Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(3) (Part - II): 997-1005
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6319.43

Comparative Evaluation of Different Doses of Intravenous Clonidine in Attenuation of Haemodynamic Responses to Laryngoscopy and Intubation

Sandeep Sharma[1], Santosh[2], Vikram Bedi[3], Yogendra Singhal[4]

[1,2,4]Assistant Professor, [3]Professor, Department of Anaesthesiology, RNT Medical, College, Udaipur, Rajasthan 313001, India.

Abstract

Background: Now days, more and more patients with cardiovascular disorders are presenting themselves for surgery so anaesthesiologists are in search of safe and efficient drugs and techniques which can prevent cardiovascular responses due to laryngoscopy and intubation. Clonidine possesses beneficial effects on haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation. We undertook this study to compare the effect of different doses of clonidine in attenuating the presser response to laryngoscopy and intubation in patients posted for elective surgery under general anaesthesia. *Materials and Methods:* This prospective randomized double blind controlled study was conducted on ASA Physical Status I and II patients in the age group of 20–60 years of either sex, scheduled for elective noncardiac surgeries under general anaesthesia requiring endotracheal intubation. Group A received 20 ml normal saline IV as infusion over 15 min whereas Group B, C and D received IV Clonidine 1, 2 and 3 µg/kg respectively, diluted to 20 ml with normal saline as infusion over 15 min. The parameters recorded were HR, SBP, DBP and MAP at 1,2,3,5,10 and 20 min after intubation. Postoperatively, heart rate, blood pressure, oxygen saturation (SpO_2) and sedation level were noted at 1 hour interval for 6 hours. Results were compiled and statistically analysed. *Results:* After laryngoscopy and intubation, the mean heart rate and blood pressure (SBP, DBP and MAP) showed a much lesser increase in clonidine treated groups B and C as compared to control group A and this was dose related. In clonidine treated group D, the mean pulse rate and blood pressure even did not show any rise despite the stimulus of laryngoscopy and intubation and remained near the basal value throughout the study period but this was clinically not worrisome and did not required any therapeutic intervention. The heart rate and blood pressure (SBP, DBP and MAP) returned to baseline values much earlier at 5 and 2 minutes in clonidine treated groups B and C respectively. Patients in all the three clonidine treated groups showed a dose related higher level of sedation as compared to control group. *Conclusion:* Clonidine at all the three different doses not only attenuated the intensity of haemodynamic responses to laryngoscopy and endotracheal intubation but also decreased the duration of the response. The effect of clonidine was clearly protective and was dose related.

Keywords: Clonidine; Haemodynamic response; Laryngoscopy; Endotracheal intubation.

How to cite this article:

Sandeep Sharma, Santosh, Vikram Bedi. Comparative Evaluation of Different Doses of Intravenous Clonidine in Attenuation of Haemodynamic Responses to Laryngoscopy and Intubation. Indian J Anesth Analg. 2019;6(3):997-1005.

Corresponding Author: Santosh, Assistant Professor, Department of Anaesthesiology, RNT Medical, College, Udaipur, Rajasthan, India.

E-mail: drsanchoudhary@gmail.com

Received on 15.03.2019, **Accepted on** 16.04.2019

Introduction

Endotracheal intubation is indeed one of the most remarkable contributions of anaesthesiologist to patient care. Laryngoscopy is a basic and essential step during tracheal intubation under general anaesthesia but both laryngoscopy and intubation are associated with haemodynamic changes which are transient and variable [1]. The hemodynamic response manifests as tachycardia and hypertension and it may have deleterious respiratory, neurological and cardiovascular effects such as cardiac arrhythmias, myocardial infarction, acute LVF, increased ICP and ruptured cerebral aneurysm [2,3].

As of today, more and more patients with cardiovascular disorders are presenting themselves for surgery so anaesthesiologists are also in search of safe and efficient drugs and techniques which can prevent cardiovascular responses due to laryngoscopy and intubation.

Several drugs have been used to attenuate haemodynamic changes such as lignocaine intravenous and topical) [4], calcium channel blockers like nicardipine [4], verapamil, nifedipine, diltiazem, beta blockers like esmolol [5], labetalol [5], metoprolol, atenolol, opiates like morphine, fentanyl [6], alfentanil, sufentanil, nalbuphine, nitroglycerine [7], gabapentin but administration of each is associated with related side effects.

Alpha-2 adrenoceptor agonists [8,9] have been used as premedication because of their beneficial properties in anaesthesia. Clonidine which is mainly used as an antihypertensive agent also possesses beneficial effects on haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation. Clonidine reduces anaesthetic requirements, attenuates adrenergic, hormonal and haemodynamic stress responses to surgery, reduces anxiety and also causes sedation [10].

Studies on comparison of different doses of intravenous clonidine for this purpose are limited. Hence we undertook this study to compare the effect of different doses of clonidine in attenuating the presser response to laryngoscopy and intubation in patients posted for elective surgery under general anaesthesia.

Material and Methods

After obtaining Institutional Ethical Committee clearance and written informed consent from participants, the study was conducted on ASA Physical Status I and II patients in the age group of 20–60 years of either sex, scheduled for elective noncardiac surgeries under general anaesthesia requiring endotracheal intubation.

Patients with known allergy to clonidine, substance abuse, base line heart rate < 60 beats/min, base line systolic BP <100 mm of Hg, neurologic illness, respiratory illness, cardiac illness, renal disease, hepatic disease, endocrinal disorders, anticipated difficult airway were excluded from the study.

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. So we had taken 25 patients in each group.

All patients were evaluated day before surgery. The patients who enrolled for study, received tablet ranitidine 150 mg and tablet alprazolam 0.25 mg orally at night before surgery and were kept nil by oral after midnight.

The patients were randomly allocated into four groups of twenty five patients each. Randomisation was done using computer-generated random number tables and sealed envelope technique. The procedure was double blinded, in which the anaesthesiologist administering the drug and the patients both were unaware of group allocation. Intravenous (IV) infusions were prepared by one anaesthesiologist who was not involved in further study. Another anaesthesiologist administered the infusion and recorded the parameters.

Group A received 20 ml normal saline IV as infusion over 15 min. Group B received IV Clonidine 1 μg/kg diluted to 20 ml with normal saline as infusion over 15 min. Group C received IV clonidine 2 μg/kg diluted to 20 ml with normal saline as infusion over 15 min. Group D received IV Clonidine 3 μg/kg diluted to 20 ml with normal saline as infusion over 15 min.

On arrival to operating room, all patients were monitored with electrocardiography, pulse oximetry and non-invasive blood pressure. An IV line was secured with 18 G intravenous cannula and Ringer's lactate infusion was started. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SpO_2) were measured. Inj glycopyrrolate 0.004 mg/kg, inj midazolam 0.03 mg/kg and inj fentanyl 2 μg/kg were given just before infusion of study drug. The study drug infusion was given over 15 min. Any

hypotension (SBP fall >20% from the baseline) was treated with increments of IV mephentermine 3 mg, and incidence of bradycardia (HR <50 beats) was treated with IV atropine 0.6 mg and such patients were excluded from further study.

After monitoring the haemodynamics for 10 min, the anaesthetic procedure was initiated. All the patients were pre-oxygenated for 3 min. General anaesthesia technique was standardised for all the four groups. All the patients were induced with IV propofol 2 mg/kg and IV succinylcholine 2 mg/kg body weight. Following laryngoscopy and endotracheal intubation, the parameters recorded were HR, SBP, DBP and MAP at 1, 2, 3, 5, 10 and 20 min after intubation. Anaesthesia was maintained with oxygen-nitrous oxide (40:60) and isoflurane. Muscle relaxation was maintained with Inj vecuronium 0.1 mg/kg loading then 0.02 mg/kg intermittent doses. Patients were monitored throughout intraoperative period with continuous ECG, SpO_2, heart rate and Blood pressure. After surgery, reversal was achieved with Inj neostigmine 0.05 mg/kg and Inj glycopyrrolate 0.01 mg/kg. After adequate recovery, patients were shifted to post-anaesthesia care unit.

Postoperatively, patients were monitored for 6 hours for heart rate, blood pressure, oxygen saturation (SpO_2) and sedation score [11] at 1 hour interval. Any complications like nausea, vomiting, bradycardia and hypotension were also recorded postoperatively for 6 hours. Level of sedation was assessed by using Ramsay sedation score [11].

Ramsay Sedation Score

1. Patient anxious, agitated, or restless
2. Patient cooperative, oriented, and tranquil alert
3. Patient responds to commands
4. Asleep, but with brisk response to light glabellar tap or loud auditory stimuli
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6. Asleep, no response

Results were compiled and statistically analysed. One way analysis of variance (ANOVA), paired t-test and chi square test were applied where deemed appropriate. p-value ≤0.05 was considered as statistically significant.

Results

All four groups were comparable with respect to their age, weight and gender distribution (Table 1)

The baseline mean heart rate was comparable among all the groups (Table 2). Just after study drug infusion, mean heart rate decreased by 0.047, 1.11, 2.27 and 4.70% in groups A,B,C and D respectively as compared to baseline values but the changes were statistically insignificant compared to preoperative values($p>0.05$) (Table 3). Before induction, the changes in heart rate in group A, B and C were statistically insignificant (0.47%, 4.77% and 4.45%; $p>0.05$) in groups A, B and C respectively whereas in group D, the decrease was statistically significant (8.13%, $p<0.05$). Statistically significant increases in mean heart rate with respect to basal value after laryngoscopy and endotracheal intubation were seen in groups A, B and C (58%, $p<0.001$;36.67%, $p<0.001$; 10.02%, $p<0.01$ respectively). However, a rise in mean heart rate was also observed in group D but this was statistically insignificant throughout the study period. The heart rate returned to baseline values at 10, 5 and 2 min in groups A, B and C respectively and thereafter remained near basal values till the study period.

The mean systolic blood pressure, mean diastolic blood pressure and mean arterial blood pressure were comparable among all the groups (Table 2). Just after study drug infusion, mean systolic blood pressure showed statistically insignificant changes in group A, B and C while it decreased significantly in group D but this was clinically not worrisome and did not require any therapeutic intervention (Table 4). Before induction, a statistically insignificant increase in mean systolic blood pressure was observed in group A. The decrease in mean systolic blood pressure in group B, C and D was statistically significant (6.10%, $p<0.05$, 8.37%, $p<0.01$ & 7.93%, $p<0.01$)) although none of the patients required any therapeutic intervention. After laryngoscopy and intubation, the mean systolic blood pressure showed a progressively

Table 1: Demographic profile

Variables	Group A	Group B	Group C	Group D
Age (years)	38 ± 14	39 ± 14	37 ± 12	38 ± 12
Weight (kg)	56 ± 6.8	57 ± 6.5	54 ± 7.2	57 ± 7.9
Sex ratio (M:F)	10:15	11:14	11:14	13:12

lesser increase in groups B and C as compared to group A but the increase was statistically significant in all three groups as compared to basal systolic blood pressure. In group D, the mean systolic blood pressure did not show any rise, infact it remained statistically significantly lower than baseline value throughout intraoperative period. The raised mean systolic blood pressure returned to baseline values at 10, 5 and 2 minutes in groups A, B and C respectively.

Just after study drug infusion, mean diastolic blood pressure decreased in all groups but that had no clinical significance (Table 2, 5). Before induction, the mean diastolic blood pressure decreased in all groups but no therapeutic intervention was needed in any patient. After laryngoscopy and intubation, the mean diastolic blood pressure showed a progressively lesser increase in groups B and C as compared to group A but the increase was statistically highly significant in all three groups. The mean diastolic blood pressure returned to baseline values at 5 and 2 minutes in groups B and C respectively but it remained high even till 10 minutes in control group A. While in group D, the mean diastolic blood pressure showed a significant fall than baseline diastolic blood pressure throughout the intraoperative period.

Just after study drug infusion, mean arterial blood pressure showed statistically insignificant increase in group A whereas there was decline noted in group B, C and D which was statistically significant only in group D (7.19%, $p<0.01$) (Table 6). Before induction, statistically insignificant increase in mean arterial blood pressure was observed in group A. The mean arterial blood pressure in all the clonidine treated groups (B, C and D) showed a decline which was statistically significant in all three groups but this needed no therapeutic intervention. After laryngoscopy and endotracheal intubation, mean arterial blood pressure increased in groups A, B and C to 129.20 ± 7.74, 114.17 ± 7.25 and 102.74 ± 9.33 mmHg respectively but it decreased in group D to 91.2 ± 8.90 mmHg (Table 2). The mean blood pressure remained at significantly higher level as compared to basal value till 10, 5 and 2 min in groups A, B and C respectively. In group D, the mean arterial blood pressure remained lower than the baseline value throughout the intraoperative period.

The mean sedation score observed at 0 hours postoperatively in groups A,B,C and D was 2.08 ± 0.27,3.16 ± 0.37, 3.28 ± 0.45 and 4.12 ± 0.33

Table 2: Haemodynamic parameters during induction and intubation

Parameter	Baseline	Just after study drug	Before induction	After intubation at 0 min	at 1 min	at 2 min	at 3 min	at 5 min	at 10 min	at 20 min
Heart Rate										
Group A	83.96 ± 6.07	83.92 ± 5.28	84.36 ± 5.52	133 ± 8.13	126.68 ± 6.67	121.76 ± 8.70	110.28 ± 7.42	93.20 ± 5.99	85.92 ± 5.93	86.40 ± 4.87
Group B	82.88 ± 9.13	81.96 ± 7.86	78.92 ± 6.29	113.28 ± 8.67	110.84 ± 8.59	104.88 ± 7.23	88.72 ± 6.69	84.2 ± 4.36	82.56 ± 5.03	82 ± 6.04
Group C	82.6 ± 8.38	80.72 ± 5.59	78.02 ± 6.72	90.88 ± 4.63	90.92 ± 4.70	83.92 ± 4.37	83.68 ± 5.23	81.96 ± 5.09	81.64 ± 5.32	81.24 ± 5.15
Group D	85.04 ± 9.35	81.04 ± 6.66	78.12 ± 5.01	85.84 ± 5.12	84.84 ± 4.74	84.56 ± 8.37	82.68 ± 10.07	83.36 ± 7.08	84.32 ± 7.39	83.92 ± 8.39
p value	0.720	0.414	.0005	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	0.0631	0.0216
Systolic BP										
Group A	124.96 ± 7.99	128.76 ± 6.83	126.88 ± 7.26	174.24 ± 8.49	167.40 ± 8.27	161.6 ± 8.68	152.56 ± 11.59	142.0 ± 9.02	125.64 ± 9.47	125.88 ± 6.14
Group B	125.16 ± 10.56	120.72 ± 10.28	117.52 ± 9.92	152.12 ± 9.46	143.66 ± 11.61	138.96 ± 12.65	134.88 ± 13.90	125.8 ± 13.49	119.2 ± 9.92	121.36 ± 10.36
Group C	124.96 ± 10.31	119.32 ± 10.85	114.68 ± 9.36	135.6 ± 9.99	132.84 ± 11.65	126.76 ± 10.19	116.96 ± 8.38	115.76 ± 9.47	116.76 ± 7.31	117.72 ± 7.64
Group D	125.96 ± 10.34	117.72 ± 7.34	115.96 ± 7.10	122.84 ± 7.38	116.6 ± 6.82	114.6 ± 6.68	115.64 ± 6.20	115.36 ± 6.86	117.48 ± 6.08	119.36 ± 6.29
p value	0.980	0.00015	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	0.00100	0.00249
Diastolic BP										
Group A	78.72 ± 7.56	77.96 ± 6.56	77.92 ± 6.71	106.68 ± 11.39	108.44 ± 9.70	107.20 ± 9.18	102.96 ± 9.25	98.08 ± 10.14	81.12 ± 9.34	80.84 ± 7.69
Group B	79.88 ± 5.46	75.52 ± 6.15	73.92 ± 5.82	95.2 ± 7.48	90.96 ± 7.65	87.24 ± 7.60	84.72 ± 9.78	79.84 ± 8.60	80.44 ± 7.93	83.92 ± 9.67
Group C	78.8 ± 7.45	74.36 ± 6.60	72.76 ± 6.11	86.32 ± 9.86	84.96 ± 11.31	80.76 ± 7.46	73.28 ± 7.99	70.96 ± 8.85	72.68 ± 8.12	77.2 ± 7.02
Group D	82.08 ± 8.39	75.76 ± 6.28	74 ± 5.26	74.92 ± 9.39	72.56 ± 7.83	72.04 ± 8.89	76.16 ± 7.96	73.64 ± 8.22	76.2 ± 7.10	76 ± 5.73
p value	0.3436	0.2543	0.0180	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	0.00015	0.00155
Mean BP										
Group A	94.13 ± 7.23	94.89 ± 5.62	94.24 ± 5.72	129.20 ± 7.74	128.09 ± 7.61	125.33 ± 7.27	119.49 ± 9.02	112.72 ± 9.28	95.96 ± 5.57	95.85 ± 6.64
Group B	94.97 ± 6.41	90.58 ± 7.00	88.45 ± 6.41	114.17 ± 7.25	108.6 ± 5.84	104.48 ± 8.72	101.44 ± 10.98	95.16 ± 9.76	93.36 ± 6.86	96.4 ± 8.25
Group C	94.24 ± 7.88	89.34 ± 7.84	86.73 ± 7.01	102.74 ± 9.33	100.92 ± 11.08	96.09 ± 8.03	87.84 ± 7.95	85.89 ± 8.92	87.37 ± 7.42	90.70 ± 6.98
Group D	96.70 ± 8.85	89.74 ± 6.46	88.06 ± 5.40	91.2 ± 8.90	86.68 ± 6.71	87.8 ± 7.90	89.88 ± 7.33	88.84 ± 8.21	90.04 ± 6.39	90.88 ± 5.96
p value	0.6053	0.0178	0.00018	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	0.00008	0.00299

respectively. It came to basal value at 1, 2,3 and 4 hours in groups A, B, C and D respectively (Fig 1). All the three clonidine treated groups showed a dose related higher sedation score as compared to the control group A and the difference was statistically highly significant(p<0.001). However it was noted that no hypoxic episode occurred in any patient included in the study during the postoperative period Two and four patients in group C and D respectively had episodes of bradycardia intraoperatively which was managed with intravenous injection atropine 0.6 mg. There were no episodes of hypotension in any of the patients in any of the groups.

Table 3: Percentage change in mean heart rate

Observations	Group A Basal heart rate (per min) 83.96 ± 6.079		Group B Basal heart rate (per min) 82.88 ± 9.134		Group C Basal heart rate (per min) 82.6 ± 8.386		Group D Basal heart rate (per min) 85.04 ± 9.35	
	% Change	p value	% Change	p value	% Change	p value	% Change	p value
Just after study drug infusion	-0.047	>0.05	-1.11	>0.05	-2.27	>0.05	-4.70	>0.05
Before induction	0.47	>0.05	4.77	>0.05	-4.45	>0.05	-8.13	<0.05
After intubation at 0 min	58.00	<0.001	36.67	<0.001	10.02	<0.01	9.40	>0.05
at 1 min	50.88	<0.001	33.73	<0.001	10.07	<0.01	-0.23	>0.05
at 2 min	45.00	<0.001	26.54	<0.001	1.59	>0.05	-0.56	>0.05
at 3 min	31.34	<0.001	7.04	<0.05	1.30	>0.05	-2.77	>0.05
at 5 min	11.00	<0.001	1.59	>0.05	-0.77	>0.05	-1.97	>0.05
at 10 min	2.33	>0.05	-0.38	>0.05	-1.16	>0.05	-0.84	>0.05
at 20 min	2.90	<0.05	1.06	>0.05	-1.64	>0.05	-1.31	>0.05

Table 4: Percentage change in mean systolic blood pressure

Observations	Group A Basal SBP (mmHg) 124.96 ± 7.99		Group B Basal SBP (mmHg) 125.16 ± 10.58		Group C Basal SBP (mmHg) 125.16 ± 10.53		Group D Basal SBP(mmHg) 125.96 ± 10.34	
	% Change	p value	% Change	p value	% Change	p value	% Change	p value
Just after study drug infusion	3.04	>0.05	-3.54	>0.05	-4.46	>0.05	-6.54	<0.01
Before induction	1.53	>0.05	-6.10	<0.05	-8.37	<0.01	-7.93	<0.01
After intubation at 0 min	39.43	<0.001	21.54	<0.001	8.34	<0.001	-2.47	>0.05
at 1 min	33.96	<0.001	14.95	<0.001	6.13	<0.05	-7.43	<0.001
at 2 min	29.32	<0.001	11.02	<0.001	1.27	>0.05	-9.01	<0.01
at 3 min	22.08	<0.001	7.76	<0.01	-6.55	<0.05	-8.19	<0.001
at 5 min	13.63	<0.001	0.51	>0.05	-7.51	<0.01	-8.41	<0.01
at 10 min	0.54	>0.05	-4.76	>0.05	-6.71	<0.05	-6.73	<0.01
at 20 min	0.73	>0.05	-3.03	>0.05	-5.94	>0.05	-5.23	<0.05

Table 5: Percentage change in mean diastolic blood pressure

Observations	Group A Basal DBP(mmHg) 78.72 ± 7.56		Group B Basal DBP (mmHg) 82.88 ± 9.13		Group C Basal DBP (mmHg) 78.88 ± 7.45		Group D Basal DBP (mmHg) 82.08 ± 8.39	
	% Change	p value	% Change	p value	% Change	p value	% Change	p value
Just after study drug infusion	-0.96	>0.05	-5.45	<0.05	-5.73	<0.05	-7.69	<0.01
Before induction	-1.01	>0.05	-7.46	<0.01	-7.75	<0.01	-9.84	<0.01
After intubation at 0 min	35.51	<0.001	19.17	<0.001	9.43	<0.01	-8.72	<0.05
at 1 min	37.75	<0.001	13.87	<0.001	7.70	<0.05	-11.59	<0.001
at 2 min	36.17	<0.001	9.21	<0.001	2.38	<0.05	-12.23	<0.001
at 3 min	30.79	<0.001	6.05	<0.05	-7.09	<0.05	-7.21	<0.05
at 5 min	24.59	<0.001	-0.05	>0.05	-10.04	<0.01	-10.28	<0.01
at 10 min	3.04	>0.05	0.70	>0.05	-7.86	>0.05	-7.16	<0.05
at 20 min	2.69	>0.05	5.05	>0.05	-2.12	>0.05	-7.16	<0.01

Table 6: Percentage change in mean of mean arterial blood pressure

Observations	Group A Basal MBP (mmHg) 94.13 ± 7.23		Group B Basal MBP (mmHg) 94.97 ± 6.41		Group C Basal MBP (mmHg) 94.30 ± 8.02		Group D Basal MBP (mmHg) 96.70 ± 8.85	
	% Change	p value	% Change	p value	% Change	p value	% Change	p value
Just after study drug infusion	0.80	>0.05	-4.62	>0.05	-5.25	>0.05	-7.19	<0.01
Before induction	0.11	>0.05	-6.86	<0.05	-8.02	<0.01	-8.93	>0.001
After intubation at 0 min	37.25	<0.001	20.21	<0.001	8.95	<0.01	-5.68	<0.05
at 1 min	36.07	<0.001	14.35	<0.001	7.02	<0.05	-10.36	<0.001
at 2 min	33.14	<0.001	10.01	<0.001	1.89	>0.05	-9.20	<0.001
at 3 min	26.94	<0.001	6.81	<0.05	-6.85	>0.05	-7.05	<0.01
at 5 min	19.74	<0.001	0.20	>0.05	-8.91	<0.01	-8.12	<0.01
at 10 min	1.94	>0.05	-1.16	>0.05	-7.34	>0.05	-6.88	<0.01
at 20 min	1.82	>0.05	1.51	>0.05	-3.81	>0.05	-6.07	<0.01

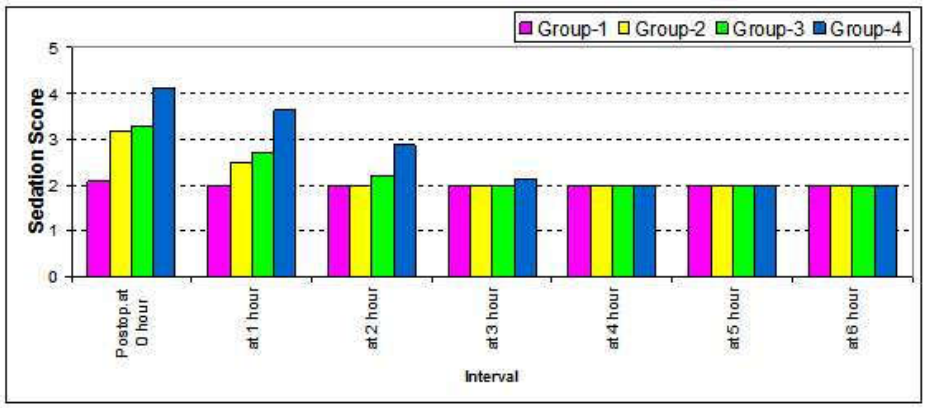

Fig 1: Sedation score

Discussion

The sympathoadrenal response to laryngoscopy and intubation includes hypertension, tachycardia, predisposition to cardiac arrhythmia and increased myocardial oxygen consumption [12]. The sympathetic responses are associated with an acute increase in plasma concentration of epinephrine and norepinephrine [13]. Thus it is logical to select an agent which would prevent and minimize the laryngoscopy stimulation by the intubation process or an agent which would block the sympathetic activity associated with this stimulation. The measures for controlling haemodynamic responses aim to stabilize heart rate and blood pressure during laryngoscopy and intubation, in order to prevent any rise in myocardial work load and oxygen demand and hence, any complication thereof. Secondly, the aim to preserve perfusion of vital organs. At the same time, safety of such technique is also a prime concern. It is desirable to use a drug with least numerous, rapidly recognizable and easily treatable adverse effects. It is also desirable that the procedure should be simple so that it can be recommended as a routine measure.

Clonidine, α2 adrenergic receptor agonist, has been studied as a premedication in a dose of 1-3 µg/kg due to its beneficial effect on the hyperdynamic response to endotracheal intubation [14]. The haemodynamic effects of clonidine are both peripheral and central. Centrally it stimulates α2 adrenergic inhibitory neurons in the medullary vasomotor center [12]. 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 [15]. Clonidine doses up to 4-5 µg/kg have been investigated frequently, though primarily for their anaesthetic-sparing effects in the intraoperative period and for their opioid-sparing effects in the postoperative period [16]. Oral premedication with clonidine 5 µg/kg has been used successfully to improve intraoperative haemodynamic stability and reduce anaesthetic and opioid requirements [17]. As bioavailability of clonidine after oral intake varies between 75% to 95%, so IV route of administration was chosen

to relate pharmacodynamic effects more precisely to a certain dose. Also, IV route produces a more immediate effect than oral route and is under direct clinical supervision of an anaesthesiologist who is able to respond to any adverse effects.

We selected 3 different doses of IV clonidine to find out optimal dose for attenuation of sympathoadrenal responses to laryngoscopy and intubation without side effects. We had compared 1 (Group B), 2 (Group C) and 3 (Group D) µg/kg IV clonidine with control group (Group A) and found that just after intubation, the rise in mean BP was 37.25% in group A, 20.21% in group B, 8.95% in group C and decreased 5.68% in group D and returned to baseline values at 5 min and 2 min in group B and C respectively but it remained significantly high even till 10 min in control group A. In group D mean BP remained significantly lower than baseline values throughout the intraoperative period. Heart rate just after intubation increased 58 % in group A, 36.67% in group B, 10.02% in group C and 9.40% in group D which returned to baseline values at 10, 5 and 2 min in group A, B, C respectively. Intraoperatively, none of the patients in group A and B had episodes of bradycardia whereas 8% patients in group C and 16% patients in group D had bradycardia.

Kulka PJ et al. [18] had noted that clonidine 2 µg/kg although decreased the rise in pulse rate after laryngoscopy and endotracheal intubation but this was not statistically significant. However, they noted that clonidine at doses of 4 µg/kg and 6 µg/kg equally attenuated the tachycardia seen after laryngoscopy and endotracheal intubation. However, Carabine et al. [19] demonstrated that clonidine at doses of 0.625 and 1.25 µg/kg administered IV 15 minutes prior to induction of anaesthesia attenuated the increase in pulse rate after laryngoscopy and endotracheal intubation. On the contrary, Wright et al. [20] noted, under almost identical conditions, that clonidine 1.25 µg/kg IV was not effective in preventing this response.

Sakshi Arora et al. 12 studied iv clonidine in a dose of 1 mcg/kg and 2 mcg/kg with iv fentanyl 2 mcg/kg and concluded that minimal dose of IV clonidine 1 µg/kg cause maximum attenuation of pressor response with minimal side effects. Kotak N et al. [21] and Sameenakousar et al. [22] used 2 mcg/kg safely to attenuate hemodynamic responses to laryngoscopy and intubation.

Ray M et al. 2010 [23] used 3 mcg/kg of clonidine IV over 15 min before induction and 1 mcg/kg/hr by continuous infusion during surgery and observed significance incidence of bradycardia and hypotension in their study. In contrast to our study, Ambrose C et al. [24] didn't found bradycardia with clonidine infusion (0.1-2 µg/kg) in critically ill children. However their study was conducted on paediatric population.

In our study, no patient showed any ECG signs of ischaemia. This might be due to fact that myocardial perfusion pressure was maintained as all the patients of this study belonged to ASA grade 1 and 2 and were free from any major systemic disorder. But the significant increase in haemodynamic parameters (Heart rate and Blood pressure) for a longer duration of period in the control group might have been deleterious in a hypertensive or patient with pre-existing IHD. Clonidine drug at the different doses used in this study definitely provides a benefit in this setting as it not only decreased the intensity of haemodynamic response to laryngoscopy and endotracheal intubation but it also decreased the time for which the haemodynamic parameters remained high after laryngoscopy and endotracheal intubation. Clonidine at dose of 3 µg/kg completely abolished any haemodynamic response to laryngoscopy and endotracheal intubation but had high incidences of bradycardia intraoperatively and more sedation postoperatively.

Although blood pressure remained less than the basal value in clonidine group D probably due to the higher dose (3 µg/kg) used but it did not require use of intravenous fluids or vasopressors. However, we feel that occurrence of hypotension with clonidine is not worrisome and it can be easily managed with proper administration of IV fluids during intraoperative as well as in postoperative period as the cause of hypotension after clonidine is usually hypovolaemia which is unmasked by clonidine induced decreased sympathetic outflow.

The mean systolic blood pressure was lower in clonidine groups C and D compared to other groups during the studied postoperative period. This can be explained by the higher drug dose used in these two groups. However, this decrease in blood pressure caused no concern and required no intervention. Similar observations were recorded for the mean diastolic blood pressure as well as the mean arterial blood pressure postoperatively during the first 6 hours. None of the patients in any of the groups had incidence of bradycardia postoperatively.

Sedation is a well known side effect of clonidine. In our study also, patients in all the three clonidine treated groups showed a higher level of sedation as compared to the control group. This is an advantageous situation as the patients were calm and comfortable throughout the studied

postoperative period and required no airway management in the clonidine groups which used lower doses (1 μg/kg and 2 μg/kg) indicating a well maintained airway and oxygenation. However in clonidine group D (3 μg/kg), 4 patients out of 25, required insertion of Guedel's airway and all these patients were comparatively elderly. Hence, caution must be exercised before administrating this higher dose of clonidine to elderly patients. In a study conducted by Ghignone M et al. [25], they observed that patients were better sedated in the clonidine group as compared to diazepam group. Similarly Rudra Segal et al. [26] found the sedative effect of clonidine better than in placebo group.

Clonidine though does not possess an antiemetic effect but this drug is supposed to non emetic. No difference in incidence of nausea and vomiting was noted between control group and clonidine groups in this study.

No incidence of rebound hypertension after clonidine withdrawal was seen in this study. Wing LMH [27] had noted similar finding and concluded that no evidence of an increased sympathetic nervous system activity was seen after single dose of clonidine. Rebound phenomenon after the sudden withdrawal of clonidine is seen only after treatment for 6-30 days.

Limitation

The present study was carried out in patients who were normotensive, not having hypertension or coronary artery disease. Hence our findings cannot be extrapolated in patients with hypertension and coronary artery disease. Further studied should consider this limitation.

Conclusion

Clonidine at all the three different doses (1 μg/kg, 2 μg/kg and 3 μg/kg) not only attenuated the intensity of haemodynamic responses to laryngoscopy and endotracheal intubation but also decreased the duration of the response. The effect of clonidine was clearly protective and was dose related however caution must be exercised while using higher dose in elderly patients.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

References

1. King BD, Harris LC Jr, Greifenstein FE, Elder JD Jr, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anaesthesia. Anaesthesiology. 1952;12(5):556-66.
2. Amar D, Shamoon H, Frishman WH, Lazar EJ, Salama MD. Effects of labetalol on perioperative stress markers and isoflurane requirements. Br J Anaesth. 1991;67(3):296–301.
3. Steinlechner B, Dworschak M, Birkenberg B, Lang T, Schiferer A, Moritz A, et al. Lowdose remifentanil to suppress haemodynamic responses to noxious stimuli in cardiac surgery: A dose-finding study. Br J Anaesth. 2007;98(5):598–603.
4. Charuluxananan S, Kyokong O, Somboonvi boon W, Balmongkon B, Chaisomboonpan S. Nicardipine versus lidocaine for attenuating the cardiovascular response to endotracheal intubation. J Anesth. 2000;14:77-81.
5. Sarvesh P Singh, Abdul Quadir, Poonam Malhotra. Comparision of Esmolol and Labetolol, in low doses for attenuation of sympathomimetic response to laryngoscopy and intubation. Saudi Journal of Anaesthesia. 2010;4:3:163-9.
6. Babita, Singh B, Saiyed A, Meena R, Verma I, Vyas CK. A comparative study of labetalol and fentanyl on the sympathomimetic response to laryngoscopy and intubation in vascular surgeries. Karnataka Anaesth J. 2015;1:64-68.
7. Fassoulki A, Kaniaris P. Intranasal administration of nitroglycerine attenuates the pressor response to laryngoscopy and intubation of trachea. Br J Anaesthesia. 1883;55(1):49-52.
8. Sunita Goel, Manju Sinha. Effect of oral clonidine premedication in patients undergoing laparoscopic surgery. Bombay Hospital Journal. 2006;48(04):587-91.
9. Anish Sharma N.G. and Shankaranarayana PP. Premedication with I.V. dexmedetomidine vs I.V. clonidine in attenuating the pressor response during laryngoscopy & endotracheal intubation, International Journal of Biomedical Research. 2014; 05(07):465-67.
10. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. J Anaesthesiol Clin Pharmacol. 2010;26:439-45.
11. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalonealphadolone. Br Med J. 1974;2:656-59.
12. Sakshi Arora, Anita Kulkarni1, Ajay Kumar Bhargava1. Attenuation of hemodynamic response to laryngoscopy and orotracheal intubation using intravenous clonidine. Journal of Anaesthesiology Clinical Pharmacology. 2015;31(1):110-14.

13. Hassal HG, El-Sharkway TY, Renck H, Mansour G, Fouda A. Hemodynamic and catecholamine response to laryngoscopy with vs. without endotracheal intubation. Acta Anaesthesiol Scand. 1991;35:442-7.
14. Houston MC. Clonidine hydrochloride. South Med J 1982;75:713-9.
15. Stoelting RK, Hiller SC. Antihypertensive drugs. In: Brain B, Frain M, editors. Pharmacology and Physiology in Anaesthetic Practice, 4th ed. Philadelphia: Lippincott Williams and Wilkins Publishers; 2006.p.343.
16. Brest AN. Hemodynamic and cardiac effects of clonidine. J Cardiovasc Pharmacol. 1980;2:S39-46.
17. Jeffs SA, Hall JE, Morris S. Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. Br J Anaesth. 2002;89:424-7.
18. Kulka PJ, Tryba M, Zenz M. Response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. Anesth Analg. 1995;80,263-68.
19. Carabine UA, Wright PMC, Howe JP, Moore J. Partial attenuation of the pressor response to intubation by clonidine. Anaesthesia. 1991;46(8):634-37.
20. Wright PMC, Carabine UA, Kearney E, Howe JP. Intravenous clonidine: effect on the cardiovascular response to intubation. Anesth Analg. 1991;72:S1-S336.
21. Nirav Kotak, Aditi Lakhotia. Premedication with iv clonidine v/s iv labetalol for hemodynamic stability during air. International journal of scientific research. 2018;7(3):39-41.
22. Sameenakousar, Mahesh, Srinivasan KV. Comparison of fentanyl and clonidine for attenuation of the haemodynamic response to laryngocopy and endotracheal intubation. J Clin Diagnostic Res. 2013;7(1):106–11.
23. Ray M, Dhurjoti bhattacharjee. The effect of intravenous magnesium sulphate and clonidine on anaesthetic consumption, hemodynamic and postoperative recovery in upper limb orthopaedic surgery under general anaesthesia. Indian J. anaesth 2010;54:137-41.
24. Ambrose C, Sale S, Howells R, Bevan C, Jenkins I, Weir P, Murphy P, Wolf A. Intravenous clonidine infusion in critically ill children: dose dependent sedative effects and cardiovascular stability. BJA. 2000;84:794-96.
25. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: The effect of clonidine on perioperative hemodynamic and isoflurane requirements. Anesthesiology. 1987;67:3-10.
26. Rudra Segal, David J Javis, Steven R Duncan, Paul F White, Merven Maze. Clinical efficacy of oral- transdermal clonidine combination during the postoperative period. Anaesthesiology. 1991;74:220-25.
27. Wing L.M.H. Clinical efficacy of oral clonidine as a preanaesthetic medicant. Indian Journal of Anaesthesia. 1995;43;133-9.