Original Research Article

Comparative study of oral clonidine and oral gabapentin in attenuation of pressor response to direct laryngoscopy and tracheal intubation

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Abstract

Background: Laryngoscopy and intubation causes reflex sympatho-adrenal response in the form of tachycardia and hypertension. 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. The present study compared the effect of oral clonidine with oral gabapentin for attenuating hemodynamic pressor responses to laryngoscopy and tracheal intubation.

Methods: Total ninety patients of ASA grade I and II, age between 18-50 years, BMI 18 to 25 and who were posted for elective surgeries under general anesthesia were selected for the study. They were divided into three groups of 30 patients in each. Group P received oral placebo (control), group –C received 0.2mg of oral clonidine and group G received 800mg oral gabapentin. Heart rate, systolic blood pressures, diastolic blood pressures mean blood pressures and rate pressure product were noted before induction, after induction, during laryngoscopy and 1,2,3,4,5,10 and 15 minutes after laryngoscopy and intubation.

Results: There was significant rise in hemodynamic parameters after laryngoscopy and intubation. Oral clonidine (0.2 mg) and oral gabapentin (800 mg) when given 90mins prior to surgery effectively attenuated the rise in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product to laryngoscopy and intubation as compared to oral Placebo.

Conclusion: Both the drugs, tablet clonidine 0.2mg and capsule gabapentin 800mg when given orally was found to be safe and without any side effects like hypotension and bradycardia.

Keywords: Laryngoscopy, Endotracheal intubation, Clonidine, Gabapentin, placebo Tachycardia, Bradycardia.

1. Introduction

Since the inception of general anaesthesia it has been well-recognized that laryngoscopy followed by tracheal intubation is a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory, and other physiological systems which are transient [1]. The stress response is the name given to the hormonal and metabolic changes which follow injury or trauma. [2] The pressor response is a part of the stress response associated with hemodynamic changes due to reflex sympathetic discharge caused by direct laryngoscopy and tracheal intubation. This increased sympathoadrenal activity may result in hypertension, tachycardia and arrhythmias [3-5]. Transient hypertension and tachycardia are probably of no consequence in healthy individuals, but either or both may be hazardous to those with hypertension, myocardial insufficiency and cerebrovascular diseases which are common occurrences in elderly individuals [6-8]. At least in such individuals there is a necessity to blunt this response.

Anesthesiologists have been trying a variety of drugs from their armamentarium to suppress this notorious "pressor response." Drugs which can be used to control this hemodynamic response include vasodilators, beta blockers, calcium channel blockers, α agonists, lignocaine, and opioids.

Clonidine is a selective α_2 adrenoceptor agonist with sedative and analgesic effects, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation [9]. Gabapentin, a structural analogue of γ-aminobutyric acid [10], is used as an anticonvulsant drug [11]. Premedication with gabapentin can prevent the development of hyperalgesia and has a selective effect on the nociceptive process relating central sensitization. It has also been shown to attenuate the pressor response to direct laryngoscopy and tracheal intubation [12]. However its mechanism of action is not known. Recently, few studies have shown it to be useful for attenuation of intubation responses [13].

In the present study the efficacy of oral clonidine and oral gabapentin in attenuatting hemodynamic pressor response to direct laryngoscopy and tracheal intubation was compared with each other and control group that has not received any of the two drugs.

2. Materials and Methods

After obtaining approval from Institutional Ethics Committee and written informed consent from the patients, this study was conducted in Department of Anaesthesiology, at a tertiary care hospital, Mumbai. Total ninety hemodynamically stable patients of ASA grade I and II, age between 18-50 years, BMI 18 to 25, posted for elective surgeries under general anaesthesia as well as those having anticipated duration of surgery less than 4 hrs and no history of allergy to anaesthetic and study drug were selected for the study. Patient with history of severe hypertension, diabetes and liver disease, respiratory, renal, cerebral and cardiovascular disease, pregnant patient, patient with known psychiatric disorder, difficult airway, obesity, patient on antihypertensive, antipsychotic, sedative hypnotic drugs with effect on central nervous system, those taking oral clonidine or oral gabapentin, patient's pulse rate less than 60bpm and blood pressure less than 90mmgHg at the time of study drug medication were excluded from the study. Patients were randomly divided into three groups of 30 patients in each group. Group P received oral placebo (control), Group C received 0.2mg of oral clonidine and Group G received 800mg oral gabapentin.

All patients underwent pre-anaesthetic checkup consisting of a detailed history, general, airway and systemic examination with respect to respiratory system, circulatory system, per abdominal examination and investigation including HB, CBC i.e. hemogram, RFT, LFT, RBS, ECG and Chest X ray. All patients were kept NBM for 8hrs before the surgical procedure. The peak concentration of study drugs were achieved in 2 – 4 hours after oral administration and excreted unchanged in urine. So, all cases were given the study medication orally 90 minutes prior to surgery.

In the operating room, multipara monitors were applied to the patient and baseline parameters such as heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were noted. All cases were premedicated intravenously with glycopyrrolate 0.004mg/kg, ondesateron 4mg, midazolam 0.015mg/kg and fentanyl 2mcg/kg and then pre-oxygenated with 100% O_2 for 3 minutes. Anaesthesia was induced with I.V. propofol 2mg/kg. Neuromuscular blockade was achieved with I.V. vecuronium 0.1mg/kg. Laryngoscopy and intubation was performed after 3 minutes of injection of vecuronium. The endotracheal tube was secured firmly in place after confirming equal air entry bilaterally. Anaesthesia was maintained with 60% nitrous oxide 40% oxygen using closed circuit and intermittent dose of injection vecuronium at the doses of 0.02mg/kg.

Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noted at baseline, after study drug (30 min, 60 min, 90 min), before and after induction, during laryngoscopy and at 1,2,3,4,5,10 and 15 minutes after intubation. The rate pressure product (RPP) was calculated by formula: RPP = HR X SBP

2.1 Statistical analysis

Continuous variable (age, weight and hemodynamic parameters) were presented as Mean± SD. Categorical variable (Gender, ASA status) were expressed in actual number and percentages. Demographic variable were compared between 3 groups by performing One-way ANOVA. Hemodynamic parameters were compared within group at different time point by performing Repeated Measures ANOVA. Changes in hemodynamic parameters at different time point between 3 groups were compared by one-way Analysis o Variance (ANOVA). P-value <0.05 was considered as statistical significant and p-value <0.001 was considered as highly significant. Statistical software STATA version 10.0 and SPSS version 16.0 were used for statistical analysis.

3. Observations and Results

A total of 90 patients who underwent elective surgeries under general anesthesia were enrolled for the study and were randomly allocated into 3 groups of 30 patients in each. The demographic profiles of the patients were comparable in all the three groups and difference was statistically not significant (Table 1).

Table 1: Demographic profile of patients

Parameters	Group P	Group C	Group G	P value
Age (years)	34.26±9.66	31.56±9.31	32.0±8.48	0.4753
Sex (M/F)	14(46.7%)/ 16(53.3%)	14(46.7%)/ 16(53.3%)	18(60%)/ 12(40)	0.491
Weight (kg)	52.9± 8.37	53.9 ±7.55	53.76 ±8.67	0.8773

In all three groups, the mean haemodynamic parameters (HR, SBP, DBP, MAP and RPP), at baseline, 30mins, 60mins and 90mins till before induction were comparable and there was no significant change observed among groups. After induction there was fall in all haemodynamic parameters as compared to baseline, which was not significant and may be due to hemodynamic effect of propofol. While after laryngoscopy and intubation, there was significant rise in the hemodynamic parameters as compared to baseline. However on comparing the difference due to rise in mean HR, SBP, DBP, MAP, RPP at respective events in each groups viz. during laryngoscopy, 1min, 2mins, 3mins, 4mins, 5mins, 10mins and 15mins after intubation, it was observed that there was statistically highly significant difference (p <0.0001) between group P and group C as well as in between group P and group G.

When comparing mean haemodynamic parameters (HR, SBP, DBP, MAP and RPP) in group C and group G (Figure 1 and 2), it was observed that there was no statistical significant difference between two groups from the point before drug, 30mins, 60mins, 90mins, before induction, after induction. Similarly, there was no statistically significant difference observed in HR, SBP, DBP and RPP during laryngoscopy, 1min, 2mins, 3mins, 4mins, 5mins, 10mins and 15mins after intubation while in MAP difference was not observed during laryngoscopy, 1min, 2mins, 3mins, 4mins, 5mins after intubation. At 10mins it was observed that there was highly significant difference (p<0.001) between two groups. Similarly at 15mins the mean MAP was significant (p<0.039) after intubation.

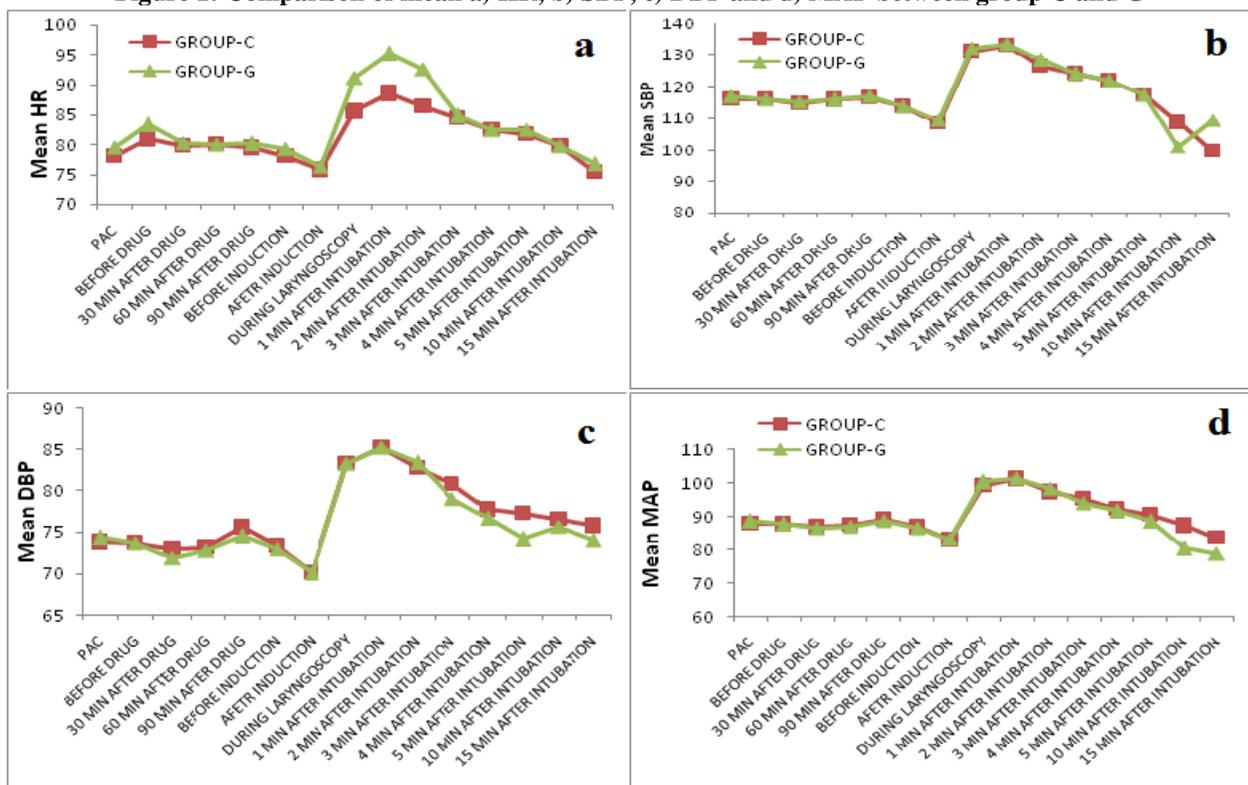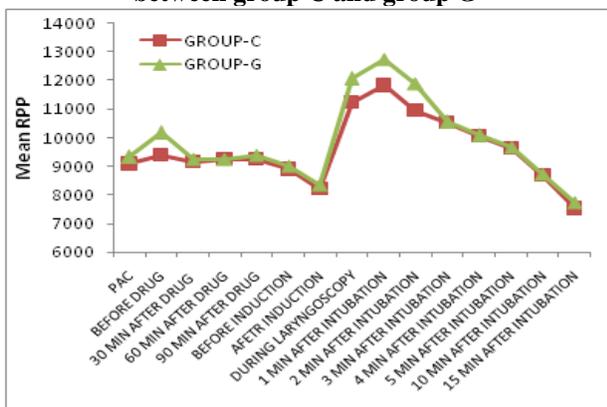**Figure 1: Comparison of mean a) HR, b) SBP, c) DBP and d) MAP between group C and G**

Figure 2: Comparison of mean Rate pressure product between group C and group G

4. Discussion

In the present study we have compared clonidine an α_2 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 Ca^{2+} 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 Ca^{2+} channel blockers [14]. We used gabapentin at a single dose of 800 mg as Bafna *et al* [15] used 1000mg; Memis and co workers [16] used 800 mg for attenuation of hemodynamic responses for laryngoscopy and intubation.

All the three groups of our study were comparable demographically in terms of their age; sex ratio; weight and were also comparable with respects of the duration of laryngoscopy and intubation. Our reason for studying the patients up to 50 years of age was that elderly patients more often are on drugs such as antidepressants, hypnotics and antihypertensives and also exhibit increased sensitivity to drugs. The hemodynamic pressor response to direct laryngoscopy and intubation as observed by change in heart rate, SBP, DBP, MAP and RPP. We found significant rise in the hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product after laryngoscopy and intubation as compared to baseline. Oral clonidine (0.2 mg) and oral gabapentin (800 mg) when given 90mins prior to surgery effectively attenuated the rise in haemodynamic parameters to laryngoscopy and intubation as compared to oral Placebo. Hence, both the drugs were equally effective to control HR, SBP, DBP, MAP and RPP. The findings of the present study regarding hemodynamic pressor response to direct laryngoscopy and intubation were correlated with previous studies [12, 13,16-20].

Gabapentin's efficacy on attenuating hemodynamic responses following laryngoscopy was revealed by Fassoulaki and colleagues in 2006 [12]. Kaya and co workers [18] 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 and Verma [14] 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 with these studies regarding control of pressor changes to laryngoscopy and intubation by gabapentin. The attenuating effect of clonidine on hemodynamic responses to airway manipulation has previously been documented by many studies. Raval *et al* [21] and Talebi and colleagues [22], have documented that orally administered clonidine in preanesthetic period attenuates the stress response to laryngoscopy and intubation.

Clonidine and gabapentin have certain adverse effects inherent to their structure. Clonidine can cause dry mouth, sedation, hypotension and marked bradycardia. The most frequent sideeffects reported with gabapentin are somnolence, dizziness, ataxia, fatigue, unsteadiness, nystagmus, headache, tremors, diplopia, and nausea. In our study, none of the patients at any time during the study had developed severe bradycardia (heart rate less than 40 per minute or required injection atropine) and severe hypotension with systolic blood pressure less than 90mmHg, or required intravenous fluid resuscitation and vasopressors.

Hemodynamic pressor response is a complex process that is affected by multiple factors including depth of anesthesia, opioid use in premedication, i.v. anesthetics, inhalational agents and use of supraglottic airway devices to name a few. Future studies can be directed toward the effect of these confounding factors on the efficacy of clonidine and gabapentin. These can be supplemented by concurrent measurement of catecholamine and cortisol levels for better correlation.

5. Conclusion

Oral clonidine in a dose of 0.2 mg and Oral gabapentin in dose of 800 mg when given 90mins prior to surgery is effective in attenuating the hemodynamic pressor response to laryngoscopy and intubation as compared to oral Placebo. Finally we concluded that both drugs, tablet clonidine 0.2mg and capsule gabapentin 800mg when given orally was found to be safe and without any side effects like hypotension and bradycardia.

Acknowledgement

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