International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2023; 6(2): 37-40
Received: 15-02-2023
Accepted: 21-04-2023

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To study the Hemodynamic effects of intravenous clonidine as premedication for endotracheal intubation

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DOI: https://doi.org/10.33545/26643766.2023.v6.i2a.393

Abstract
Direct laryngoscopy and intubation can lead to increase in heart rate and blood pressure by 20-27% and 30-50% respectively
It produces stimulation of laryngeal and tracheal sensory receptors resulting in a marked increase in the release of sympathetic amines and may cause a hypertensive crisis.
Clonidine has anti-hypertensive properties and helps to enhance the effects of anaesthetic agents while decreasing their requirements intraoperatively and simultaneously also providing post operative analgesia, hence we consider it to be an ideal agent to blunt the pressor response to laryngoscopy and intubation.
Here we have studied the clinical efficacy of intravenous clonidine an alpha 2 agonist in a dose of 1mcg/kg as pre medication for laryngoscopy and endotracheal intubation in patients undergoing general anaesthesia
There was a significant difference in the haemodynamic parameters such as heart rate, systolic and diastolic blood pressures and mean arterial pressures without much change from baseline in the patients premedicated with clonidine as compared to those who were premedicated with placebo, immediately at and 5 minutes post intubation.
Clonidine given intravenously as premedication in a dose of 1mcg/kg can safely attenuate the pressor response to laryngoscopy and endotracheal intubation.

Keywords: clonidine, laryngoscopy, intubation, sympathetic amines

Introduction
Alpha- 2 agonists like clonidine and dexmedetomidine have been used to attenuate the intense sympathetic activity associated with laryngoscopy and endotracheal intubation.
Clonidine, an imidazoline derivative is a selective alpha-2 adrenergic agonist and a potent antihypertensive drug which produces a fall in the heart rate, blood pressure, SVR and cardiac output. It inhibits the release of catecholamines and vasopressin and thus modulates the hemodynamic changes.
Through their selective action on central and peripheral α 2 receptors they cause reduction in heart rate and systemic vascular resistance decreasing cardiac output and systolic blood pressure.
Several studies have been done in the past using oral clonidine as premedicant and have been found to be useful in the prevention of adverse hemodynamic changes during laryngoscopy and intubation**.**
It can be given both orally and IV for control of sympathoadrenal response during laryngoscopy and endotracheal intubation with its action lasting for 3-7 hours.
Clonidine also reduces the intra operative requirements of inhalational agents and analgesics.
Even during recovery from anaesthesia, clonidine prevents tachycardia and hypertension. It is also known to decrease the requirement of post operative analgesics.
It is known to be associated with dose dependent effects like bradycardia, hypotension, prolonged sedation etc. However a lower dose may not bring about the desired haemodynamic control. Therefore a proper dose, which gives the desired control with minimal adverse effects needs to be titrated based on type of surgical procedure, duration of surgery, patient characteristics etc.

While dexmeditomidine is highly selective alpha 2 agonist (Alpha-2: alpha-1 1620:1 as compared to 220:1 for clonidine) and would ideally provide better control over haemodynamics during a pressor response.
Since clonidine is more cost effective as compared to dexmedetomidine, we have studied the effectiveness of a dose of 1mcg/kg of clonidine given IV before induction for control of haemodynamic response to intubation.

Material and Methods
The study was conducted prospectively in 60 patients of ASA grade I/II aged 18 to 60 years of age scheduled to undergo elective surgeries under general anaesthesia. The study was conducted in the Department of Anaesthesiology of the tertiary care centre for the period of 30 months.
The patients were included in the study by applying the following inclusion and exclusion criteria.

Inclusion criteria
- Patients of either sex, aged between 18-60 years.
- Patients belonging to American Society of Anaesthesiologists' physical status I or II.

Exclusion criteria
- Elderly patients and patients with chronic hypertension
- ASA physical status III/ IV / V patients having any other co-morbidity
- Patients having ischemic heart diseases, aortic stenosis, atrio ventricular blocks, past h/o heart failure.
- Patients on drugs such as clonidine, methyl dopa, beta blockers or calcium channel blockers
- Pregnant women or lactating mothers
- Patients having any renal or hepatic derangement.
- Patients not giving consent.

Thorough preoperative examination was done including relevant clinical history, significant past history, general systemic examination and routine laboratory tests were performed

Preoperative Investigations
- Complete Haemogram
- BT/CT
- PT-INR
- ECG
- Chest X -Ray
- Urine routine & microscopy
- Blood sugar –fasting and post prandial
- LFT and RFT

Facilities and Equipment
All equipment and drugs for general anesthesia and emergency were kept ready
1. Anaesthesia machine was checked for any leaks or other problems.
2. Resuscitation equipment's which includes appropriate size gloves, mask, suction catheter, oropharyngeal airways, self –inflating bag with reservoir, supraglottic airway device with syringes, lubrication and ties /tapes, oxygen cylinder with oxygen tubing.
3. Equipment for laryngoscopy & intubation –appropriate size laryngoscope and endotracheal tubes and connections
4. Monitors such as non-invasive blood pressure, continuous electrocardiography Monitor, pulse oximeter and ETCO2 were checked.

Randomisation
Patients were allocated to 2 groups (Group A and Group B) of 30 each by computer generated random Number table.
Group A received 10cc saline
Group B (Control group) – Received 1mcg/kg body weight of clonidine diluted in 10cc 10 minutes before intubation.

Anaesthesia Procedure
Written valid and informed consent was taken after explaining the details of the study to patients satisfying the inclusion criteria. NBM status and pre operative temperature, pulse, blood pressure were measured. All drugs and instruments needed for general anaesthesia were kept prepared. The patients were randomly allocated by computer generated number assigned to two groups. Group B (Clonidine group) received Inj. clonidine 1 mcg/kg body weight diluted in 10cc saline intravenously (IV) 10 minutes before intubation, whereas patients in group A (control group) receive plain10cc of normal saline as placebo. The observer was blinded about the groups or medications received by the patients.
On arrival in the operation theatre, baseline parameters such as heart rate (HR), Systemic arterial blood pressure were noted. Pre-medicated with injection glycopyrrolate 0.2 mg, ondesetrone 4 mg, injection Midazolam 0.02mg/kg IV and fentanyl citrate 2 µg/kg intravenously and pre-oxygenation were started. The baseline parameters before induction were noted. Patients were induced with induction dose of Inj. propofol 2 mg/kg and endotracheal intubation were done facilitated by Inj. succinylcholine 1.5 mg/kg.
Heart rate, systolic and diastolic blood pressures and mean arterial pressures were noted as follows

At baseline before premedication
Prior to intubation
1 minute after intubation
5 minutes after intubation

Sample size was calculated using power analysis. [Alpha 0.05 and beta 0.2 (i.e., 80% power) Value] sample size was calculated for primary outcome of hemodynamic responses after laryngoscopy

Statistical Analysis Method
Primary data was collected using paper-based Case Report forms. Collected data was entered in the Microsoft Excel spreadsheets 2016. Statistical analysis was performed on IBM SPSS Statistics Version 20.
Categorical variables were taken in the form of frequencies and percentages and cross tabulations were done for the chosen parameters and column proportions were compared using Chi square test.
Distribution was represented by pie charts or bar graphs. Continuous variables were expressed in the descriptive statistics tables as means, standard deviation, median, maximum and minimum value. Average values were compared using independent sample t test.
P value < 0.05 was considered significant and p value < 0.01 was considered highly significan

Results

Effect on Heart rate

In the present study Heart rate increased in group A at intubation (89.67±4.29 to 110.23±4.03), pneumoperitoneum, and extubation (89.67±4.29 to 109.10±4.59) when compared to baseline. In Clonidine group at intubation it did not change significantly (93.93±6.61 to 94.83±7.73) however it changed significantly in group A (93.93±6.61 to 111.97±6.88).

Effect of Clonidine on Systolic Blood Pressure

In this study Average SBP fell significantly from baseline in Clonidine group till intubation and at 5 and 10 Minutes after the drug was given average SBP was lower in Clonidine compared to Placebo Group (p<0.001).

At intubation there was significant rise from baseline in placebo group (153.57±6.25) but was comparable to baseline in Clonidine group (132.83±6.75). The difference between groups was significant. (p<0.001)

Effect of Clonidine on Diastolic Blood Pressure

In the present study, DBP fell significantly from baseline in Clonidine Group till intubation and at 5 Minutes after the test drug was given average DBP was lower in Clonidine group compared to placebo (p<0.001).

At intubation there was small rise in DBP from baseline in Clonidine group (From 84.47±4.74to 85.97±4.64) and very significant rise in average DBP from baseline in placebo group (From 83.63±6.46 to 99.1±6.48).

Table 1: Effect on heart rate

Heart rate (bpm)	Group A (N=30)	Group B (N=30)	A vs B (P value)
Baseline Before premedication	89.67±4.29	90.9±6.61	0.38
Prior to Intubation	85.83±6.78	74.40±5.44	<0.001**
Intubation	110.23±4.03	83.83±7.73	<0.001**
5 min Post intubation	108.63±4.14	85.7±7.66	<0.001**

Table 2: Effect on systolic Blood pressure

SBP (mm Hg)	Group A (N=30)	Group B (N=30)	A vs B (p value)
Baseline Before premedication	134.67±6.18	135.83±6.42	0.995
Prior to intubation	125.77±5.96	114.27±6.03	<0.001**
Intubation	153.57±6.25	132.83±6.75	<0.001**
5 min Post intubation	151.43±5.79	135.47±6.53	<0.001**

Table 3: Effect on diastolic blood pressure

DBP (mm Hg)	Group A (N=30)	Group B (N=30)	P
Baseline Before premedication	83.63±6.46	84.47±4.74	0.993
Prior to intubation	76.47±6.19	68.77±4.78	<0.001**
Intubation	99.1±6.48	85.53±4.72	<0.001**
5 min Post intubation	95.50±6.13	85.07±4.64	0.004**

Table 4: Effect on mean arterial pressure

MAP (mm Hg)	Group A (N=30)	Group B (N=30)	P
Baseline Before premedication	100.70±6.16	101.60±5.01	0.997
prior to intubation	92.83±5.68	83.77±4.39	<0.001**
Intubation	117.07±5.54	102.63±5.06	<0.001**
5 min Post intubation	114.07±5.34	104.80±4.86	<0.001**

Discussion

Endotracheal intubation stimulates the laryngeal and tracheal sensory receptors, resulting in an increase of sympathetic amines. This sympathetic stimulation results in tachycardia and elevation of blood pressure that may produce an exaggerated hypertensive response [3, 4].

- Clonidine is an anti-hypertensive medication with action on the presynaptic α 2 receptors causing decrease in heart rate and blood pressure by reducing sympathetic outflow.

  The peripheral and central nervous systems' adrenoceptors are both partially agonists by clonidine. With a ratio of affinities at these sites of about 300:1, it is more selective for α2 than for α1 adrenoceptors. Within the central nervous system, α2 adrenoceptors are located both 25 presynaptically on terminals of neurons which release a variety of transmitters - norepinephrine, epinephrine, serotonin and acetylcholine, and postsynaptically on non-nor-adrenergic neurons. It is likely that Clonidine acts at all central α2 receptors, stimulation of which is associated with decreased neuronal excitability and inhibition of membrane bound adenylate cyclas
  - This study was done between 60 ASA I and II patients of 30 in each group
  - oGroup A receiving 1mcg/kg of IV clonidine diluted in 10cc NS 10 minutes before intubation
  - oGroup B receiving 10 cc of NS 10 minutes before intubation as control group

- Clonidine is rapidly and completely absorbed after IV administration and reaches peak plasma concentrations within 10 min. In our study, IV clonidine was given 10 min before scheduled surgery.
- Hypertension and tachycardia were noticeable during endotracheal intubation in the placebo group. Patients premedicated with clonidine had more stable haemodynamics than those pre-treated with placebo.

- Sakshi arora *et al*. [4] studied IV clonidine in a dose of 1mcg/kg and 2 mcg/kg with 2 mcg/kg of IV fentanyl and concluded that a minimal dose of 1mcg/kg of Iv clonidine caused maximum attenuation of pressor response with minimal side effects.
- Carabine *et al*. [5] demonstrated that 0.625 and 1.25 µg/kg clonidine IV 15 min prior to induction of anesthesia attenuates the pressor response to laryngoscopy and intubation. However this was sometimes found to be ineffective in controlling the pressor response
- In a study by Sameena kousar *et al*. [6] the effect of intravenous fentanyl was compared with intravenous clonidine on hemodynamic responses to laryngoscopy and tracheal intubation. They found that clonidine was better than fentanyl for attenuating the hemodynamic responses, and it remained so till the end of 10 minutes.
- Taittonen *et al*. (1997) [7] have also shown similar response patterns while comparing clonidine, dexmedetomidine and placebo In all groups, blood pressure and HR increased after tracheal intubation; both were significantly lower in the dexmedetomidine and clonidine groups than in the placebo group ($P< 0.05$). A similar observation was made by Yildiz *et al*. (2006) [8].

Conclusion
From our study it can be concluded that IV Clonidine in the dose of 1mcg/kg can safely be recommended as pre medication for attenuation of haemodynamic response to endotracheal intubation in ASA grade I and II patients.

Limitations of this study
Post operative sedation scores couldn't be assessed as the surgeries were of varying durations ranging from 1-4 hours.

Conflicts of interest
None

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How to Cite This Article
Dr. Dsouza SJ, Dr. Dongare D, Dr. Valake KC. To study the Hemodynamic effects of intravenous clonidine as premedication for endotracheal intubation. International Journal of Medical Anesthesiology. 2023;6(2):37-40.