed only hypotension. Only 1 patient (1%) in the clonidine group developed tachycardia which was not observed in the gabapentin group . This was not statistically significant.

Shreedhara NS et al[27] found that in the clonidine group, of the 56.7% overall incidence of side effects ,50.0% of the patients had drowsiness and 6.7% (2 patients) had an episode of bradycardia, while from the total of 13.33% of patients with gabapentin group with side effects, 6.7% had drowsiness and 6.6% dizziness.

MS Hossain et al[45] found that 46% of the patients in group A (clonidine 200µg) complained of dry mouth preoperatively and post operatively and 3% cases had bradycardia which did not warrant any treatment. Similarly, in group B (Gabapentin 900mg), patients had minor complaints such as headache, drowsiness and dizziness.

From our observations stated above, though both drugs are comparable in effect, clonidine proves to cause better attenuation of the haemodynamic response laryngoscopy and intubation compared to gabapentin. Clonidine also maintains an overall stable lower pulse rate in comparison to gabapentin. Gabapentin has a lower incidence of side effects when compared to clonidine.

In the study by Shreedhara NS et al,[27] better control of systolic, diastolic, and mean arterial pressures was observed in clonidine group than gabapentin group which is comparable to our study. Galat JS et al[16] in their study using oral clonidine (0.2 mg) and oral gabapentin (800 mg) 90mins prior to surgery found comparable significant attenuation of HR, SBP, DBP when compared to oral placebo for the initial 15 minutes, but showed a significant difference in the MAP only at 10mins and 15 minutes post-intubation. The MAP was lower in the gabapentin group compared to the clonidine group. They concluded that both oral clonidine (0.2mg) and oral gabapentin (800mg) are effective in attenuating the pressor response.

Mishra PR et al[38] conducted a study on 90 patients, one group received oral clonidine(0.2mg), the other oral gabapentin (800mg) and the third placebo respectively. They concluded that both 0.2mg oral clonidine and 800mg oral gabapentin administered as premedication 90minutes prior to laryngoscopy, are effective and safe in blunting the haemodynamic stress response to laryngoscopy and tracheal intubation with oral 0.2mg clonidine showing slight better results as compared to 800mg gabapentin.

Contrary to our study, Chauhan A et al,[46] in their study using 900mg oral gabapentin and 0.2mg clonidine, administered 2 hours before surgery to determine the attenuation of pressor response, noticed that even though clonidine group showed a consistently lower heart rate compared to gabapentin, (though a peak rise noticed at 1 minute post intubation),the lowest mean SBP, DBP and MAP was seen with gabapentin after 10 minutes of laryngoscopy. Hence proving gabapentin to be a better alternative due to minimal side effect profile and better maintainence of haemodynamics.

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Propofol was used in the study since it is l also shown to be more effective in attenuating the cardiovascular and catecholamine responses to endotracheal intubation when compared to thiopentone.[47]Vecuronium was used as the neuromuscular blocking agent to facilitate laryngoscopy and endotracheal intubation since it provides excellent intubation condition and duration of action in the dose used[48] and is devoid of significant cardiovascular adverse effects. We used Sevoflurane as the inhalational anesthetic as it has the advantage of maintaining relatively stable haemodynamics compared to other inhalational agents.[49]

Direct laryngoscopy initiates changes in the haemodynamics within seconds which further increases with endotracheal intubation. The observed trend includes a rise within 5 seconds of laryngoscopy, peak effect within 1–2 min of the stimulus and fall to normal level by 5 minutes.[29] Endotracheal intubation was performed by a skilled blinded anaesthesiologist to avoid excessive airway manipulation and aimed at securing the airway within 15 seconds of initiation of intubation. It has been shown in some studies that the heart rate and arterial pressure responses are greater when the laryngoscopy duration exceeds 30 seconds.[27]

Conclusion

Based on our present study, the following were the conclusions made.

Following premedication with 0.2mg clonidine and gabapentin 600mg, clonidine proved to cause better attenuation of the haemodynamic response to laryngoscopy and intubation compared to gabapentin. Clonidine also maintained a significantly lower pulse rate in comparison to gabapentin throughout the study period.

Clonidine was also associated with a higher incidence of adverse effects such as bradycardia and hypotension.

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