Original Article

Evaluation of Oral Clonidine as a Premedicant in Attenuating Hemodynamic Stress Response to Laryngoscopy and Intubation - A Clinical Study

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Abstract

Context: Endotracheal intubation constitutes a period of extreme hemodynamic stress. The search for an ideal agent to attenuate this pressor response still continues. Clonidine, α_2 adrenergic agonist, slows down the heart rate and leads to a dose-dependent decrease in systolic and diastolic blood pressure. It has 100% bioavailability following oral administration. **Aims:** To evaluate the efficacy of oral clonidine in attenuating the hemodynamic responses to laryngoscopy and endotracheal intubation and to study associated side effects. **Setting and Design:** This was a prospective, randomized controlled, double-blind study. **Materials and Methods:** Fifty patients of either sex, aged 20-60 years, ASA grade I/II undergoing elective surgeries under general anesthesia were included. Group A received Clonidine 3 mcg/kg orally 90 min before induction and group B received 5 ml distilled water. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, and rate pressure product were noted at baseline, preinduction, postinduction, intubation and thereafter, 1, 3 and 5 min following intubation. **Statistical Methods:** Student's t-test was used to find the significance of study parameters on a continuous scale. A Chi-square and the Fisher exact test has been used to find the homogeneity of samples on categorical scale. **Results:** There was a statistically significant difference in heart rate, systolic, diastolic, mean arterial pressure and rate pressure product between two groups during laryngoscopy and the difference in parameters persisted for 5 minutes. Clonidine group had more stable hemodynamic parameters throughout. **Conclusion:** Oral clonidine premedication in the dose of 3 mcg/kg can effectively attenuate the hemodynamic stress response to laryngoscopy and intubation with minimal side effects.

Key words: Clonidine, hemodynamic stress response, intubation, laryngoscopy, oral

Introduction

Airway management is a fundamental aspect of anesthesia practice and emergency and critical care medicine. Endotracheal intubation has a potential to induce highly noxious stimuli to the patient and therefore constitutes a period of extreme hemodynamic stress. Noxious autonomic reflexes lead to hypertension, tachycardia, arrhythmias, and a rise in intraocular and intracranial pressure. Though transitory, it may have delerious effects in susceptible patients.[1-3]

Various nonpharmacological methods and pharmacologic agents have been tried to attenuate this hemodynamic response, but none of the approaches or agents has proved to be ideal. Hence the search for an ideal agent is still continuing.

Clonidine, an imidazoline derivative with α_2 adrenergic agonistic properties, slows down the heart rate and leads to dose dependent decrease in blood pressure, both systolic and diastolic. It is well absorbed after oral administration with nearly 100% bioavailability. It has been used in varying doses of 3-5 mcg/kg.[4-6] A smaller dose of 3 mcg/kg offers a safe alternative with minimal hemodynamic side effects and oral route offers easy administration.[7,8]

Thus, we undertook this study with objectives to evaluate the efficacy of oral clonidine in attenuating the hemodynamic responses to laryngoscopy and endotracheal intubation and to study associated side effects.

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Materials and Methods

After obtaining institutional ethical committee approval and informed consent, this prospective, randomized controlled, double-blind study was conducted on 50 patients of either sex, between 20-60 years old, belonging to ASA grade I or II undergoing elective surgeries under general anesthesia. Exclusion criteria included patient refusal, ASA grade III, IV,

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morbid obesity, pregnancy and anticipated difficult airway. The patients were randomly divided into two groups of 25 patients each by a computer-assisted chart. A standard anesthesia protocol was followed. All patients were premedicated with tab alprazolam 0.25 or 0.5 mg according to body weight and tab ranitidine 150 mg the night prior to the surgery. On the morning of surgery, 90 min before induction, heart rate (HR), systolic blood pressures (SBP) and diastolic blood pressures (DBP) were recorded and an anesthesiologist blinded to the study administrated the premedication.

Group A: Received Clonidine 3 mcg/kg orally 90 min before induction as a solution (prepared by diluting the calculated dose with distilled water to make 5 ml) along with tab Ranitidine 150 mg.

Group B: Control group received 5 ml distilled water orally 90 min before induction along with tab Ranitidine 150 mg.

Inside the operation theatre, a multimodal monitor was attached to the patients that monitored electrocardiogram (ECG), HR, non-invasive blood pressure (NIBP) and arterial oxygen saturation (SpO_2). All patients were preoxygenated with 100% oxygen for 5 min. HR, SBP and DBP were recorded before induction. Anesthesia was induced with injection propofol 2 mg/kg. Injection Atracurium 0.5 mg/kg body weight was given after confirming satisfactory mask ventilation to facilitate endotracheal intubation. Patients were intubated with the appropriate size cuffed endotracheal tubes under direct laryngoscopy in the first attempt, with duration of laryngoscopy and intubation not exceeding 20 s. Our study ended at the 5th min post-intubation and no surgical stimulus was allowed until then.

HR, SBP and DBP were noted in postinduction period, during laryngoscopy and intubation, and thereafter 1 min, 3 min and 5 min after intubation. Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated using following formulas.

MAP = DBP + 1/3 Pulse pressure (PR)

PR = SBP – DBP

RPP = SBP × HR

Anesthesia was maintained with nitrous oxide (60%) and oxygen (40%). No narcotics or inhalational agents were used till 5 minutes of intubation. After 5 minutes of intubation, intravenous fentanyl 2 mcg/kg and atracurium 0.5 mg/kg were administered and isoflurane was started. At the end of the surgery residual neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 10 mcg/kg. After clinical assessment of recovery, extubation was done. Post-operatively patients were observed in the recovery room for hypotension and bradycardia.

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± SD and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student's *t*-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis). Chi-square and Fisher's exact test have been used to find the homogeneity of samples on categorical scale. Statistical software, namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1, and Systat 11.0, were used for the analysis of data.

Results

The two groups were statistically comparable with respect to age, sex, weight, and American Society of Anesthesiologists (ASA) physical status as in Table1.

The mean HR, SBP, DBP and MAP were statistically similar in patients of both the groups 90 min prior to induction as shown in Tables 2-5. Preinduction HR was higher in Group B and the difference between two groups was statistically significant. After induction there was a drop in HR in both the groups. During laryngoscopy and intubation, there was increase in HR in both the groups, but the difference between two groups at the time of laryngoscopy and intubation was statistically strongly significant and persisted until 5 min after intubation. In Group A, HR was well under control and returned to preinduction value at 3 min as opposed to Group B, where tachycardia persisted for more than 3 min after intubation as in Table 2.

In the preinduction period, SBP, DBP and MAP were decreased in Group A and slightly increased in Group B with statistically significant difference. There was a pressure drop in both the groups after induction. Maximum difference was seen at the time of laryngoscopy and intubation. It was noted that the patients of Group B had a marked increase in SBP, DBP and MAP at the time of laryngoscopy and intubation which persisted for 5 min after intubation where as Group A patients had small increase which came back to less than baseline value within 5 minutes of intubation as per [Tables 3-5].

In our study, there always remained a very significant difference between two groups as far as RPP was concerned except at the time of administration of premedication. 90 min before induction it was 11072.4 ± 1914.79 in Group A patients and 10739.68 ± 1358.00 in Group B patients with $P = 0.482$. So there was no significant difference in rate pressure product between two groups [Table 6].

At pre induction period there was a drop in the value in Group A whereas Group B patients showed higher values. Maximum difference was noted at the time of laryngoscopy and tracheal intubation where both the groups showed a rise in the value but in Group B it was very high with a mean value of 19226.00 ± 2848.23 compared to a value of 12000.40 ± 1663.60 in Group A.

The difference in the value of RPP between the two groups remained very significant at even 5 min following intubation as per Table 6. In Group A the value dropped below the baseline

Table 1: Demographic data

Parameter	Group A	Group B	*P* value
Age	37.04±9.93	41.60±11.44	0.139
Sex (male/female)	5/20	7/18	0.508
Weight	59.80±7.14	62.80±7.89	0.165
ASA status (I/ II)	16/9	13/12	0.390

Table 2: Comparison of Heart rate (HR) between two groups

HR	Group A	Group B	*P* value
Baseline	84.60±8.42	83.48±8.49	0.642
Pre induction	82.40±8.22	88.92±11.08	0.022*
Post induction	75.56±7.85	82.04±9.60	0.012*
At laryngoscopy and intubation	92.80±9.11	113.96±10.20	<0.001**
1 min after intubation	89.48±9.20	106.64±10.35	<0.001**
3 min after intubation	81.56±10.48	93.20±8.43	<0.001**
5 Min after intubation	72.68±6.30	83.48±8.55	<001**

*moderately significant, **strongly significant

Table 3: Comparison of SBP (mm Hg) between two groups

SBP	Group A	Group B	*P* value
Baseline	130.40±11.56	128.16±5.91	0.393
Pre induction	119.00±9.76	133.08±8.52	<0.001**
Post induction	109.72±10.49	124.08±8.28	<0.001**
At laryngoscopy and intubation	129.16±10.08	168.48±16.73	<0.001**
1 min after intubation	121.28±11.06	157.32±17.08	<0.001**
3 min after intubation	110.52±10.77	131.48±12.18	<0.001**
5 min after intubation	103.36±9.27	120.60±9.05	<0.001**

**strongly significant

Table 4: Comparison of DBP (mm Hg) between two groups

DBP	Group A	Group B	*P* value
Baseline	82.52±7.12	79.92±4.30	0.125
Pre induction	76.44±8.00	83.32±4.49	<0.001**
Post induction	72.24±7.70	78.72±4.66	0.001**
At laryngoscopy and intubation	83.28±6.97	97.96±8.64	<0.001**
1 min after intubation	78.20±7.08	91.76±7.24	<0.001**
3 min after intubation	72.08±6.12	83.6±5.74	<0.001**
5 min after intubation	67.76±4.93	75.36±4.96	<0.001**

**strongly significant

Table 5: Comparison of MAP (mm Hg) between two groups

MAP	Group A	Group B	*P* value
Baseline	98.51±8.23	95.72±4.85	0.152
Pre induction	90.39±8.12	99.90±5.63	<0.001**
Post induction	84.72±8.24	93.801±5.30	<0.001**
At laryngoscopy and intubation	98.38±7.21	121.46±10.09	<0.001**
1 min after intubation	92.47±7.69	113.60±9.08	<0.001**
3 min after intubation	84.88±7.14	99.51±6.86	<0.001**
5 min after intubation	80.39±7.09	90.44±5.62	<0.001**

**strongly significant

Table 6: Comparison of RPP between two groups

RPP	Group A	Group B	*P* value
Baseline	11072.4±1914.79	10739.68±1358.00	0.482
Pre induction	9855.04±1608.32	11865.76±1895.39	<0.001**
Post induction	8337.04±1473.59	10185.60±1431.48	<0.001**
At laryngoscopy and intubation	12000.40±1663.60	19226.00±2848.23	<0.001**
1 min after intubation	10854.00±1502.28	16835.24±2801.53	<0.001**
3 min after intubation	8980.56±1291.05	12177.52±1598.30	<0.001**
5 min after intubation	7495.20±763.26	10016.32±1581.36	<0.001**

**strongly significant

and after 5 min it was 7495.20 ± 763.26 where as in Group B it remained high at 10016.32 ± 1581.36.

Discussion

It is a well-established fact that laryngoscopy and endotracheal intubation act as mechanical stimuli to activate a reflex, mediated by the sympatho adrenal axis and causes significant hemodynamic stress.[9-11] Airway instrumentation leads to stimulation of nerves that carry afferent impulses to the vasomotor center located in brain stem which in turn activates the sympatho adrenal system to release catecholamines resulting in increase in the heart rate and blood pressure.[1] There is a significant association between incidence of myocardial infarction and tracheal intubation or extubation.[12] It may also lead to potentially dangerous rise in intracranial and intraocular pressures. Various pharmacologic agents like beta-blockers, lignocaine, calcium channel blockers, ganglion blocking drugs, vasodilators, opioids, and α_2-adrenergic agonist have been tried to attenuate this hemodynamic response with varying success.

Clonidine is an imidazoline derivative with selective agonistic action at α2 adrenergic receptors. Its mechanism of action involves stimulation of central α2 adrenergic receptors in the vasomotor center of medulla and presynaptically at the peripheral nerve terminals, blocking release of norepinephrine from the nerve terminals leading to hypotension and bradycardia. It also stimulates parasympathetic outflow, increasing vagal tone contributing to the slowing of HR.[4-6]

When given orally, its bioavailability is 100%. Peak plasma concentration and maximal hypotensive effects are seen 90 min after the oral dose.[4-6] Therefore we decided to give clonidine orally 90 min prior to induction in our study.

We chose 3 mcg/kg as the dose of clonidine in accordance with previous studies demonstrating safety with lower incidence of obvious side effects like severe bradycardia and hypotension.[13]

Clonidine blunts the reflex tachycardia associated with direct laryngoscopy and tracheal intubation. Carabine *et al*.[14] suggested that cardiovascular responses by short lasting laryngoscopies can be attenuated with very low doses of oral clonidine. It also decreases the intra operative lability of heart rate.

In Group A, there were lesser increments in heart rate during laryngoscopy and intubation compared to control group. Also in preinduction period there was less tachycardia in Clonidine group compared to non Clonidine group. These findings corroborated the studies of Roy and Rudra,[15] Raval *et al*.,[16] Joshi *et al*.[17] Prevention of tachycardia in response to laryngoscopy and intubation and slowing of heart rate induced by clonidine share a complex underlying mechanism. It consists of 3 components: centrally, activation of alpha-2 adrenoceptors causing both a reduction in peripheral sympathetic tone and increased vagal induced reflex bradycardia, peripherally stimulation of presynaptic alpha adrenoceptors leading to diminished release of norepinephrine from the nerve endings and a reduction in peripheral sympathetic tone. In this study one patient of group A had bradycardia that was short-lived and not associated with significant hypotension and was corrected automatically after surgical incision.

In our study we found that in group A, mild tachycardia induced by airway instrumentation resolved within 5 min of intubation where as Chaurasia *et al*.,[18] in a similar study, had noted that it takes 15-20 min for the tachycardia to return back to base line value. On analysis we found that they had used a smaller dose of clonidine for premedication. Persistence of tachycardia could be attributed to the smaller dose inadequate to control the rise in HR. Filos[19] noted that there was 8.2% and 18.5% decrease in HR following 150 mcg and 300 mcg clonidine in elderly patients undergoing cataract surgery. Bradycardia was noticed in 10% patients with low dose where as 50% in the high dose group. The difference could be attributed to younger age and healthy status of our patients. Ghignone *et al*.[20] found HR consistently lower throughout the operative period which never rose above baseline in the per intubation period. The better attenuation as compared to our study could be because of higher clonidine dose (5 mcg/kg) as well as co-administration of lignocaine and fentanyl.

Clonidine controls SBP more than DBP.[7,8] Baseline SBP was comparable between two groups. In group A, there was a decrease in mean SBP 90 min after premedication with Clonidine, whereas in group B a slight increase in SBP was noted, indicating hypotensive and anxiolytic effect of the drug. There was a slight decrease in mean systolic blood pressure after induction in both the groups, followed by an increase during laryngoscopy and intubation.

There was an increase in mean systolic blood pressure in both the groups during laryngoscopy and tracheal intubation but this rise was highly significant in group B. It rose from a baseline value of 128.16 ± 5.91 mmHg to 168.48 ± 16.73 mmHg during laryngoscopy and intubation in group B patients. In the Clonidine group this rise was not as significant as non Clonidine group rather systolic blood pressure dropped significantly below the base line value at 5 min after intubation, which is from a mean of 130.40 ± 11.56 mmHg to 103.36 ± 9.27 mmHg.

On analyzing these observations it can be concluded that Clonidine reduces the systolic blood pressure in preoperative period. These observations strongly reflect the hypotensive effects of Clonidine and its ability to attenuate rise in SBP during laryngoscopy and intubation.[7,8]

These findings were in agreement with the studies conducted by Das *et al*.[21] and Raval *et al*.[16] It was in contrast with Ghignone *et al*.[20] study where SBP and DBP never rose beyond the baseline value. This difference could be attributable to different study design and co-administration of drugs like lignocaine and fentanyl.

The changes in mean DBP followed the changes in mean SBP. In both the groups mean DBP was highest during laryngoscopy and intubation.

In group B, mean DBP rose significantly high during laryngoscopy and intubation which persisted even 3 minutes after induction. There was significant difference in mean DBP in both the groups at all intervals of time except the period 90 min before induction.

With these observations it can be concluded that Clonidine produces a dose-dependent decrease in DBP. But the homeostatic cardiovascular reflexes are maintained, so there is no orthostatic hypotension. Raval *et al*.[16] also found similar results with the use of oral Clonidine premedication.

In our study, at all intervals of time starting from preinduction period, there were highly significant differences in mean arterial pressures between two groups. It can be concluded that Clonidine by virtue of its hypotensive effects, systolic more than diastolic, controls the rise in MAP in the study group that was on clonidine premedication. These findings correlate with those of Roy *et al*.[15] and Raval *et al*.[16]

Rate pressure product is calculated by multiplying SBP with pulse rate. It is an indirect indicator of myocardial oxygen consumption. It is very important for patients with ischemic heart disease as it bears constant relationship to the onset of angina pectoris. To keep myocardial oxygen consumption within normal limits, RPP should be less than 15,000.[16]

In our study rate pressure product was well within control in group A patients with a peak during endotracheal tube placement which was slightly more than the baseline value but within the safe range.

In group B patients, rate pressure product was higher than group A patients at all intervals of time. The peak values were found during laryngoscopy and tracheal intubation which were beyond safe limit. This high rate pressure product value persisted even 5 minutes after intubation in non-Clonidine group patients. Thus it can be concluded that patients who were on Clonidine premedication had a better control on myocardial oxygen consumption as their rate pressure product value was well under control at all stages starting from induction and intubation. Deepak Raval[16] in their study also found similar results.

None of our patients had significant hypotension (25% fall from baseline value). None had significant bradycardia (HR < 60). Side effects such as rash, pruritis, and angioneurotic oedema

were not observed in any of the patients. This could be attributed to the smaller dose of clonidine used in our study.

Conclusion

To summarize, oral clonidine premedication in the dose of 3 mcg/kg given to adult patients of ASA I and II status can successfully attenuate the hemodynamic stress response to laryngoscopy and tracheal intubation with minimal side effects.

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