ORIGINAL RESEARCH PAPER

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# DOSE RESPONSE EFFECTS OF INTRAVENOUS CLONIDINE ON STRESS RESPONSE DURING INDUCTION OF ANESTHESIA

**KEY WORDS:** CLONIDINE DOSE STRESS HEMODYNAMIC RESPONSE ATTENUATION

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ABSTRACT

**Objectives:** To evaluate the hemodynamic stress response of two different doses of clonidine during laryngoscopy and induction of anesthesia.

**Materials and Methods:** After taking permission of the ethical committee 90 ASAI/II patients meeting our inclusion criteria requiring GA for elective general surgery were equally and randomly enrolled into three groups, groupC0 (recieving0.9%NS), GroupC2 (recieving2µg/kg Inj.Clonidine) and group C4 (recieving4µg/kg Inj. Clonidine). All the three groups were comparable in terms of Age, Sex, Weight and Baseline hemodynamic variables and none of the patients had any associated comorbid diseases. Premedication and anesthetic induction technique was kept similar in all the three groups. The Sedation score, Cardiovascular parameters (SBP,DBP, MABP, $SP0_2$,Rate pressure product)and ECG were assessed at various time intervals starting before premedication till 5 minutes post intubation and documented appropriately.

**Results:** Stress response during anesthesia was significantly lower, particularly during laryngoscopy and 1st min after intubation in group C4 compared to group C2 and Placebo. The maximum pulse rate in group C2 was 94.93 at 1 minute post laryngoscopy but in group C4 was 85 at 1 minute post laryngoscopy. Overall pulse rate values of group C4 were lower than that of C2. Similarly fall in SBP, DBP and MAP was seen after clonidine infusion in both clonidine groups more in group C4 with complete attenuation of hemodynamic response in group C4. Rate pressure product also showed a similar lower trend in both clonidine groups which was much lower in group C4 compared to C2 and placebo. A higher dose of Clonidine (4µg/kg) produces more sedation than a lower dose (Clonidine2µg/kg) and Placebo.

## INTRODUCTION

Safety of general anesthesia relies on securing the airway mainly through Laryngoscopy and Intubation which invariably is associated with increased autonomic nervous system response along with an increased adrenomedullary catecholamine activity (Derbyshire et al., 1983). Though the predominant sympathetic stress response producing tachycardia, hypertension and increased ICT are well tolerated by most of the patients, but patients with comorbid diseases like coronary artery disease, hypertension, increased ICT etc. poses a high risk of morbidity.

A wide variety of drugs as adjuncts are recently being introduced into the clinical practise with the primary aim of nullifying this adverse stress response. Clonidine an 2 blocker is one such anesthetic adjunct which is proposed and claimed to reduce the anesthetic requirement, attenuate stress response to laryngoscopy and intubation, reduce anxiety and provide sedation.

The aim of our study is to evaluate the effect of two different drug doses of clonidine on attenuation of stress response to anesthetic induction.

## MATERIALS AND METHODS

After obtaining approval of institutional ethical committee, 90 patients aged 18-50 years of both sexes belonging to ASA grade I and II undergoing elective surgery requiring endotracheal intubation for maintenance of anesthesia in Silchar Medical College and Hospital were selected. Sample size was calculated statistically assuming 95% confidence interval and 10 percent margin of error.

A written informed consent was taken from all patients included in the study groups.

Patients with the under mentioned conditions were excluded from the study:

1. Patients scheduled for emergency or reoperation
2. Pregnant patients
3. Anticipated difficult airway
4. Hypertension/ Hypotension
5. Ischemia
6. Patient on α/β blocker.
7. Allergy to study drug.

Before proceeding for the study, a written informed consent was taken from all the patients individually. The patients were randomly allocated into three groups irrespective of age, gender, socio-economic status and proposed operation.

Each group included 30 patients. General anesthesia (balanced technique) was applied to all patients:

| GROUP | DRUG | ROUTE | DOSE |
|---|---|---|---|
| GROUP C4 | INJ. CLONIDINE | INTRAVENOUS | 4µg/kg Body Weight |
| GROUP C2 | INJ. CLONIDINE | INTRAVENOUS | 2µg/kg Body Weight |
| GROUP C0 | 0.9% NS (PLACEBO) | INTRAVENOUS | |

Pre anesthetic check up was done on the evening prior to surgery. A good rapport was established with all the patients and queries about the forthcoming procedure were explained. Premedication common to all three groups were:

1. Inj. Ranitidine 50 mg iv
2. Inj. Glycopyrrolate 0.2 mg i.v
3. Inj. Tramadol 2mg/kg i.v
4. Inj. Ondansetron 4 mg i.v.
5. Tab Alprazolam 0.5 mg night before surgery.

## METHOD OF ASSESSMENT:

**1. SEDATION SCORING**: Sedation was scored prior to and 15 minutes after the end of clonidine or placebo according to scale:

0=patient awake
1=patient sedated but awake
2=patient asleep, reacting immediately to verbal command
3=patient asleep, reacting to verbal command with delay
4=patient asleep, not reacting to verbal command

**2. CARDIOVASCULAR PARAMETERS:**
1. Pulse rate/minute (P.R.)
2. Systolic blood pressure in mm of Hg. (S.B.P)
3. Diastolic blood pressure in mm of Hg (D.B.P)
4. Rate pressure product (Calculated as: P.R X S.B.P)

Time intervals at which readings were observed:
T0- Baseline, before premedication
T1-15 minutes after premedication
T2- After administration of clonidine or placebo infusion
T3- At laryngoscopy
T4- 1 min after laryngoscopy
T5- 2 minutes after laryngoscopy
T6- 3 minutes after laryngoscopy
T7- 4 minutes after laryngoscopy
T8- 5 minutes after laryngoscopy

**Technique**: A standard general anesthesia technique was used in all the three groups of patients. An intravenous line was started with 18G i.v cannula. All patients were premedicated with Tab. Alprazolam (0.5 mg night before surgery), Inj. Ranitidine (50 mg i.v), Inj. Tramadol (2mg/kg i.v), Inj. Glycopyrrolate (0.2 mg i.v), and Inj. Ondansetron (4mg i.v). Fifteen minutes after premedication, clonidine or placebo diluted in 100 mL of 0.9% NaCl was infused over a period of fifteen minutes. Sedation was scored prior to and fifteen minutes after the end of clonidine or placebo infusion. Patients were then preoxygenated for 3 minutes. Induction was done with sleep dose of Inj. Thiopentone Sodium (2.5%) followed by Inj. Vecuronium bromide (0.1mg/kg body weight) to facilitate laryngoscopy which was done with a Macintosh curved laryngoscope and trachea was intubated with a cuffed endotracheal tube within 30 seconds. Heart rate and blood pressure were measured continuously and were recorded every minute. Anesthesia was then maintained with oxygen and nitrous oxide in the ratio of 33:66 percent using the closed circuit with a circle absorber system and Isoflurane 1-2 MAC was used. Vecuronium bromide 0.01 mg/kg body weight top up doses were used as and when necessary. At the end of surgery neuromuscular blockade was reversed with Inj. Neostigmine (0.05mg/kg body weight) and Inj. Glycopyrrolate (0.01 mg/kg body weight).

**STATISTICAL ANALYSIS:**
The data compiled were analysed with Graphpad Instat® 3 statistical software. For intergroup comparison analysis of variance was performed. A two-tailed paired t-test was used ($p<0.05$) for comparison of variables with baseline values.

**RESULTS AND OBSERVATIONS**
The present study comprised of 90 patients in the age group of 18-50 years, of either sex and of ASA-I and ASA- II physical status undergoing various surgical procedures under general anesthesia at Silchar Medical College & Hospital, Silchar.

The results and observations of the present study are shown in the following tables and figures and explained thereby:

**Table 1: Intergroup comparison of demographic data**

| CHARACTERISTICS | GROUP-C0 (PLACEBO) | GROUP-C2 (CLONIDINE-2µg/kg) | GROUP-C4 CLONIDINE-4µg/kg) |
|---|---|---|---|
| Number of patients | 30 | 30 | 30 |
| Mean age (years) | 33.73 ± 8.64 | 34.04 ± 9.06 | 34.27 ± 9.88 |
| Mean weight (kg) | 49.23 ± 6.81 | 49.53 ± 7.24 | 49.73 ± 7.47 |
| Sex (M/F) | 11/19 | 12/18 | 10/20 |
| ASA Status (I/II) | 23/7 | 22/8 | 23/7 |

The demographic details which appear in table shows that patients under the three study groups were comparable with respect to age, weight, gender and physical status.

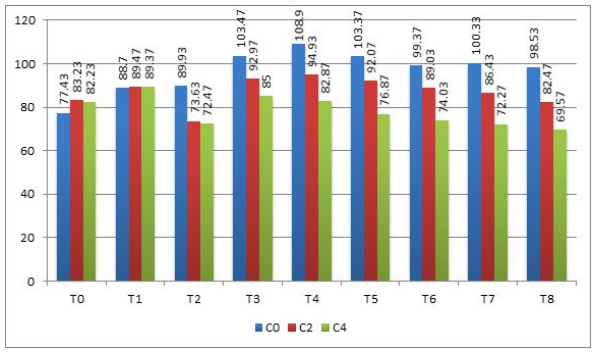
Sedation scoring

**Table 2: Intergroup comparison of level of sedation**

| GROUP | SEDATION | | | | | |
|---|---|---|---|---|---|---|
| | BEFORE | | | AFTER | | |
| | Mean± SD | Median | Range | Mean± SD | Median | Range |
| C0 | 0.03±0.18 | 0 | 0-1 | 0.77±0.82 | 1 | 0-2 |
| C2 | 0.07±0.25 | 0 | 0-1 | 1.7±0.47 | 2 | 1-2 |
| C4 | 0.07±0.25 | 0 | 0-1 | 2.67±0.48 | 3 | 2-3 |

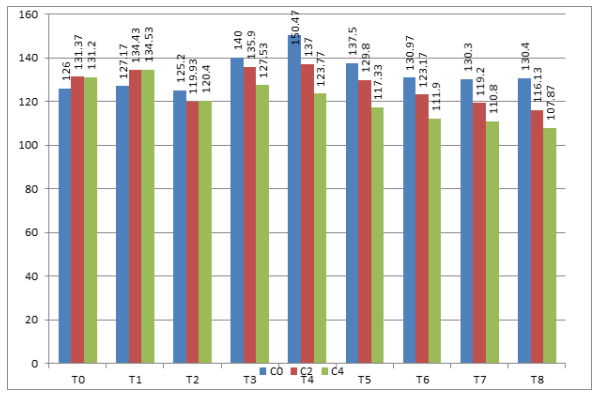
The table above shows that the level of sedation goes on increasing with increasing dose of clonidine. But none of the patients in any clonidine group had unacceptable level of sedation.

Pulse rate analysis

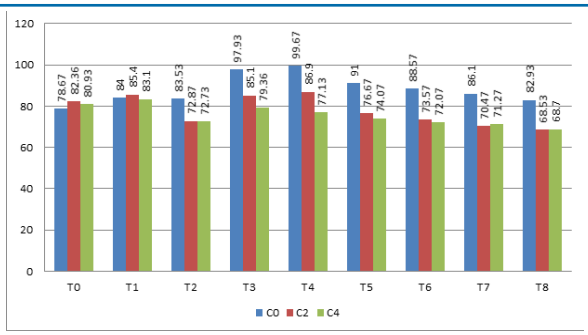



**Graph1: Intergroup comparison of Pulse rate at different time intervals.**

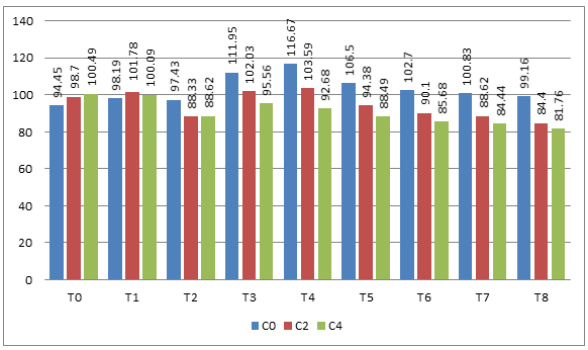
From the above mentioned graph it is observed that the mean baseline pulse rate of patients in Group C0, Group C2 and Group C4 was not found to be statistically different. In all the three groups pulse rate increased after premedication. In group C0 pulse rate increased at laryngoscopy and was above baseline till 5th minute post laryngoscopy. In groups C2 and C4 pulse rate decreased after clonidine infusion which was approximately 11% below baseline but hemodynamically significant bradycardia was not seen. The maximum pulse rate in Group C2 was 94.93 at 1 minute post laryngoscopy but in Group C4 was 85 at 1 minute post laryngoscopy. Overall pulse rate values of Group C4 were lower than that of C2.




**Graph 2: Intergroup comparison of Systolic blood pressure at different time intervals.**

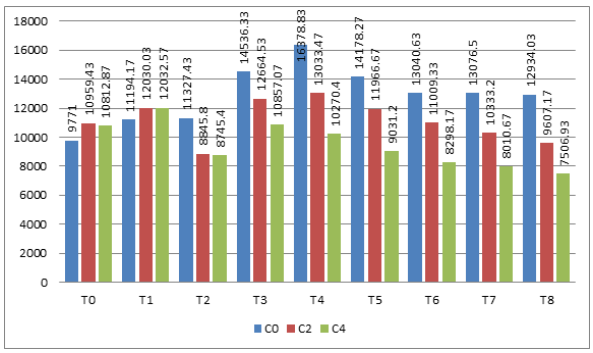



**Graph3: Intergroup comparison of Diastolic blood pressure at different time intervals.**




**Graph4: Intergroup comparison of Mean blood pressure at different time intervals.**

The mean baseline systolic, diastolic and mean blood pressures were statistically similar in all the groups. After premedication SBP, DBP and MAP increased in all the groups. After infusion of placebo there was slight fall in SBP in group C0 not statistically significant, but statistically significant fall in SBP DBP and MAP was seen after clonidine infusion in both clonidine groups more in group C4. During laryngoscopy and 1st minute post laryngoscopy hemodynamic response was completely attenuated in group C4. The fall in BP continued till 5th minute post laryngoscopy in group C4.




**Graph 5: Intergroup comparison of Rate pressure product at different time intervals.**

The mean baseline rate pressure product in Groups C0, C2 and C4 was not found to be statistically different. In group C0 rise in rate pressure product was seen since premedication till 5th minute post laryngoscopy. In groups C2 and C4 after the infusion of test drug there was fall in rate pressure product which continued in Group C4 till 5th minute post laryngoscopy with complete attenuation at laryngoscopy and post laryngoscopy.

## Discussion

The reflex sympathoadrenal stimulation causing tachycardia and increase in arterial blood pressure is well documented(BURSTEIN, LoPINTO, & NEWMAN, 1950; Derbyshire et al., 1983; KING, HARRIS, GREIFENSTEIN, ELDER, & DRIPPS, 1951; Reid LC, 1940; TAKESHIMA, NODA, & HIGAKI, n.d.). This response is of particular concern in patients with cardiovascular and cerebrovascular disease where it might lead to increased mortality and morbidity. Clonidine is a alpha2 agonist that can be used as an adjunctive drug to reduce the anesthetic drug requirement, attenuate adrenergic stress response, reduce anxiety and provide sedation (Hayashi & Maze, 1993). In this study we enrolled 90 ASA I/II patients requiring general anesthesia dividing them randomly and equally (30 patients each) into three groups group C0 (recieving0.9%NS), group C2 (receiving clonidine2µg/kg) and group C4 (receiving Clonidine4 µg/kg. An intravenous route of administration was chosen in favour of safety and predictable bioavailability (Davies et al., 1977; Frisk-Holmberg, Paalzow, & Edlund, 1981; Kulka, Tryba, & Zenz, 1995). We recorded the heart rate, ECG changes, $SPO_2$, systolic and diastolic blood pressure. The mean blood pressure and rate pressure product (as an index of myocardial O2 consumption) were calculated. The percentage change of hemodynamic variables from baseline was observed and student T-test and ANOVA were used to find the statistical significance.

Hemodynamic variables:

The HR in all the three groups (C0/C2/C4) increased 15 minutes after premedication which may be attributed to Inj.Glycopyrolate as in accordance to the finding of D. Preiss and P. Berguson (Preiss & Berguson, 1983). We also observed that increasing the Clonidine dose had a significantly favourable effect on attenuating sympathetic response as compared to placebo in accordance with the study of Peter J. Kulka, Micheal Tryba, and Michael Zenz (Kulka et al., 1995). In group C4 (Clonidine 4 µg/kg) the HR attained was the lowest during laryngoscopy and post intubation (sinceT2 till T8) followed by groupC2 (clonidine2µg/kg) where it transiently but significantly rose during laryngoscopy till 3 minutes post intubation before again decreasing. The decrease in the HR in both the Clonidine groups (C2/C4) was postulated to be due to reduction in sympathetic outflow, simultaneous increase of centrally mediated PNS tone and the influence of clonidine in neurons which receive baroreceptor afferent(Kulka et al., 1995; Sleight et al., 1975).However in The group C0 (placebo) rise in HR continued throughout right after premedication till 5 minutes post laryngoscopy which was in accordance with the observation of Reid and Brace 1940(Davies et al., 1977); King, Harris and Griefenstain 1950(KING et al., 1951); Burstein, Lopinto and Newman, 1950(BURSTEIN et al., 1950) and Takeshima, Noda and Higaki, 1964(TAKESHIMA et al., n.d.).

The mean baseline SBP values were not statistically different between the three groups and SBP increased 15 minutes after premedication in all the three groups. The SBP increased significantly in the placebo group C0 from laryngoscopy till 3 minutes post intubation (T2 till T6) the cause being interpreted as sympathoadrenal stimulation(BURSTEIN et al., 1950; KING et al., 1951; Reid LC, 1940; TAKESHIMA et al., n.d.). The best response in attenuating the sympathoadrenal stimulation, thereby decreasing the SBP in our study was seen in group C4 (Clonidine4 µg/kg) particularly at 1st min post intubation ($p<0.05$) and thereafter till 5 minutes post intubation ($p<0.001$). Clonidine at 2µg/kg decreased the SBP more effectively than placebo except the fact that the control of rise of SBP during laryngoscopy was not effective an observation that is in accordance with findings of Peter J. Kulka, Micheal Tryba, and Michael Zenz(Kulka et al., 1995), M. Ghignone and co-workers (Ghignone, Calvillo, & Quintin, 1987) Engelman and colleagues(Engelman et al., 1989).

The DBP followed a similar trend as the SBP in our study and was in accordance with the findings of Reid and Brace (Reid LC, 1940), King, Harris and Griefenstain (KING et al., 1951), Burstein, Lopinto and Newman, Takeshima, Noda and Higaki(TAKESHIMA et al., n.d.) where the placebo group experienced a significantly increased DBP 15 minutes after premedication and then a highly significant increasing trend till 4th min post intubation($p<.001$). Quite similar to the finding of Peter J Kulka using Clonidine in a dose of 2µg/kg our study also observed a poor control of the pressor response in group C2 during laryngoscopy and 1min after intubation. However increasing the dose of Clonidine to 4µg/kg (groupC4) affectively controlled the pressor responce throughout

the study time intervals an observation that correlated with the findings of J. Poutto and colleagues (Pouttu, Scheinin, Rosenberg, Viinamäki, & Scheinin, 1987) and Dipak Raval and co-workers (Raval & Mehta, 2002).

The observation of our study comparing the MABP in the three groups was in accordance with Quintin and colleagues(Quintin et al., 1990), Carabine et al.(CARABINE, WRIGHT, & MOORE, 1991) ,Martino Aho, A.M. Lehtinen et al.(Aho, Lehtinen, Laatikainen, & Korttila, 1990), S. Roy and colleagues(Roy S, Rudra A, Gupta K, Mondal T, 1993) and Peter J. Kulka(Kulka et al., 1995) where they found Clonidine at a dose range of 4µg/kg to 5µg/kg was significantly more affective in attenuating MABP rise in response to laryngoscopy and immediate post intubation period compared to a lower dose of Clonidine(2µg/kg or less) which in turn was significantly better than placebo(p<.01).

In our study a favourable outcome with regards to the Rate Pressure product (an index of myocardial oxygen consumption) was observed in group C4 where the Rate pressure product decreased significantly starting from the infusion of clonidine(T2) till 5minutes post intubation. Although Rate pressure product decreased significantly in group C2 as well, both after drug infusion and then 4minutes post intubation compared to the placebo group(p.<.001),but the control was unacceptable during laryngoscopy an obserbation which matched that with Yozo Manabe and co-workers (Yozo Manabe, Shigeru Iwamoto, Yuko Tsuru, Kentarou Nogami, 2007)where they concluded Clonidine to be beneficial in IHD patients.

ECG tracings did not reveal ST-T wave changes suggestive of myocardial ischemia in any group during the course of our study.

$SPO_2$ did not show any significant change in any of the groups during the study.

The Sedation level was seen to be increasing with increasing doses of Clonidine. group C4 showed higher sedation levels compared to group C2 (p<.0001) which in turn showed higher levels compared to groupC0 (p<.001). Our study gave comparable results with that done by J. Poutto and colleagues (Pouttu et al., 1987), A. Rudra and co-worker in 1993(Roy S, Rudra A, Gupta K, Mondal T, 1993) and Peter J. Kulka and co-workers in 1995(Kulka et al., 1995) where it was seen that Clonidine at different drug doses produces predictable and acceptable levels of sedation that should not be considered as a deterrent to provision of effective hemodynamic control particularly at a dose range near 4µg/kg.

## CONCLUSION

Clonidine in a dose of 4µg/kg produces better attenuation of sympathoadrenal response to laryngoscopy and intubation with an increased but acceptable level of sedation as compared to a lower dose of 2µg/kg and placebo.

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