



# A comparative evaluation of gabapentin and clonidine for attenuating pressor responses to laryngoscopy and endotracheal intubation in hypertensive patients-A prospective double-blinded clinical study

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## ABSTRACT

**Background:** Endotracheal intubation forms an indispensable part of general anesthesia. Various adjuvants have been added to diminish the hemodynamic stress response associated with it. These changes are more marked in hypertensive individuals. **Aims and Objectives:** The aim of the present study was to compare the efficacy of oral clonidine and oral gabapentin and their associated side effects if any; for attenuation of hemodynamic responses following laryngoscopy and tracheal intubation in hypertensive patients. **Materials and Methods:** A total of 108 hypertensive patients with American Society of Anesthesiologists grade II/III scheduled for elective surgeries requiring general anesthesia were randomly allocated into three groups receiving Group G Tablet gabapentin 800 mg, Group C Tablet clonidine 0.2 mg, and Group P placebo (multivitamin tablets) given 2 h before surgery with a sip of water. The hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and adverse events during the perioperative period were noted. The statistical analysis was done by paired t-test, ANOVA, and Chi-square test and by SPSS22 software. **Results:** The demographic data were comparable in all three groups. There was no significant difference at baseline for HR, SBP, DBP, and MBP in all three groups. The mean HR was significantly lower in Group C as compared to Group G and Group P ( $P < 0.013$ ). The mean SBP, DBP, and MBP was significantly lower in Groups C and G as compared to Group P ( $P < 0.01$ ) before induction, after induction after laryngoscopy and intubation, then at 5, 10, 15, 20, 25, and 30 min after intubation. **Conclusion:** Clonidine and gabapentin in the abovementioned doses can be safely used for attenuating hemodynamic stress response. Clonidine proved to have better hemodynamic stability and tends to be more effective in attenuating pressor response laryngoscopy and intubation in hypertensive patients when compared to gabapentin.

**Key words:** Clonidine; Gabapentin; Hemodynamic stability; Hypertensive patients

## INTRODUCTION

Laryngoscopy with or without tracheal intubation leads to a highly noxious stimulus that arises due to activation of the sympathoadrenal system and is due to the release of norepinephrine and epinephrine.<sup>1</sup>

Stress response was first described by Reid and Brace in the 1940s.<sup>2</sup> Pressor responses such as hypertension, tachycardia, ischemic ST changes, and dysrhythmias<sup>3</sup> are observed during laryngoscopy and endotracheal intubation. Patients with hypertension (treated/untreated) are more prone to an increased pressure response to intubation than normotensives.<sup>4</sup>

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Several strategies are being used to circumvent these changes which include the duration of laryngoscopy to <15 s, deepening the patient, increasing the concentration of inhalational agents, beta-blockers, calcium channel blockers, vasodilators, local anesthetics, magnesium sulfate, alpha-2 agonists, labetalol, sedatives, and anxiolytics.<sup>5</sup> Clonidine, an imidazoline derivative, is a selective alpha-2 agonist that has proved its role as a pre-medication for reducing hemodynamic stress response, reducing the dose of an induction agent, and sedation.<sup>6</sup> Gabapentin, 1-(amino-methyl) cyclohexane acetic acid, is a structural analog of the neurotransmitter, g-aminobutyric acid it is being used to attenuate the stress response to direct laryngoscopy and intubation.<sup>7</sup>

A number of studies have evaluated the efficacy of both these drugs.

### Aims and objectives

The aim of the present study was to compare and evaluate the efficacy of clonidine and gabapentin for attenuation of hemodynamic stress response to intubation in hypertensive patients scheduled for elective surgeries under general anesthesia.

### Primary objective

1. To assess the efficacy and compare oral clonidine and oral gabapentin premedication for the attenuation of hemodynamic responses (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], and mean arterial pressure [MAP]) following laryngoscopy and tracheal intubation in hypertensive patients.

### Secondary objective

1. To assess side effects associated with the drugs
2. To evaluate the effect of oral gabapentin 800 mg on hemodynamic response to laryngoscopy and intubation in hypertensive patients
3. To evaluate the effect of oral clonidine 200 µg on hemodynamic response to laryngoscopy and intubation in hypertensive patients.

## MATERIALS AND METHODS

The present study was conducted in a cohort of 108 hypertensive patients admitted to JA Group of Hospitals, belonging to the physical status of ASA grade II and III, aged 18–70 years, undergoing elective surgeries requiring general anesthesia, after obtaining approval from the ethics committee of the institute during January 2021–June 2022 and after getting informed written consent from the patient.

This study was conducted in a prospective, randomized, and double-blinded manner.

### Sample size

On the basis of the study by Nanda et al.,<sup>8</sup> for HR at 5 min was used to calculate the sample size, and it was found that the mean±SD in group gabapentin was 86.93±10.83, while in group clonidine, it was 78.73±8.27, and the mean effect size was 8.2.

At a 5% level of significance ( $Z_{\alpha/2}=1.96$ ) and at 95% power of the test ( $Z_{1-\beta}=1.64$ ), the sample size was calculated for two-group comparisons (in the case of continuous data) from the article by Noordzij et al.<sup>9</sup> The calculated sample size in each group was 36. Hence, the total sample size for three group comparison is 108.

### Inclusion criteria

- Age -18–70 years of either sex
- American Society of Anesthesiologists physical status –11 and 111
- Hypertensive patients on treatment
- Surgery elective surgery under general anesthesia
- Mallampatti score-1 and 11
- Patients giving valid informed consent.

### Exclusion criteria

- Patients not satisfying the inclusion criteria
- Patients posted for emergency surgeries
- Patients with coronary artery disease, diabetes mellitus, renal failure, asthma, COPD, liver dysfunction, and morbid obesity
- Anticipated difficult intubation
- Patients refusing informed consent
- Patients having a history of drug allergy
- Patients on antipsychotic medications
- Pregnant patients.

All patients satisfying the inclusion criteria were investigated for routine baseline pre-operative CBC, RBS, LFT, RFT, serum electrolytes, chest X-ray, and a 12-lead ECG. Patients were explained about the procedure and their consent was taken in written format. Patients were subsequently randomized into three groups of 36 each using slips in the box technique, allocated into three groups, Group G, Group C, and Group P.

In the preoperative room, the patients were again assessed and vitals were recorded 2 h before the scheduled time of surgery and given the oral formulation of the drug (gabapentin/clonidine/multivitamin) with a sip of water, and vitals were recorded before taking the drug, after drug the consumption and every half hour for 2 h before taking the patient to the operation theatre.

After taking the patient into the operation theater, good intravenous access was secured with either an 18G or 20G cannula. Monitors were attached and baseline vital parameters such as HR, SBP, DBP, MAP, and SPO<sub>2</sub> were noted.

Then, all the patients were pre-medicated with/an injection of glycopyrrolate 0.2 mg iv slowly, an injection of midazolam 1 mg iv, and an injection of pentazocine 0.5 mg/kg.

Patients were pre-oxygenated with 100% oxygen for 3 min. Patients were induced with injection of thiopentone 3–5 mg/kg, adequate to abolish eyelash reflex. Endotracheal intubation was performed with an injection of succinylcholine (1–1.5 mg/kg). IPPV was done for 60 s. Laryngoscopy was done with a Macintosh laryngoscope and intubation was performed with an appropriate-sized endotracheal tube. Anesthesia was maintained by N<sub>2</sub>O: O<sub>2</sub> (66:33) with intermittent isoflurane (0.5 MAC) and injection of atracurium 0.25 mg/kg bolus, followed by 0.1 mg/kg as a maintenance dose. At the end of the surgery, residual neuromuscular blockade was reversed by injection of neostigmine 0.04–0.08 mg/kg ± injection of glycopyrrolate 0.005–0.01 mg/kg. Patients were extubated and oxygenated with 100% O<sub>2</sub> for 10 min and vitals were monitored.

During the intraoperative period, patients were monitored for HR, MAP, systolic pressure, and diastolic pressure. SPO<sub>2</sub> and ECG were recorded at different periods where T<sub>0</sub> - before administration of the drug (baseline), T<sub>1</sub> - before induction, T<sub>2</sub> - after induction, and T<sub>3</sub> - after laryngoscopy and intubation, then at 5, 10, 15, 20, 25, and 30 min after intubation.

### Observation and adverse events

Any side effect or complication due to the drug or technique was noted including hypotension, hypertension, bradycardia, tachycardia, postoperative nausea vomiting, sedation, shivering, and respiratory depression.

### Statistical analysis

Evaluation of study data in the electronic form required performing additional statistical analyses. Data were composed in a suitable spreadsheet i.e., Excel and SPSS. After the compilation of data, it was analyzed statistically by SPSS software version 22.0. To compare the three groups for the hemodynamic stress response attenuation, after checking the assumption for the normality either the Chi-square test, ANOVA, or paired t-test was applied. The significance level was 95% confidence level (P<0.05). Data were described as a frequency (percentage) distribution as well as in mean ±SD. Data were presented through suitable statistical graphs.

All the observations and particulars of each patient were recorded in a proforma.

## RESULTS

The 108 patients included in the study were comparable between the groups with respect to demographic variables, such as age, sex, and weight (P>0.05) (Table 1).

The difference between the three groups was statistically insignificant (P>0.05).

The pulse rate was higher in the placebo group as compared to clonidine (P<0.001) and gabapentin groups (P<0.001).

Significant difference in mean SBP was observed at all-time intervals except T<sub>0</sub> and T<sub>2</sub>. In clonidine group shows better control in SBP than the gabapentin and placebo group (P<0.001).

Significant difference in mean DBP was observed at all-time intervals but in clonidine group shows better control in DBP than the gabapentin and placebo group (P<0.001).

Significant difference in the mean of MAP was observed at all-time intervals except T<sub>0</sub>. Clonidine group had shown better control over MAP than the gabapentin and placebo group (P<0.001).

## DISCUSSION

Sympathoadrenal activation due to laryngoscopy and endotracheal intubation causes tachycardia, a rise in blood pressure, and dysrhythmias.<sup>1</sup> Attenuation of these remains an important anesthetic concern for anesthesiologists. Several strategies have been used to blunt inadvertent hemodynamic responses to laryngoscopy and intubation, but each method has its advantages and disadvantages. Clonidine and gabapentin are being investigated as an adjunct to anesthesia.

Clonidine<sup>10</sup> is an alpha-2 agonist, traditionally used in the treatment of hypertension, migraine, and menopausal flushing. It possesses analgesic, anxiolytic, and sedative

**Table 1: Distribution of groups**

Group G (n=36)	Oral gabapentin 800 mg given 2 h before surgery with a sip of water
Group C (n=36)	Oral clonidine 200 mcg given 2 h before surgery with a sip of water
Group P (n=36)	Oral multivitamin tablet given 2 h before surgery with a sip of water

properties. Recent studies have proved its role in attenuating hemodynamic instability during intubation and in intensive care units due to its central sympatholytic action which manifests as peripheral vasodilation, a decrease in blood pressure, HR, and cardiac output.

Gabapentin,<sup>11</sup> a structural analog of gamma-aminobutyric acid, inhibits calcium influx, thereby reducing excitatory neurotransmitters in the pain pathway by binding to the alpha2 subunit of presynaptic voltage-gated calcium channels. It has shown efficacy in reducing convulsions, diabetic neuropathy, postherpetic neuralgia, HIV-related neuropathy, trigeminal neuralgia, inflammatory pain, malignant pain, complex regional pain syndrome, prevention of post-operative surgical pain, and prevention of post-operative nausea and vomiting.

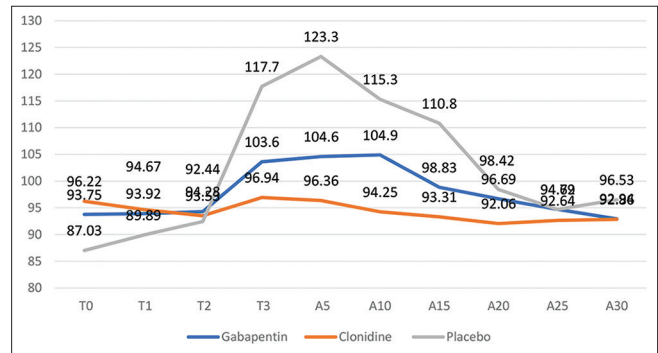
In our study, we have studied the efficacy of oral clonidine 0.2 mg and oral gabapentin 800 mg administered 120 min before induction of anesthesia for controlling cardiovascular responses during laryngoscopy and tracheal intubation.

Demographic variables depicted by Table 2 (including age, weight, and gender) were comparable in all 3 groups, making the difference statistically insignificant ( $P > 0.05$ ).

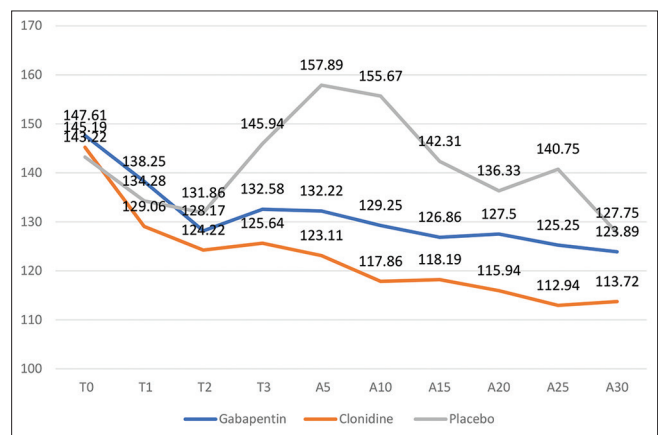
In our study, mean ( $\pm$ SD) baseline values of pulse rate in Group G, Group C, and Group P were comparable (Graph 1). Intergroup statistical analysis of the pulse rate between Group G, Group C, and Group P shows a highly significant ( $P < 0.001$ ) decrease in pulse rate in Group C as compared to Group P at the time of laryngoscopy and intubation and continued up to 15 min after intubation. Furthermore, gabapentin was better in reducing HR as compared to the placebo but was inferior to the clonidine group at T3, 5, 10, and 15 min. Our finding correlated with Kaur et al., in 2014<sup>12</sup> ( $P < 0.001$ ), and Kapse et al., in 2016<sup>13</sup> ( $P < 0.05$ ) who found that oral clonidine was more effective in blunting cardiovascular responses HR to laryngoscopy and intubation as compared to oral gabapentin ( $P < 0.05$ ), whereas gabapentin provided better sedation.

In other studies, Gupta et al.,<sup>14</sup> Raichurkar et al.,<sup>15</sup> Soni et al.,<sup>16</sup> and Murari et al.,<sup>17</sup> concluded that oral clonidine in a dose of 0.2 mg was effective in blunting sympathoadrenal responses HR to laryngoscopy and intubation.

In our study SBP, mean ( $\pm$ SD) baseline values of SBP in Group P, Group G, and Group C were comparable ( $P > 0.05$ ) (Graph 2). A highly significant ( $P < 0.001$ ) decline in SBP was seen in Group C at the time of laryngoscopy and intubation and continued up to 30 min after intubation. Our study correlates with the findings of Brijesh et al., in



Graph 1: Intergroup statistical analysis of pulse rate (bpm)



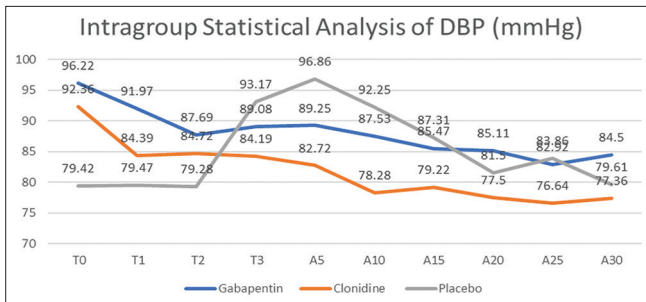
Graph 2: Intergroup statistical analysis of SBP (mmHg)

2015<sup>18</sup> and Sharma et al., in 2020<sup>19</sup> compared the efficacy of clonidine 0.03 mg and gabapentin 900 mg for attenuation of hemodynamic response to intubation. They concluded that oral clonidine in a dose of 0.3 mg was more effective in suppressing SBP, DBP, and MAP than oral gabapentin in a dose of 900 mg during laryngoscopy and intubation ( $P < 0.05$ ).

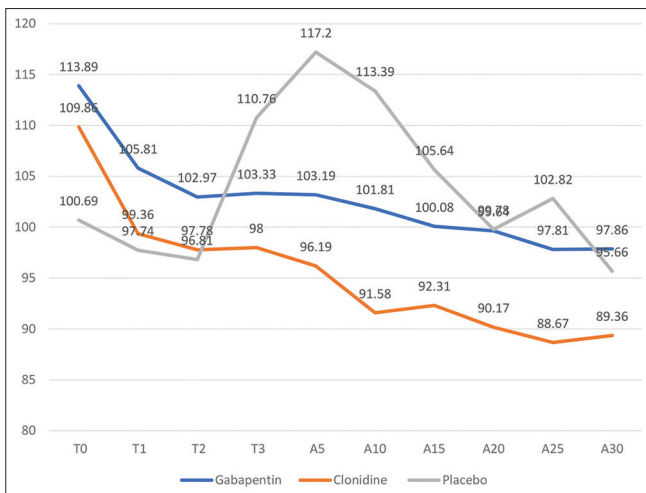
In our study, mean ( $\pm$ SD) baseline values of DBP (Graph 3) and MAP (Graph 4) in Group P, Group G, and Group C were comparable. A highly significant ( $P < 0.001$ ) reduction in DBP was observed in Group C at the time of laryngoscopy and intubation and continued up to 25 min after intubation. A significant MAP reduction was observed in Group C at the time of laryngoscopy and intubation and continued up to 20 min after intubation ( $P < 0.001$ ). The results were in accordance with studies of Mishra et al., in 2018<sup>20</sup> and Das et al., in 2022;<sup>5</sup> similar to our study, they also found that both were efficacious but 0.2 mg of oral clonidine was superior to 800mg of oral gabapentin in attenuating hemodynamic responses HR at the time of laryngoscopy and endotracheal intubation ( $P < 0.05$ ).

**Table 2: Demographic profile of study participants**

Demographic parameter	Gabapentin	Clonidine	Placebo	p-value
Age (years)	48.19±13.67	44.83±12.22	47.61±10.93	0.468
Weight	64.97±10.92	59.83±8.82	64.42±8.95	0.049
Gender				
Male	12	12	19	0.151
Female	24	24	17	



**Graph 3:** Intergroup statistical analysis of DBP (mmHg)



**Graph 4:** Intergroup statistical analysis of mean arterial pressure (mmHg)

The results of our study were contrary to the study of Marashi et al.,<sup>21</sup> who compared the effects of oral gabapentin 900 mg and oral clonidine 0.2 mg on hemodynamic responses to laryngoscopy and found that gabapentin was more effective than clonidine in blunting hemodynamic responses to laryngoscopy.

There was associated hypotension in 3 patients out of 36 patients of Group C who were treated with an injection of mephentermine 6 mg iv. This finding was in agreement with the study conducted by Filos et al., in 1993<sup>22</sup> on elderly patients undertaking ophthalmic surgery in local anesthesia, in which 30% of patients premedicated with 0.3 mg clonidine were treated for hypotension. This was

not seen in the groups receiving 150 mcg of clonidine or placebo (P<0.05).

**Limitations of the study**

BIS for knowing the depth of anesthesia or adequacy of muscle relaxation which also affects hemodynamic changes was not monitored in our study.

**CONCLUSION**

The present study concluded that oral clonidine in a dose of 0.2 mg and oral gabapentin in a dose of 800 mg are effective in attenuating hemodynamic responses to laryngoscopy and intubation in hypertensive individuals. Oral clonidine 0.2 mg is convincingly better and superior to oral gabapentin 800 mg in attenuating hemodynamic responses during intubation and laryngoscopy and with minimal adverse effects.

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#### Authors' Contributions:


**RP**- Concept and design of the study and prepared the first draft of the manuscript; **AG**- Interpreted the results; reviewed the literature and manuscript preparation; **NE**- Concept, coordination, statistical analysis and interpretation, and preparation of manuscript and **SG**- Revision of the manuscript.

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