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*Original Research Article*

# Effect of oral clonidine as premedication for anxiety and attenuation of pressor response during laryngoscopy and intubation undergoing laparoscopic cholecystectomy

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**Abstract**

**Background:** Surgery is an event that causes anxiety among the majority of patients. In addition, laryngoscopy and intubation cause disturbance in the heart rate and blood pressure rhythm. Together preoperative anxiety and intubation can prove harmful for some patients.

**Aim:** To observe the clinical effects of Clonidine on anxiety & cardiovascular parameters (pressor response) during direct laryngoscopy and tracheal intubation.

**Material and Methods:** A single-centre, parallel-group, two-arm, 1:1, double-blind, placebo-controlled, randomised, intervention study. A total of 100 participants: 50 in the clonidine group and 50 in the placebo group were enrolled in the present study. Participants in the clonidine group were given oral clonidine at a dose of 200 micrograms 90 minutes before induction.

**Results:** The increase in heart rate and mean arterial blood pressure was significantly less among patients given clonidine in comparison to placebo. In addition, participants given Clonidine showed fewer fluctuations in their heart rate and blood pressure throughout the surgery. Participants given Clonidine were more less anxious before surgery in comparison to those given the placebo. None of the participants given Clonidine had any adverse effect.

**Conclusion:** Clonidine is effective at attenuating the haemodynamic response to laryngoscopy and intubation. In addition, Clonidine has an anxiolytic action.

**Keywords:** Clonidine, anxiolysis, pressor response

## Introduction

Direct Laryngoscopy and endotracheal intubation (LETI) elicit a rise in heart rate (HR), arterial pressure and dysrhythmias due to afferent stimulation of the vagus and sympathoadrenal response [1]. Tachycardia and hypertension result in an imbalance between the supply and demand of oxygen in the myocardium, predisposing patients to ischemia, infarction, and heart failure [2, 3]. Myocardial ischemia is the most common sequelae in patients with heart disease caused by the neuroendocrine reactions to airway manipulation [2-4]. When patients with arteriosclerosis are intubated, bouts of ischemic electrocardiographic ST-segment depression and elevated pulmonary artery diastolic blood pressure (BP) may occur; occasionally, these episodes indicate the possibility of a perioperative myocardial infarction [2, 4, 5]. Even though healthy persons can generally tolerate this sympathetic reaction, it can be extremely dangerous for patients with weakened cardiovascular function [2, 4, 5]. These

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alterations are also severe in patients with elevated intracranial pressure, intracranial aneurysm, and open eye trauma [6]. Patients who have an aneurysmal disease of the cerebral and aortic circulation may also be at an increased risk of problems during airway instrumentation due to sudden surges in blood pressure (BP) [6, 7]. In critically sick patients, pathophysiological alterations significantly increase the likelihood of unfavourable events following LETI [3].

The majority of individuals anticipating elective surgery are anxious beforehand [8, 9]. Preoperative anxiety is related to a greater amount of postoperative pain. Increased stress, which is a direct result of anxiety, leads to stimulation and activation of the autonomic nervous system [8, 10]. Furthermore, as laryngoscopy force and duration increase, the amplitude of haemodynamic response to LETI also increases [9, 11]. Inadequate identification of at-risk patients, improper planning and absence of-or failure to accurately identify heightened anxiety have been cited as important culprits in LETI-related incidents [12, 13]. Current evidence suggests that the neurological and biochemical inputs of anxiety to the central nervous system are minimal with pre-emptive analgesia [12, 13]. In addition, the pre-emptive analgesia with premedication given to reduce the intensity of pressure response also decreases the requirements of anaesthetic and narcotic doses during the intra- and postoperative period [14-16].

The search for the appropriate premedication to reduce the pressor response to intubation has spanned decades. An ideal premedicant should also mitigate anxiety among patients impatiently waiting for surgery [16, 17]. To allay unfavourable hemodynamic response to laryngoscopy and tracheal intubation, many pharmacological and non-pharmacological interventions have been tested either as premedication or during induction [18, 19]. Appropriate premedication, smooth induction, and quick intubation would reduce the associated dangers [18, 19].

The classical alpha-2 agonist agent Clonidine is a selective partial agonist for alpha 2 adrenoreceptors. Clonidine has antihypertensive, sedative, and analgesic properties [20-22]. It exerts its antihypertensive effects via central and peripheral inhibition of sympathetic outflow and central stimulation of noradrenergic imidazoline-preferring receptors. These qualities imply that clonidine may be an effective adjuvant in the anaesthetic management of individuals. Despite dose-dependent adverse effects such as hypotension and sedation, as well as idiosyncratic adverse symptoms such as bradycardia, Clonidine does not generate significant respiratory depression and only weakly potentiates opiate-induced respiratory depression [20-22]. Little empirical data are available comparing the efficacy of clonidine in peri-intubation phase hemodynamic response regulation. Therefore, we undertook this study to examine and compare the clinical effect(s) of oral Clonidine given as premedication on cardiovascular parameters, and anxiety levels during direct laryngoscopy and tracheal intubation.

## Material and Methods

**Study Design:** A single-centre, parallel-group, two-arm, 1:1, double-blind, placebo-controlled, randomised, intervention study.

**Study Setting:** Department of Anaesthesiology, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh.

**Study Duration:** The total duration of the study was 6 months.

**Study Outcomes:** Haemodynamic Parameters (Heart Rate and Mean Arterial Blood Pressure) and Anxiety.

**Time Points:** The primary outcomes were measured at the following prescribed time interval: Haemodynamic variables: before giving drugs, after induction, during laryngoscopy, 1-, 3-, 5- and 10 minutes thereafter. Anxiety levels were measured 1 hour after premedication.

**Measurement of the outcome**

**Anxiety score**

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- Score 0= Patient relax
- Score 1= Uneasy
- Score 2= Worried or anxious
- Score 3= Very worried or very upset.

**Comparative groups**

All the participants were allocated to two groups using randomization:

i) **Group C:** Participants in this group were given oral Clonidine at a dose of 200 micrograms 90 minutes before induction.
ii) **Group P:** Participants in this group were given an oral Placebo (Vitamin C 500mg) 90 minutes before induction.

**Participants' recruitment:** The participants were recruited into the study after verifying that they fulfilled the following:

**Inclusion criteria**

i) Patients between 18-65 years of age (both inclusive).
ii) Patients of all genders.
iii) Patients belonging to grades I and II of the American Society of Anaesthesiologists (ASA).
iv) Patients consenting to participate in the study.

**Exclusion criteria**

i) Patients undergoing emergency surgeries.
ii) Patients with a systemic disorder like uncontrolled hypertension, diabetes, seizure disorder, respiratory disorders, kidney or liver disease, coronary artery disease, and recent history of myocardial infarction.
iii) Patients on regular medication of Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRI), Monoamine oxidase inhibitors or opioids, and patients with any known allergy or hypersensitivity to drugs to be used.
iv) Obese patients; anticipated difficult airways and pregnant women.
v) Patient is on sedatives, β-blocker and Antipsychotic medication.
vi) A patient refused to take part in the study.

**Sample size**

The minimum required sample size for the study was calculated using the formula recommended by Zhong B (2019) for a randomised controlled trial. Using the formula for randomised control trial, the minimum sample size was calculated as 100 participants, with 50 participants in each group. The sample size was calculated based on the following assumptions: 95% confidence interval, 80% power, and a standard error of 2.34.

**Informed consent**

Everyone who participated was provided with a copy of the consent form to read. Following that, the contents of the permission form were explained to every potential participant in easy-to-understand language. All of the participants' inquiries about the study, treatment, investigations and the confidentiality of their data were addressed and answered. It was made clear to the participants, both verbally and in writing, that they are free to discontinue their participation in the research at any moment. After that, those participants who were willing to

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take part were asked to sign the consent form.

**Randomization**

A statistician unaffiliated with the study generated random numbers for group allocation. Using the statistical software version 17.0 random numbers were generated using the permuted block design (n=5) and the participants were randomly allocated to the two study groups.

**Allocation concealment**

The details of the assigned groups were disguised from the primary investigator and study team using opaque, sealed envelopes containing random numbers. Using impregnated tapes, the envelope was rendered impervious to bright light.

**Blinding**

This was a double-blind study, both participants and the researcher (including surgeons, anaesthesiologists, nurses, and other members of the operating room personnel) were unaware of the study group.

**Plan and Procedure**

A detailed history and a thorough clinical examination of every patient were completed by the surgical team. Appropriate laboratory and radiological investigations were conducted. A detailed pre-anaesthetic evaluation was completed one day before the surgery by the anaesthesiologist's team. Various monitors were attached to measure the multiple vital parameters viz. pulse rate, non-invasive blood pressure, pulse oximetry, Electrocardiogram, and body temperature during the peri-operative period. Pre-oxygenation was done for 3 minutes, i.v. Glycopyrrolate 10μg/kg, i.v. Midazolam 0.05 mg/kg and i.v. Tramadol 1mg/kg was given, then induction was done with i.v Propofol 2 mg/kg followed by i.v. Vecuronium 0.1 mg/kg was given. Manual ventilation with 100% oxygen was done for 3 minutes. Direct laryngoscopy was performed with an appropriate laryngoscope blade and endotracheal intubation, by using an appropriate-sized endotracheal tube. Heart rate and blood pressure (SBP, DBP and MAP) were measured before induction, during laryngoscopy and following intubation (i.e. immediately after intubation and at 1, 3, 5 & 10 minutes post laryngoscopy). Extubation was performed after recovery from anaesthesia.

**Statistical Analysis Plan**

The primary outcome was the difference in the various haemodynamic parameters and level of anxiety among the participants in the two groups. The coded data were imported into Stata 17.1 version for analysis. A comparison of continuous variables with baseline values was analysed using a student's t-test in each group. Categorical variables were analysed using chi-square ($\chi^2$) tests. A *P*-value $< 0.05$ was considered statistically significant. All tests are two-sided; the nominal level of type I error was 5% and the confidence level for all confidence intervals was 95%.

**Funding**

The present study did not receive any financial support. The researchers did not provide the participants with any financial avarice, presents, or other forms of inducement.

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## Results

We approached a total of 123 patients who were scheduled to have elective surgery under general anaesthesia to enrol the minimum number of participants necessary for this study. Of these 123 patients, 10 patients declined to take part in the study, 13 patients were disqualified based on the selection criteria and the remaining 100 patients were included in the investigation. There were no dropouts and all one hundred people who participated in the study ended up completing it.

The mean age of the participants in the Clonidine and Placebo groups was 44 and 42.9 years, respectively (p = 0.087). Overall, the sex ratio of the participants in the study was approximately equal (48% female versus 52% male). The participants in the clonidine group had a mean of 27.3 and the mean BMI of the subjects in the Placebo group was 28.8 (p=0.37). In the clonidine group: 56% and 44% of subjects were categorised as ASA-I and II grades, respectively. In the Placebo group: 46% and 54% of subjects were categorised as ASA-I and II grades, respectively (Table 1). In the present study, the mean time taken to intubate participants in the Clonidine and Placebo group were 20.48 seconds and 26.04 seconds, respectively (p =0.0348).

**Table 1:** Descriptive Characteristics of participants

| Variable | Clonidine | Placebo | P-value |
|---|---|---|---|
| Age | 44.0 (±14.68) | 42.9 (±13.77) | 0.087 |
| Female | 22 (44.0%) | 26 (52.0%) | 0.423 |
| Male | 28 (56.0%) | 24 (48.0%) | |
| BMI (SD) | 27.3 (±4.12) | 28.8 (±4.43) | 0.37 |
| ASA Grade-II | 22 (44.0%) | 27 (54.0%) | 0.317 |

At baseline, the difference in the mean heart rate among the participant in the Clonidine group (88.3) and Placebo group (82.9) was statistically insignificant (p=0.36) (Figure 1). However, as the study progressed, the difference in the heart rate between the participants in the two groups became more apparent. Following intubation, there was an abrupt increase in HR among the participants in both groups. However, at the time of intubation, the heart rate among the participants in the Clonidine group was significantly lower (87.5) in comparison to the Placebo group (92.3; p-value = 0.009). Also, the difference in heart rate among the two groups was significant on multiple occasion's viz. at 1, 3, and 5 minutes after the intubation.

Figure 2 shows the trend in mean arterial pressure among the participants in the Clonidine and Placebo groups throughout the study. At baseline, the mean MAP among the participant in group C (90 mm Hg) and group P (89 mm Hg) was almost equal. At the time of induction, the mean MAP among the participant in group C and group P was also almost equal. However, as the surgery progressed, the difference in the MAP between the participants in the two groups became more apparent. Similar to the trend observed for heart rate, immediately following intubation there was an abrupt rise in the MAP among the participants in both groups. However, at the time of intubation, the MAP among the participants in the Clonidine group was significantly lower in comparison to the Placebo group. At the endline i.e., 10 minutes after intubation, the MAP among the participants in the Clonidine group (90 mm Hg) was lower in comparison to the Placebo group (92 mm Hg). The difference in MAP among the two groups was statistically significant at the time of intubation and all time points thereafter viz. 1, 3 5, and 10 minutes after the intubation.

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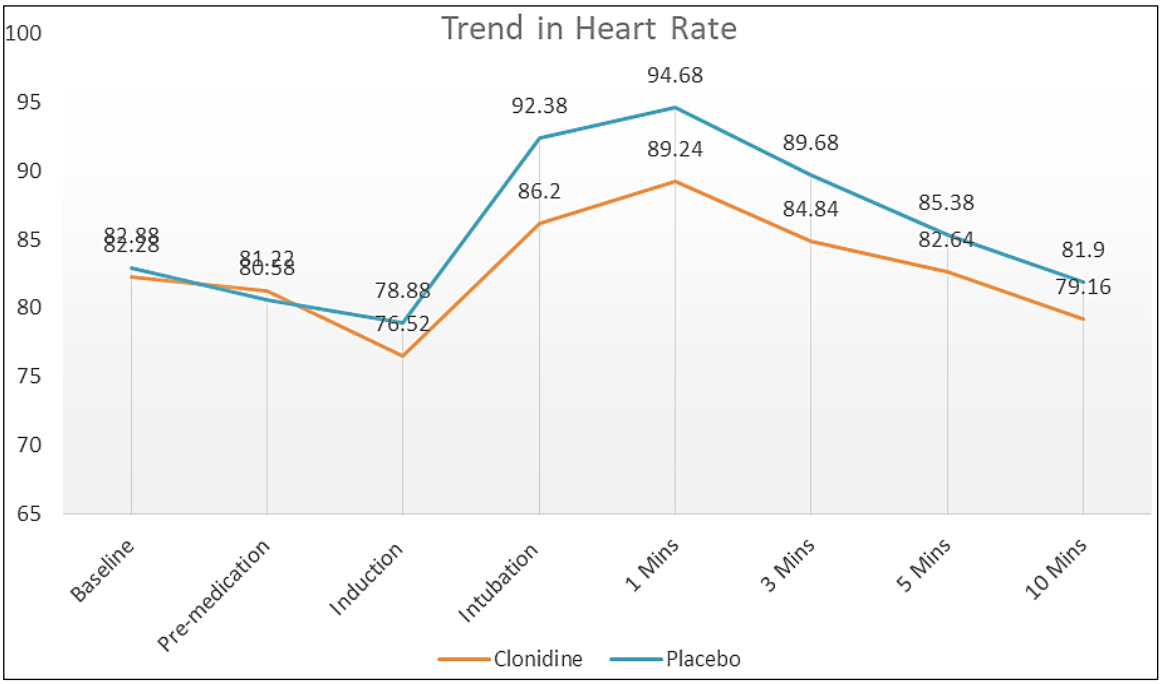


**Fig 1:** Trend in Heart Rate among two groups

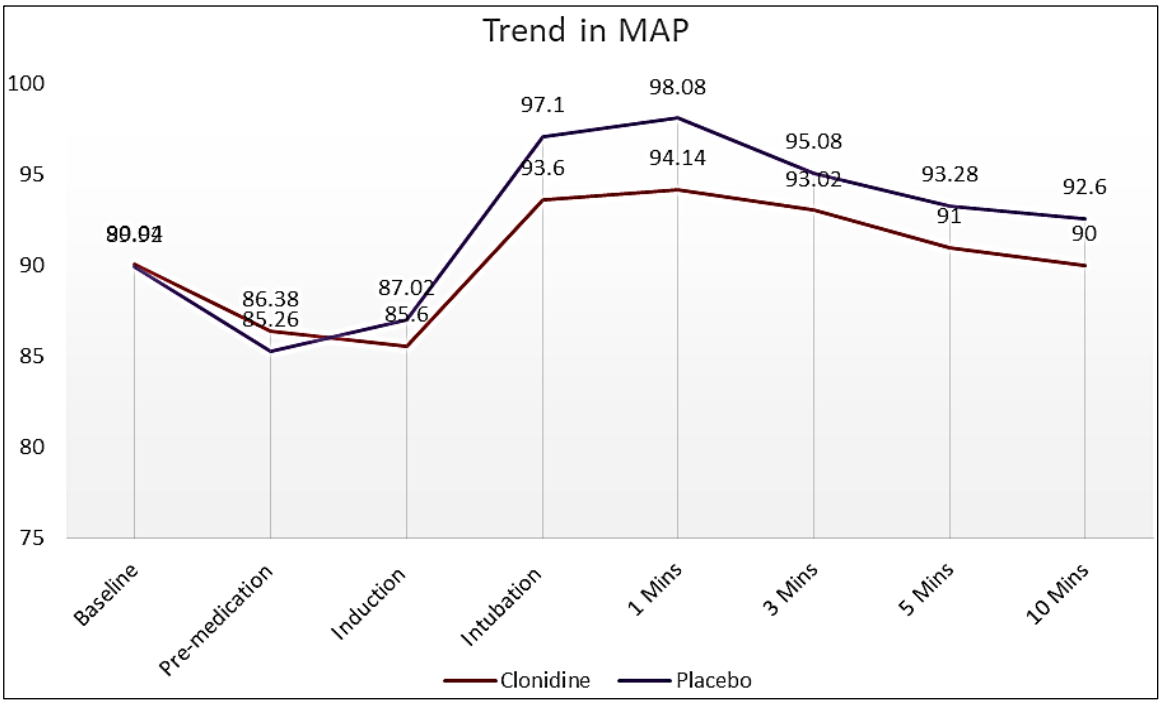


**Fig 2:** Trend in Mean Arterial Pressure

**Table 2:** Anxiety score among participants (n=100)

| Anxiety Score | Anxiety Score | | | |
|---|---|---|---|---|
| | Pre-medication | | After 60 Minutes | |
| | Group C | Group P | Group C | Group P |
| Relax | 12 (24.0) | 14 (28.0) | 23 (46.0) | 12 (24.0) |
| Uneasy | 20 (40.0) | 22 (44.0) | 17 (34.0%) | 18 (36.0) |
| Anxious | 18 (36.0) | 14 (28.0) | 10 (20.0) | 20 (40.0) |
| Very worried or upset | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| P-value | 0.17 | | 0.033 | |

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At the time of premedication, most of the participants in both the clonidine and Placebo groups were a bit anxious, however, the difference between the two groups was insignificant ($p>0.5$). After 60 minutes of premedication, participants in the Clonidine group were less anxious than participants in the Placebo group ($p = 0.033$).
None of the participants in either groups had any untoward side effect or adverse events e.g., bradycardia, tachycardia, hypotension etc.

## Discussion

The haemodynamic response to laryngoscopy and intubation was thoroughly described by King and colleagues in 1951 [23]. According to King *et al*., patients under general anaesthesia experienced a mean rise in systolic arterial pressure of 53 mmHg and an increase in heart rate of 23 beats per minute following tracheal intubation [23]. According to King *et al*. the effector system is triggered by decreased parasympathetic or increased sympathetic adrenal activity. Forbes and Dally (1970) reported that during laryngoscopy and endotracheal intubation, the mean arterial pressure of all 22 patients with normotension rise on average by 25 mm Hg [24]. Blood pressure and heart rate rises in hypertension patients are significantly more dramatic, according to Robert PC *et al*. (1971) [25]. They also reported that the highest values of systolic, diastolic, mean arterial pressure, and heart rate occur within 30 to 60 seconds of laryngoscopy and intubation. The strength of the pressure reaction is also significantly influenced by the duration of the laryngoscopy. As an illustration, the mean arterial pressure increased during a 60-s laryngoscopy up until 45s; after that, there was no further increase until tracheal intubation [25]. Within 30 seconds of the stimulation, blood pressure and heart rate commonly rise and they can continue to rise for up to 5 minutes.
Following intubation, there was an abrupt increase in HR among the participants in both groups at intubation, 1min, 3min, 5min & 10 min. However, the increase in heart rate among the participants in the Clonidine group was significantly lower (87.5) in comparison to the Placebo group (92.3; p-value = 0.009). However, when compared to the baseline values, the heart was 5.9% and 11.5% higher among the participants in the clonidine and Placebo groups respectively due to sympathetic stimulation and the release of catecholamines. Moreover, immediately following intubation i.e., at 1 minute after intubation, the HR was 8.6% and 14.2% higher than baseline values. Lastly, even at 3 and 5 minutes after the intubation the values of HR in both the Clonidine group and Placebo group were higher than the baseline value. Only 10 minutes after intubation the HR was lower than the baseline value. It has been noted by several researchers that the increase in heart rate is observed within seconds of intubation and that it continues to rise for several minutes after intubation before returning to the values that were present before the procedure. The findings of the current investigation are comparable to those of earlier studies that reported a similar pattern of changes in the hemodynamic parameters.
In the present study, the difference in heart rate among the two groups was significant at intubation, 1, 3 and 5 minutes after the intubation. Therefore, in the present study, attenuation in the heart rate following intubation was better with Clonidine than Placebo. Attenuation of the hemodynamic response to intubation was reported to be better with 300 micrograms of clonidine in comparison to the Placebo in a study conducted by Sharma V *et al*. [20] Gupta K *et al*. also showed that, when comparing placebo and oral clonidine 200 micrograms, the control of heart rate was significantly better with clonidine [26]. Raval DL *et al*., reported that the rise in pulse rate during laryngoscopy and intubation from basal value was statistically highly significant in placebo in comparison to clonidine group ($P = 0.032$)(27). Bhuava A *et al*., also reported that among patients given placebo the mean HR was $77.42 \pm 10.76$ at baseline, one minute after the laryngoscopy, HR rose to 97.12 (an increase of 25.44%) and at 3 minutes HR was 94.68. In comparison, among patients given 200 micrograms of Clonidine the mean HR was at baseline, 1 minutes, and 3 minutes after intubation was 73, 83 and 81 bpm, respectively [28]. According to Sung CS *et al*., patients in the Clonidine group displayed greater hemodynamic stability perioperatively and the isoflurane requirement was also

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reduced (30% less) [29].

Similar to the trend observed for heart rate, immediately following intubation there was an abrupt rise in the MAP among the participants in both groups. Although at the time of intubation, the MAP among the participants in the Clonidine group was significantly lower in comparison to the Placebo group. Nevertheless, the MAP values observed at intubation and immediately after it were considerably higher than baseline values. The MAP values among the participants given Clonidine at intubation and 1-, 3-, and 5-minutes after intubation were 3.9%, 4.5%, 3.3% and 1.1% higher than baseline values. The corresponding changes in MAP values among the participants given Placebo at intubation and 1-, 3-, and 5-minutes after intubation were 8%, 9.1%, 5.7% and 3.7% higher than baseline values. The difference in MAP among the two groups was statistically significant at the time of intubation and all time points thereafter viz. 1, 3, 5, and 10 minutes after the intubation. Therefore, in the present study, clonidine was more effective at controlling the abrupt rise in MAP following intubation in comparison to Placebo.

Raval DL *et al*., reported that during laryngoscopy and endotracheal intubation, decrease in systolic, diastolic and mean arterial pressure in Clonidine group was not significant whereas rise in the systolic, diastolic and mean arterial pressure from the basal value was statistically highly significant in Placebo groups. They observed that systolic, diastolic and mean arterial pressure remained lower than the basal value upto 5 min of endotracheal intubation in Clonidine group. Whereas all these values returned to the basal value after 3 min of intubation in Diazepam group but did not return to the basal value even upto 5 min of intubation in Placebo group. As compared to basal values statistically highly significant difference in systolic, diastolic and mean arterial pressure were observed at the end of 1, 2, 3, 4 and 5 min of intubation in patients of both Clonidine and Placebo groups [29].

Bhuava A *et al*., also reported that among patients given placebo the mean SBP at baseline, 1, 3 5 and 10 minutes after intubation was 121, 143, 138, 131 and 116 mm of Hg. The DBP at baseline, 1, 3 5 and 10 minutes after intubation was 78, 92, 87, 83 and 75 mm of Hg. In comparison, among patients given 200 micrograms of Clonidine the mean SBP at baseline, 1, 3, 5 and 10 minutes after intubation was 114, 126, 121, 113, and 107 mm of Hg, respectively [28]. According to Sung CS *et al*., patients in the Clonidine group displayed greater stability of blood pressure during and after intubation in comparison to Placebo [27].

Similar to our findings, Sharma V *et al*., when comparing 300 mcg of Clonidine and Placebo reported that concerning a decrease in MAP, Clonidine is more effective than Placebo [20]. Bhandari and colleagues discovered that mean blood pressure in both groups dropped at 0 minutes, 1 minute and 3 minutes, although their findings were only statistically significant at the 3-minute mark [30]. In comparisons among participants who were administered Placebo, there was also a decrease in MAP at all periods, except for one minute after intubation, when a rise in MAP was noted, which was statistically significant (P-value < 0.05).

In the present study, we measured the anxiety score using a 4-points score, at the time of premedication and 60 minutes later. At the time of premedication, most of the participants in both the Clonidine and Placebo groups were a bit anxious, however, the difference between the two groups was insignificant ($p>0.5$). Overall, we observed that after 60 minutes of premedication, participants in the Clonidine group were less anxious than participants in the Placebo group.

Bhuava A *et al*., measured anxiety using a 3 points anxiolysis scale. Among patients given placebo and 200 milligram group; 16% and 60% had a score of 0 [28]. The anxiolysis score is found to be highly significant between the Placebo and the Clonidine groups ($p<0.001$). A better anxiolysis scores are seen in Clonidine groups than the Placebo group. Anxiolysis score is comparable with Raval *et al*., study in which after premedication 85% of patients were comfortable and 12.5% patients were uneasy, 2.5% patients were anxious in Clonidine group where as in Placebo group 50% were quiet or comfortable, 30% were uneasy and 20% were anxious [29]. Sung CS *et al*., patients in the Clonidine group displayed lesser anxiety score in comparison to those given Placebo [27].

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## Conclusion

When it came to attenuating the hemodynamic response to laryngoscopy and intubation, oral Clonidine at a dose of 200 micrograms given orally approximately 90 minutes before surgery performed significantly better than Placebo. When administered before intubation, Clonidine is superior to Placebo towards its ability to reduce increases in both heart rate and mean arterial pressure. In addition, Clonidine produced significant anxiolytic effect.

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