Original Article

Attenuation of hemodynamic response to laryngoscopy and orotracheal intubation using intravenous clonidine

Sakshi Arora, Anita Kulkarni[1], Ajay Kumar Bhargava[1]

Departments of Anesthesiology and Critical Care, Lady Hardinge Medical College and Shrimati Sucheta Kriplani Hospital, [1]Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Abstract

Background and Aims: Alpha-2 agonists are being increasingly used as adjuncts in general anesthesia and the present study was carried out to study the effect of clonidine as an adjuvant to low dose fentanyl in attenuating the hemodynamic response to laryngoscopy and orotracheal intubation.

Materials and Methods: Ninety female patients belonging to American Society of Anesthesiologists (ASA) physical status I, II, and III in age group 25-65 years, body mass index (BMI) 21-26 kg/m^2, and diagnosed as carcinoma breast scheduled for breast surgery were included in this Prospective, randomized, placebo-controlled study. One-way analysis of variance (ANOVA), paired *t*-test, and chi-square test was applied where deemed appropriate. *P*-value at or below the level of 0.05 was considered as statistically significant.

Results: Intravenous (IV) clonidine 1.0 μg kg^{-1} and clonidine 2.0 μg kg^{-1} significantly attenuated the hyperdynamic response to laryngoscopy and intubation. Clonidine 2.0 μg kg^{-1} was associated with adverse effects like hypotension at the time of induction and postoperative sedation which was not observed with clonidine 1.0 μg kg^{-1}.

Conclusions: A single intravenous low dose clonidine (1.0 μg kg^{-1}) when combined with low dose fentanyl (2 μg kg^{-1}) is a practical, pharmacological and safe method with minimal side effects to attenuate the hyperdynamic response to laryngoscopy and intubation.

Key words: Clonidine, hemodynamic response, laryngoscopy and orotracheal intubation

Introduction

Laryngoscopy and orotracheal intubation are potent stressful stimuli that provoke hemodynamic response like tachycardia and hypertension that can lead to myocardial ischemia, ventricular arrhythmia, left ventricular failure, and cerebral hemorrhage. The mechanisms of the responses to laryngoscopy and orotracheal intubation are proposed to be by somatovisceral reflexes.[1] Stimulation of proprioceptors at the base of the tongue during laryngoscopy induces impulse dependent increases of systemic blood pressure, heart rate (HR), and plasma catecholamine concentrations. Subsequent orotracheal intubation recruits additional receptors that elicit augmented hemodynamic and epinephrine responses as well as some vagal inhibition of the heart.[2] These events are especially detrimental in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmia, cardiomyopathy, congestive heart failure, hypertension, and geriatric population.[3]

Various drug regimens and techniques have been used from time to time for attenuating the stress response to laryngoscopy and intubation, including opioids, barbiturates, benzodiazepines, beta blockers, calcium channel blockers, vasodilators, etc.[4-8]

Alpha-2 agonists like clonidine[9] and dexmedetomidine[10] have been used recently for attenuation of sympathoadrenal stimulation caused by tracheal intubation and surgery.

Address for correspondence: Dr. Sakshi Arora,
61 Unique Apartments, Sector 13 Rohini,
Delhi - 110 085, India.
E-mail: drsakshi7@yahoo.com

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Clonidine stimulates α2 adrenergic inhibitory neurons in the medullary vasomotor center. As a result there is a decrease in sympathetic nervous system outflow from central nervous system to peripheral tissues.[11]

The purpose of this study was to evaluate the efficacy of clonidine as an adjuvant to fentanyl in controlling the hemodynamic response to laryngoscopy and intubation.

Materials and Methods

With approval from the Institutional Ethics Research committee and written informed consent, this prospective, randomized, placebo-controlled study was performed on 90 adult female patients, 25-65 years belonging to American Society of Anesthesiologists (ASA) physical status I, II, and III diagnosed as carcinoma breast and posted for breast surgery. According to simple random sampling technique, all patients included in the study were assigned to one of the three groups. Every first patient was assigned to group A, every second patient was assigned to group B, and every third patient was assigned to group C, as per their admission in hospital.

Patients with coronary artery disease, left bundle branch block, conduction abnormalities, congestive cardiac failure, recent myocardial infarction, anticipated difficult airway, and patients in whom time required for intubation exceeded 15 s and more than one attempt at intubation were excluded from the study.

All patients were premedicated with tab. diazepam 5 mg and tab. ranitidine 150 mg night before surgery and tab ranitidine 150 mg and tab. ondansetron 16 mg orally 1 h prior to surgery. All patients were premedicated with inj. midazolam 1 mg IV, 5 min before induction.

Patient in group A were given 5 ml normal saline IV 10 min prior to induction.
Patient in group B were given clonidine 1.0 μg kg^{-1} IV 10 min prior to induction.
Patient in group C were given clonidine 2.0 μg kg^{-1} IV 10 min prior to induction.
The volume of drug injected in all the groups was same (5 ml).

Induction of anesthesia was achieved with fentanyl 2 μg kg^{-1} followed by propofol 1-1.5 mg kg^{-1}. Atracurium 0.6 mg kg^{-1} was given to facilitate tracheal intubation. Patients were intubated with portex cuffed endotracheal tube after establishment of neuromuscular blockade confirmed with disappearance of single twitch response with a nerve stimulator. Anesthesia was maintained with 33% oxygen, 66% nitrous, and 0.5-1.5% isoflurane. Monitoring included HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), and 5 lead electrocardiograph at baseline; at time of receiving study drug, 5 min after receiving clonidine, prior to induction, 5 min after induction, and post intubation (1 and 5 min after intubation). Escape medication (ephedrine 6 mg increments) was administered for hypotension (MAP <30% from baseline for >60 s) and atropine in 0.3 mg increments, for bradycardia (HR <45 min^{-1}).

Postoperative sedation score was studied in all groups.

Sample size and sample technique

Assuming a 10% difference of the percentage rise in HR or SBP between two groups, alpha = 0.05 and power of the study = 80%, the sample size, n = 24, in each group was required. Assuming 25% as loss to follow-up in each group, we selected 30 patients in each group.

Results were compiled and subjected to statistical analysis. One way analysis of variance (ANOVA), paired t-test, chi-square test was applied where deemed appropriate. P-value at or below the level of 0.05 was considered as statistically significant.

Results

All three groups were comparable with respect to their demographic profile [Tables 1 and 2].

In control group (group A) fentanyl 2 μg kg^{-1} was unable to attenuate the hemodynamic response to laryngoscopy and intubation as the increase in SBP was 13.23%, DBP was 9.42%, MAP was 12.78%, and HR was 11.62% from baseline. Clonidine 1.0 μg kg^{-1} and 2.0 μg kg^{-1} significantly attenuated the hyperdynamic response to laryngoscopy and intubation. In group B at intubation, SBP decreased 13.31% below baseline, DBP decreased 0.58% below baseline, MAP decreased 2.23% below baseline, and HR decreased 2.81% below baseline; and in group C, SBP decreased 8.57% below

Table 1: Demographic profile

Variables	Group A (control)	Group B (clonidine 1 μg kg^{-1})	Group C (clonidine 2 μg kg^{-1})
Age (years)	44.10±8.495	44.67 ±10.196	44.33±8.507
Weight (kg)	61.80±4.972	59.83±6.639	60.73±4.510
Height (cm)	165.23±4.59	163.83±4.39	162.63±5.04
BMI (kg m^{-2})	22.58±1.36	22.21±1.96	22.90±1.27

BMI = Body mass index

baseline, DBP decreased 2.59% below baseline, MAP decreased 5.53% below baseline, and HR decreased 8.1% below baseline [Table 3].

Discussion

The sympathoadrenal response to laryngoscopy and intubation includes hypertension, tachycardia, predisposition to cardiac arrhythmia, and increased myocardial oxygen consumption. The sympathetic responses are associated with an acute increase in plasma concentration of epinephrine and norepinephrine.[2]

A variety of anesthetic techniques and drugs are available to control the hemodynamic response to laryngoscopy and intubation. The methods also include adequate depth of anesthesia and brief duration of laryngoscopy.[12] In our study, intubation was performed when patient became unresponsive to verbal commands and twitch response monitored with the neuromuscular monitor disappeared, the duration of laryngoscopy and intubation was less than 15 s when performed in first attempt.

Fentanyl is a phenylpiperidine derivative, synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75-125 times more potent than morphine. Low doses of fentanyl 1-2 μg kg^{-1} are given to provide analgesia and 2-20 μg kg^{-1} is used as an adjuvant to inhaled anesthetics to blunt circulatory responses to sudden changes in level of surgical stimulation.[13] Fentanyl has added advantages like no histamine release or bronchospasm, cardiostability, rapid onset, and short duration of action.[14]

In our study attenuation of hemodynamic response to laryngoscopy and intubation with fentanyl 2 μg kg^{-1} (group A) was not significant as the increase in SBP at intubation was 13.23%, DBP was 9.42%, MAP was 12.78%, and HR was 11.62% from baseline ($P < 0.005$). Helfman *et al.*,[15] too did not find any attenuation with either 200 μg lignocaine or 200 μg fentanyl, however they intubated 2 min after study drug injection compared to this in our study

Table 2: Hemodynamic parameters during induction and intubation

Hemodynamic parameters	Baseline (T1)	5 min after clonidine (T2)	At Induction (T3)	5 min after induction (T4)	1 min after intubation (T5)	5 min after intubation (T6)
Systolic blood pressure (SBP)						
Group A	126.8±10.08	123.70±9.81	121.87±7.51	93.00±12.06	143.57±17.87	116.93±11.46
Group B	127.7±10.98	111.93±9.93	109.40±8.78	89.73±8.63	110.77±28.33	100.07±9.28
Group C	130.63±7.23	110.90±8.43	109.57±8.59	94.47±19.21	119.43±7.92	100.73±11.15
P-value	>0.05	<0.001	<0.001	>0.05	<0.001	<0.001
Diastolic blood pressure (DBP)						
Group A	80.60±5.67	77.53±5.70	76.30±5.54	60.27±9.19	88.20±11.88	71.70±9.60
Group B	78.23±9.66	70.77±7.69	68.87±6.95	57.47±7.67	77.77±8.35	61.20±6.18
Group C	80.80±4.42	67.90±6.91	66.80±7.53	58.33±9.44	78.70±11.35	63.67±8.45
P-value	>0.05	<0.001	<0.001	>0.05	<0.001	<0.001
Mean arterial pressure (MAP)						
Group A	97.03±5.66	92.87±5.88	91.97±5.01	72.57±8.92	109.43±12.40	89.10±7.90
Group B	95.37±9.52	86.27±7.98	83.83±6.97	71.45±9.04	93.24±9.11	75.86±7.29
Group C	98.37±4.28	83.10±5.89	81.93±6.6	69.83±8.83	92.93±9.96	77.70±8.15
P-value	>0.05	<0.001	<0.001	>0.05	<0.001	<0.001
Heart rate (HR)						
Group A	86.87±9.32	84.10±9.41	85.23±9.92	74.60±7.54	96.97±11.47	83.93±6.84
Group B	86.20±19.80	82.13±16.52	81.07±18.13	74.60±15.31	83.77±16.31	71.17±11.63
Group C	83.87±7.16	79.20±7.88	75.07±7.78	64.07±7.19	77.07±9.37	68.63±9.17
P-value	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001

Table 3: Sedation score

Sedation score	Group A		Group B		Group C		Total	
	n	%	*n*	%	*n*	%	*n*	%
0 = None (patient alert)	30	100	30	100	21	70.0	81	90
1 = Mild (patient may be sleepy but easy to rousable	0	0.0	0	0.0	6	20.0	6	6.67
2 = Moderate (frequently drowsy but still fully rousable	0	0.0	0	0.0	1	3.3	1	1.12
3 = Severe (difficult to rouse)	0	0.0	0	0.0	2	6.7	2	2.23

Chi-square value 20.00, P < 0.001

intubation was performed 5 min after receiving fentanyl injection. Feng *et al.*,[16] found 75 and 45% incidence of tachycardia and 70 and 40% incidence of hypertension with lignocaine (2 μg kg^{-1}) and fentanyl (3 μg kg^{-1}), respectively. Ko *et al.*,[17] designed a study to examine the optimal time of injection of fentanyl for blunting the circulatory responses to tracheal intubation and concluded that the most effective time to administer fentanyl to protect circulatory responses to laryngoscopy and tracheal intubation is 5 min before tracheal intubation. Therefore, we selected fentanyl dose of 2 μg kg^{-1} given 5 min prior to intubation.

Clonidine, α2 adrenergic receptor agonist, has been studied as a premedication in a dose of 1-3 μg kg^{-1} due to its beneficial effect on the hyperdynamic response to endotracheal intubation.[18] The hemodynamic effects of clonidine are both peripheral and central. Peripheral stimulation of subendothelial receptors causes vasoconstriction and on peripheral sympathetic nervous system nerve endings inhibit release of norepinephrine. Centrally it stimulates α2 adrenergic inhibitory neurons in the medullary vasomotor center. As a result, there is a decrease in sympathetic nervous system outflow from central nervous system to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and decrease in systemic blood pressure, HR, and cardiac output.[11]

Clonidine doses up to 4-5 μg kg^{-1} have been investigated frequently, though primarily for their anesthetic-sparing effects in the intraoperative period and for their opioid-sparing effects in the postoperative period.[19] Oral premedication with clonidine 5 μg kg^{-1} has been used successfully to improve intraoperative hemodynamic stability and reduce anesthetic[20] and opioid requirements. A preemptive dose of 4-5 μg kg^{-1} IV followed by infusion (plasma concentration approx. 1.7 ng ml^{-1}) has also been shown to have a morphine-sparing effect for postoperative analgesia.[21,22] Several studies used similar dosing of clonidine to reduce morphine requirements and reported that sedation with clonidine was not greater than that of the morphine control.[21,23]

In our study, combining clonidine 1.0 and 2.0 μg kg^{-1} with fentanyl 2 μg kg^{-1} attenuated the hyperdynamic response to laryngoscopy and intubation. Hemodynamic variables remained stable by combining clonidine 1.0 μg kg^{-1} with fentanyl. At intubation SBP decreased 13.31% below baseline, DBP decreased 0.58% below baseline, MAP decreased 2.23% below baseline, and HR decreased 2.81% below baseline ($P < 0.05$). However, combining clonidine 2 μg kg^{-1} with fentanyl 2 μg kg^{-1} produced greater attenuation of hemodynamic response to intubation as SBP decreased 8.57% below baseline, DBP decreased 2.59% below baseline, MAP decreased 5.53% below baseline, and HR decreased 8.1% below baseline ($P < 0.05$).

The risk of undesirable side effects is extremely important in evaluating the overall safety of preanesthetic medication. In the present study during the induction of anesthesia in group B (clonidine 1 μg kg^{-1}), three out of 30 patients had hypotension; and in group C clonidine 2 μg kg^{-1}), six out of 30 patients had hypotension, with respect to control group in which none of the patients had hypotension ($P > 0.05$, not significant). Hypotension in groups B and C was treated with ephedrine 6 mg IV bolus.

Postoperative sedation in group C (clonidine 2 μg kg^{-1}), two patients had a sedation score 3 (severely sedated), one patient had a sedation score 2 (moderately sedated), and six patients had a sedation score 1 (mildly sedated). In group B (clonidine 1 μg kg^{-1}) all the patients had sedation score 0. We conclude that minimal dose of IV clonidine 1 μg kg^{-1} cause maximum attenuation of pressor response with minimal side effects like hypotension and sedation.

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