

## COMPARISON OF ORAL CLONIDINE WITH GABAPENTIN PREMEDICATION IN ATTENUATION OF HEMODYNAMIC RESPONSE FOLLOWING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION- A PROSPECTIVE RANDOMIZED PLACEBO CONTROLLED STUDY

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### Abstract

**Background:** Manipulation of airway during laryngoscopy and endotracheal intubation are associated with hemodynamic and cardiovascular responses. Usually these changes are well tolerated by healthy individual, however transient changes can result in potentially deleterious effects. Various combination of drugs have used for premedication which can influence the sympathetic response to laryngoscopy and intubation. **Materials and Methods:** This is a prospective, randomized, placebo-controlled, double blind comparative study that aimed to study the effectiveness of oral clonidine and gabapentin premedication in attenuating the hemodynamic response following laryngoscopy and endotracheal intubation. The study involved 120 patients scheduled for elective general surgical procedures under general anesthesia. Group A received clonidine 300ug, group B received gabapentin 800mg, and group C received a placebo 2 hours before induction. Duration of laryngoscopy was recorded. All the patients were monitored for changes in heart rate and mean arterial pressure values at baseline, before induction, immediately before intubation, 1 min, 3 min, 5 min, and 10 min after intubation. **Result:** The groups were comparable in terms of age, weight, and sex. There was no statistical difference in duration of laryngoscopy among the three groups. The results showed that both clonidine and gabapentin were effective in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation compared to the placebo. There were significant changes in heart rate and mean arterial pressure in all three groups following intubation, but the changes were less pronounced in the clonidine group compared to the gabapentin and placebo groups. Clonidine showed a greater reduction in heart rate and mean arterial pressure compared to other groups. **Conclusion:** These findings suggest that both oral clonidine and gabapentin can effectively attenuate the hemodynamic response to laryngoscopy and endotracheal intubation. However, clonidine appears to have a greater impact on reducing the hemodynamic response compared to gabapentin.

## INTRODUCTION

Laryngoscopy and endotracheal intubation is an integral part of anesthesiologist's contribution to patient care and are regarded as the one of the core skills of anesthesiologist. Laryngoscopy itself is a noxious and most invasive stimulus during endotracheal intubation.<sup>[1,2]</sup> Manipulation of the respiratory tract such as during laryngoscopy and

endotracheal intubation are associated with hemodynamic and cardiovascular responses consisting of increased circulating catecholamines, heart rate, blood pressure, myocardial oxygen demand, tachycardia and dysrhythmias.<sup>[3]</sup> Evidence from the laboratory data demonstrates that epipharyngeal and laryngopharyngeal stimulation augments cervical sympathetic activity in the efferent fibers to heart. This explains the increase in plasma

levels of norepinephrine, and to a lesser extent epinephrine, which occur in response to laryngoscopy and endotracheal intubation.<sup>[4]</sup>

The rise in heart rate and blood pressure is usually transient occurring 30 seconds after intubation and lasting for less than 10 minutes.<sup>[1]</sup> Usually these changes are well tolerated by healthy individual, but are of great concern in susceptible individuals particularly those with systemic hypertension, coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm and recent myocardial infarction. In such patients these transient changes can result in potentially deleterious effects such as myocardial ischemia, left ventricular failure as a result of increased myocardial oxygen demand and cerebral haemorrhage.<sup>[1,4]</sup>

Most of the patients awaiting elective or emergency surgery experience pre-operative anxiety.<sup>[5]</sup> Anxiety is an unpleasant emotion and may cause patients to avoid planned operation. It may also adversely influence anaesthetic induction and peri-operative outcome.<sup>[6]</sup> The anticipation of undergoing surgery or anaesthesia can cause psychological stress to patients which are manifested as anxiety.<sup>[7]</sup> Young patients, female patients, patients with less education and patients with no previous anesthetic experience or a previous negative anesthetic experience will have higher anxiety scores.<sup>[8]</sup>

A variable combination of drugs used for premedication, induction, relaxation and maintenance of anaesthesia can influence the sympathetic response to laryngoscopy and intubation. Oral clonidine, the prototypical  $\alpha_2$ -adrenergic agonist, has been successfully used for ambulatory premedication. Clonidine an  $\alpha_2$ -adrenoceptor agonist is under intense investigation as an adjunct to anesthesia.<sup>[9]</sup> These drugs reduced anesthetic requirements, attenuate adrenergic, hormonal, and hemodynamic stress responses to surgery, reduce anxiety, and lead to sedation.<sup>[10]</sup> A dose of 300 $\mu$ g clonidine orally or larger reduces sympathetic activity. It has been proved in many studies that clonidine is beneficial in blunting reflex tachycardia and hypertensive responses.<sup>[11,12]</sup> The risk of undesirable side effects is extremely important in evaluating the overall safety of pre-anesthetic medication. The potentially beneficial effect of  $\alpha_2$  adrenoceptor agonists may be negated by bradycardia and hypotension.<sup>[13,14]</sup> Gabapentin has been tried for attenuating pre-operative anxiety and stress response to intubation however data on efficacy, dosing, adverse effect profile, ideal timing, and duration of treatment are lacking to recommend gabapentin in routine clinical use.<sup>[15]</sup> The present study was conducted to compare the effect of oral Clonidine and Gabapentin premedication on modifying the hemodynamic stress response following laryngoscopy and endotracheal intubation.

#### **Aims and Objectives**

The study was undertaken to evaluate the effect of oral Clonidine and oral Gabapentin premedication in attenuating the hemodynamic response and to

compare them with placebo in attenuating haemodynamic response to laryngoscopy and endotracheal intubation.

## **MATERIALS AND METHODS**

After approval from the Institutional ethical committee and written consent from the patient and/or relatives, the study was conducted in the department of anesthesiology at a tertiary care center. The study was designed as a hospital based prospective randomized double blinded placebo controlled trial involving a total of 120 patients of ASA1 in the age group of 20–60 years of either sex, scheduled to undergo elective general surgical procedures under general anaesthesia. The patients were randomly allocated to three equal groups, group A, group B and group C of 40 each by means of a computer generated table of random numbers. Group A received clonidine 300  $\mu$ g, group B received gabapentin 800mg and group C received placebo tablet. The drug from the closed envelope which was labelled for each group was drawn and given to the patient by anesthetist (who was unaware of the contents of the envelopes) with sips of water 120 min before induction of anaesthesia. The identity of the tablet was not revealed to the patient. Patients did not receive any other premedication other than the study drugs mentioned. Pre-oxygenation with 100% O<sub>2</sub> was done for 3 minutes. Subsequent induction was done with inj. etomidate 0.2 to 0.3mg/kg subsequent relaxation was accomplished with inj. rocuronium 0.8 mg/kg. Direct laryngoscopy and endotracheal intubation was performed by experienced anesthesiologist. Duration of laryngoscopy was recorded in all the patients. Any patient with more than one attempt required for intubation was excluded from the study. Similarly patients requiring more than 30 seconds for intubation were excluded from the study. No stimulus was applied for the first 5 minutes. Any complications during this period viz., vomiting, involuntary movements, laryngospasm and coughing were noted. Anaesthesia was maintained with Oxygen (33%), Nitrous oxide (66%) and Isoflurane. Inj. rocuronium was used as a muscle relaxant intra-operatively. At the end of the surgical procedure, residual neuromuscular block was antagonized with Inj. Neostigmine, 50 $\mu$ g/kg IV, and Inj. Glycopyrrolate, 5 $\mu$ g/kg IV.

All the patients were monitored for changes in heart rate and Mean Arterial Pressure values were recorded at baseline, before induction, immediately before intubation, 1 min, 3 min, 5 min, and 10 min after intubation. Any side effects like hypotension, bradycardia, dry mouth, vomiting, or others were recorded.

#### **Statistical Analysis**

The data obtained was statistically analyzed and represented as Mean  $\pm$  SD. Chi-square test was used for categorical data (Age, gender, ASA grade). One way ANOVA was used for multiple group

comparison with post hoc Tuckey's test for inter group comparisons. For within the group comparison one way ANOVA was used followed by post hoc Dunetts test to assess the difference at different intervals. A P value of 0.05 or less was taken as statistically significant.

## RESULTS

All the groups were comparable with respect to age, weight and sex. No statistical difference ( $P > 0.05$ ) existed between the three groups as regards to sex,

age and weight as shown in table 1. There was 1 drop out in group 1 due to bradycardia with hypotension at the time of induction, one patient was excluded in group 2 due to more than 1 attempt during laryngoscopy and intubation and two patients excluded in group 3 due to more than 1 attempt during laryngoscopy and intubation in one patient and greater than 30 seconds required for intubation. The difference in mean duration of laryngoscopy of was not statistically significant among the 3 groups and the groups are comparable with respect to mean duration of laryngoscopy. [Table 1]

**Table 1: Clinico-Demographic Characteristics and Duration Of Laryngoscopy**

Observations	Group A, (n=40)	Group B, (n=40)	Group C, (n=40)	P value
Drop outs	1	1	2	-
Age in years	37.37 ± 2.74	38.43 ± 3.20	37.75 ± 2.63	0.25
Weight in kgs	58.92 ± 2.41	60.05 ± 1.92	59.54 ± 2.19	0.07
Sex Ratio (M/F)	18/21	22/17	22/16	0.72
Duration of laryngoscopy in seconds	14.4 ± 1.8	13.5 ± 1.9	13.9 ± 1.6	0.12

Group A = Clonidine; Group B = Gabapentin; Group C = Placebo

**Table 2: Inter group comparison of changes in mean heart rate (bpm) and mean arterial blood pressure (MAP)**

		Group A			Group B			Group C		
		Mean ± SD	Change from BL	p value	Mean ± SD	Change from BL	p value	Mean ± SD	Change from BL	p value
baseline (BL)	HR	75.6 ± 4.8	-	-	76.5 ± 7.0	-	-	75.6 ± 5.1	-	-
	MAP	91.9 ± 4.9	-	-	91.5 ± 4.9	-	-	92.5 ± 3.4	-	-
pre induction	HR	66.3 ± 5.1	9.4	<0.01	81.9 ± 4.1	5.5	<0.01	82.9 ± 3.4	7.3	<0.01
	MAP	89.8 ± 3.4	2.1	<0.05	94.1 ± 2.8	2.6	<0.05	94.9 ± 3.1	2.5	<0.05
Immed. Before intubation	HR	72.3 ± 4.6	3.4	<0.01	82.9 ± 4.0	6.4	<0.01	83.1 ± 4.9	7.5	<0.01
	MAP	84.0 ± 3.6	7.9	<0.01	97.1 ± 5.1	5.6	<0.01	98.3 ± 4.3	5.8	<0.01
1 min after intubation	HR	86.3 ± 3.9	10.7	<0.01	104.6 ± 5.2	28.1	<0.01	106.1 ± 5.4	30.5	<0.01
	MAP	97.5 ± 2.4	5.6	<0.01	118.5 ± 5.1	26.9	<0.01	119.9 ± 5.9	27.4	<0.01
3 min after intubation	HR	81.4 ± 5.3	5.8	<0.01	99.7 ± 6.2	23.3	<0.01	100.7 ± 3.91	25.1	<0.01
	MAP	93.2 ± 2.6	1.3	>0.05	110.2 ± 3.5	18.7	<0.01	113.3 ± 2.9	20.8	<0.01
5 min after intubation	HR	78.5 ± 2.1	2.9	<0.05	91.3 ± 5.2	14.9	<0.01	93.8 ± 5.9	18.1	<0.01
	MAP	90.6 ± 2.2	1.3	>0.05	101.1 ± 4.4	9.5	<0.01	103.3 ± 4.1	10.8	<0.01
10 min after intubation	HR	68.6 ± 2.1	7.0	<0.01	87.2 ± 4.0	10.7	<0.01	88.1 ± 7.0	12.5	<0.01
	MAP	84.7 ± 4.7	7.2	<0.01	97.2 ± 2.7	5.6	<0.01	99.3 ± 1.7	6.8	<0.01

Group A = Clonidine; Group B = Gabapentin; Group C = Placebo

There was a significant change in HR from the baseline value in all the three groups, after the intubation ( $P < 0.01$ ). HR increased for up to 1 min after intubation, followed by a decreasing trend and reaching back to baseline values by the end of 5 minutes in group A, 10 minutes in group B and group C. The raise in heart rate was more in group C and least in group A. During the pre-induction period there was fall in MAP with mean of 84.0 mmHg in the immediate before intubation which was not seen

with other two groups. 1 minute after laryngoscopy and intubation mean MAP was increased in all the three groups. The increase in MAP during intubation compared to baseline value was statistically significant ( $p < 0.01$ ). By 5 min MAP reached to baseline and was less than MAP after 10 minutes in group A, while as rise in MAP was maximum in group C. In group B and group C MAP remained above the baseline value during study period. ( $p < 0.01$ ). [Table 2]

## DISCUSSION

Mean duration of laryngoscopy in all the three groups was less than 15 seconds. A linear increase in heart rate and mean arterial pressure during the first 45 seconds was observed. Robert K Stoelting<sup>16</sup> noted that the best way to prevent laryngoscopic reactions was to minimize the duration of laryngoscopy and intubation and noted that if laryngoscopy and intubation were performed within 15 seconds, the hemodynamic changes seemed to be minimal. In our study the duration of laryngoscopy was restricted as much as possible and all the laryngoscopy and intubations were performed by an expert anaesthesiologist.

In the present study, the groups were comparable with respect to their demographic variables and their baseline values of heart rate and MAP. There was a significant increase in MAP and heart rate compared to baseline in all the groups during laryngoscopy and endotracheal intubation. But there was lesser rise in clonidine group when compared to other two groups. The heart rate increased by 40.3% 1 min after direct laryngoscopy and endotracheal intubation compared to baseline value in the placebo group ( $p < 0.01$ ). A similar increase in gabapentin group was 36% and in clonidine group was 14.1%. Attenuation of rise in the heart rate by clonidine is evident and statistically significant when compared with gabapentin and placebo ( $p < 0.001$ ).

Subsequently heart rate started to settle down and approached to baseline in clonidine group at the end of 5 min but was still high in gabapentin and placebo groups even after 10 min. Though there were decreased heart rate values in gabapentin group as compared to placebo however there was no statistically significant difference, indicating that gabapentin was not successful in attenuating the increase in HR following laryngoscopy and endotracheal intubation. MAP increased by 29.6% in placebo group while it increased by 29.3% in gabapentin group and only by 6.9% in clonidine group compared to baseline values during laryngoscopy & intubation. Attenuation of mean arterial pressure is significant in clonidine group as compared to both gabapentin and placebo groups ( $p < 0.01$ ).

There was significant reduction in HR, MAP in clonidine group during the pre-induction period (120 min after oral administration) which was not observed with other two groups. Bradycardia ( $HR < 60/min$ ) was observed in 13 patients and in one patient bradycardia with hypotension was seen which was treated with atropine and crystalloids and the patient was excluded from the study. Bradycardia & hypotension are well known side effects of clonidine.<sup>[17]</sup> This is because clonidine has a central sympatholytic action.<sup>[17]</sup> In the other two groups, instead of fall, a rise in HR and MAP was observed during the pre-induction period.

The efficiency of clonidine in attenuation of cardiovascular responses similar to our study has been verified by many other studies. Batra YK et al studied the attenuation of pulse rate and blood pressure response to laryngoscopy and tracheal intubation by clonidine in forty healthy patients. Heart rate and blood pressure were significantly lower in the clonidine treated group immediately after intubation ( $p < 0.001$ ).<sup>[18]</sup> Laurito et al found that clonidine blunted the hemodynamic response (HR, SBP & DBP) to 15 sec laryngoscopy but not to 45 sec laryngoscopy when compared with the corresponding control group.<sup>[19]</sup>

Ghignone M et al studied the effects of oral clonidine on depths of fentanyl anaesthesia and on cardiovascular response to laryngoscopy and intubation in 24 patients undergoing aorto-coronary bypass surgery and concluded that oral clonidine reduced the fentanyl requirement and prevented the hemodynamic response to intubation.<sup>[20]</sup>

Most studies have used  $5\mu g/kg$  clonidine which will be  $300\mu g$  in an average 60kg adult. In our study we have used single dose of  $300\mu g$  clonidine 120 min before induction. Our study fully confirms the findings of the most studies i.e. clonidine  $300\mu g$  decreases the stress response (HR, SBP and DBP) to laryngoscopy and endotracheal intubation.

Fassoulaki et al observed that SBP and DBP was significantly lower in the gabapentin group than in control group at 1 min, 3 min, and 10 min after intubation.<sup>[21]</sup> However they used higher dose of 1600mg. Indira Kumari studied the changes in systolic, diastolic and mean blood pressure and heart rate following laryngoscopy and intubation after administering gabapentin 900mg 2 hours before induction. Significant rise in SBP, DBP and MAP was observed following laryngoscopy and tracheal intubation in placebo group as compared to gabapentin group. No significant change in heart rate was documented in both the groups.<sup>[22]</sup>

Kiran has studied the effects of gabapentin (800mg) in attenuation of haemodynamic responses to direct laryngoscopy and tracheal intubation in hundred patients undergoing elective surgery. SBP, DBP & MAP was significantly lower in the gabapentin as compared to the control group at 0, 1, 3, 5 and 10 min after intubation but tachycardiac response was not completely eliminated. In this study they have used gabapentin 800 mg at 10.00 p.m. the night before surgery and again at 6.00 a.m. on the day of surgery. In our study only a single dose of gabapentin 800mg was given orally 120 minutes before surgery.<sup>[23]</sup> Our study partly confirms the findings of above authors. Even we found no significant attenuation of HR with laryngoscopy and endotracheal intubation with single dose of gabapentin 800mg.

Memis et al found that 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 (with the

same dose) we did not find significant attenuation of HR and MAP in gabapentin group.<sup>[24]</sup>

Kaya, F et al found that, when compared with the placebo group MAP values of the gabapentin group were significantly lower for the first 10 min after tracheal intubation.<sup>[25]</sup>

In our study no significant attenuation of pressor response was observed in gabapentin group during laryngoscopy and endotracheal intubation. Our study design & patient selection with respect to age, sex & ASA status was similar to the above studies. The negative result that gabapentin does not attenuate stress response could be due to the lower single dose of gabapentin (800mg) compared to Fassoulaki et al who used multiple doses before surgery.<sup>[26]</sup> Our negative result may be explained by the findings of Kong V K F & Irwin M G who reviewed many controlled trials and found that the effects of gabapentin were dose dependent and the changes in heart rate were inconsistent. The authors concluded that effects of gabapentin on attenuating haemodynamic response to tracheal intubation, preventing PONV, and reducing postoperative delirium are promising but, as yet, inconclusive and more studies are required to explore the role of gabapentin, as a potential multimodal perioperative drug.<sup>[27]</sup>

## CONCLUSION

The administration of premedication for attenuating the hyperadrenergic hemodynamic stress response to direct laryngoscopy and ETT insertion should be routinely encouraged preoperatively and clonidine (300mcg) was seen to be superior in comparison to gabapentin (800 mg) and placebo. Gabapentin 800mg is not superior to placebo in attenuating pressor response to airway manipulation. Further studies with higher dosed of gabapentin administration needs to be conducted to find the optimal dose to establish its effect in attenuating the stress response to airway manipulation.

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