COMPARISON OF CLONIDINE AND DEXMEDETOMIDINE IN BLUNTING THE CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION- A RANDOMIZED CONTROL STUDY

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ABSTRACT

BACKGROUND

Laryngoscopy and tracheal intubation activate the sympathetic system resulting in tachycardia and hypertension. Alpha-2 agonists like clonidine and dexmedetomidine blunt the sympathoadrenal stimulation caused by tracheal intubation and surgery. This study aims to compare the effect of intravenous dexmedetomidine and clonidine on the stress response resulting from laryngoscopy and endotracheal intubation.

METHODS

This is a prospective randomized control study. Ninety adult patients of age between 18 and 55 years in American Society of Anesthesiologists physical status I and II were included in this study. Patients were randomly allocated into Group A (Placebo), Group C (Clonidine) and Group D (Dexmedetomidine) of 30 patients each. In the operation theatre, placebo (0.9% normal saline, clonidine (2 µg/kg) or dexmedetomidine (1 µg/kg) or) diluted in 20 ml NaCl 0.9% were infused over a period of 10 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were recorded. Hypotension, bradycardia and sedation scores were also noted. Statistical analysis was done using Excel Data Plugin. Data is represented as mean ± standard deviation. Chi-square and two-way analysis of variance were used p < 0.05 was considered significant.

RESULTS

HR, SBP, DBP and MAP were significantly lower in Group C and D compared to Group A at all times after intubation. Comparing Group C and D also, there was a significant difference in HR, MAP (till 6th minute after intubation), SBP and DBP (till 4th minute after intubation).

CONCLUSIONS

Dexmedetomidine 1 µg/kg and clonidine 2 µg/kg used in blunting the laryngoscopic response produces significant reduction in HR and BP compared to placebo. But dexmedetomidine produced better attenuation of intubation response compared to clonidine with no major side effects.

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BACKGROUND

Laryngoscopy and endotracheal intubation are potent noxious stimuli which activate the sympathetic nervous system, inducing tachycardia and hypertension. These changes are maximum immediately after intubation and last for 5-10 minutes.^[1] These hemodynamic events are especially dangerous in patients with coronary artery disease, cardiac dysrhythmia, cardiomyopathy, congestive heart failure and hypertension.^[2] Various treatment methods like topical or intravenous (IV) lidocaine, opioids, inhaled anaesthetics, vasodilators, calcium channel blockers or adrenergic blockers have been used successfully in blunting the laryngoscopic response.^[3]

Alpha-2 agonists like clonidine and dexmedetomidine is being used recently for controlling the sympathoadrenal stimulation caused by tracheal intubation and surgery. These drugs stimulate the alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre and hence decreasing the sympathetic nervous system outflow from central nervous system.^[2] Dexmedetomidine is a highly selective a 2-adrenoreceptor agonist with short duration of action compared to clonidine.^[4]

The purpose of this study was to compare the effect of clonidine and dexmedetomidine in blunting the hemodynamic response after laryngoscopy and intubation.

METHODS

This prospective, randomized, controlled study involving 90 adult patients was conducted after approval from institutional ethics committee and written informed consent from the patients. Sample size was calculated based on the assumption that there would be a 30% reduction in the mean HR following drug administration; this required 25 patients in each group for results to be significant (With α = 0.05 and power of 80%). We enrolled 30 patients in each group considering possibility of some protocol violations.

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RESULTS

Variable	Group A	Group C	Group D	p Value
Mean age $\pm$ SD (years)	35.22 $\pm$ 8.44	36.46 $\pm$ 9.32	36.12 $\pm$ 1.44	0.379
Mean weight $\pm$ SD (kg)	66.44 $\pm$ 7.82	68.28 $\pm$ 9.32	64.18 $\pm$ 8.92	0.621
Mean height $\pm$ SD (cm)	160.56 $\pm$ 6.72	159.68 $\pm$ 8.55	161.82 $\pm$ 7.54	0.832
Male: Female	19:11	20:10	18:12	0.828
ASA status(1/2)	28/2	26/4	25/5	0.732

Table 1. Demographic Characteristics of The Patients

Variable	Group A	Group C	Group D	Significance of Difference (ANOVA) FP	
Baseline	74.49 $\pm$ 8.11	77.26 $\pm$ 8.76	78.23 $\pm$ 8.65	1.102	0.282
After drug infusion	75.02 $\pm$ 10.66	73.55 $\pm$ 9.65	77.69 $\pm$ 9.98	3.025	0.122
After intubation (AI)	105.38 $\pm$ 8.43	97.67 $\pm$ 9.54	82.81 $\pm$ 8.96	25.454	<0.001
2 mins (AI)	100.48 $\pm$ 8.58	90.71 $\pm$ 8.98	76.20 $\pm$ 8.76	25.485	<0.001
4 mins (AI)	94.90 $\pm$ 7.98	83.82 $\pm$ 8.43	74.37 $\pm$ 7.76	18.342	<0.001
6 mins (AI)	88.11 $\pm$ 10.45	77.80 $\pm$ 10.54	71.67 $\pm$ 9.89	16.587	<0.001
8 mins (AI)	85.58 $\pm$ 8.32	72.04 $\pm$ 8.54	69.43 $\pm$ 8.54	11.432	<0.001
10 mins (AI)	82.46 $\pm$ 9.34	71.72 $\pm$ 9.49	68.61 $\pm$ 9.76	10.345	<0.001

Table 2. Comparison of Heart Rates Between the Groups A, C and D

Variable	Group A	Group C	Group D	Significance of Difference (ANOVA)	
				F	P
Baseline	90.33 $\pm$ 7.56	92.37 $\pm$ 7.66	93.56 $\pm$ 6.98	0.629	0.528
After drug infusion	90.61 $\pm$ 8.62	87.51 $\pm$ 9.02	82.35 $\pm$ 8.94	14.402	<0.001
After intubation (AI)	114.69 $\pm$ 5.77	106.84 $\pm$ 6.56	96.71 $\pm$ 7.45	35.561	<0.001
2 mins (AI)	112.58 $\pm$ 6.87	97.15 $\pm$ 6.88	89.54 $\pm$ 6.87	38.430	<0.001
4 mins (AI)	107.81 $\pm$ 8.76	92.84 $\pm$ 7.53	82.69 $\pm$ 7.64	36.492	<0.001
6 mins (AI)	103.37 $\pm$ 7.44	87.13 $\pm$ 8.12	82.41 $\pm$ 5.56	31.827	<0.001
8 mins (AI)	101.59 $\pm$ 7.65	87.22 $\pm$ 8.54	83.38 $\pm$ 6.64	28.381	<0.001
10 mins (AI)	96.03 $\pm$ 5.56	86.73 $\pm$ 6.51	83.47 $\pm$ 6.21	22.419	<0.001

Table 3. Comparison of Mean Arterial Pressure Between Groups A, C and D

Sedation Score	Group A	Group C	Group D
1	3 (10%)	0 (0%)	0 (0%)
2	24 (80%)	10 (33.33%)	2 (6.67%)
3	3 (10%)	20 (66.66%)	22 (73.33%)
4	0 (0%)	0 (0%)	6 (20%)
5	0 (0%)	0 (0%)	0 (%)
6	0 (0%)	0 (0%)	0 (%)

Table 4. Comparison of Sedation Score at 10th Minute after Extubation

Figure 1. Comparison of Systolic Blood Pressure Between Groups A, C and D

Figure 2. Comparison of Diastolic Blood Pressure Between Groups A, C and D

Patients aged between 18 and 55 years in American Society of Anaesthesiologists (ASA) physical status I and II undergoing elective surgeries under general anaesthesia were included in our study. Patients with predicted difficult airway, on preoperative β -blocker therapy, systemic illness such as hypertension, significant coronary artery disease, morbid obesity, moderate to severe anaemia, hepatic failure, and renal failure were excluded from the study.

The patients were randomly allocated to three groups (Group A, C, D) with the help of a computer-generated table of random numbers.

Group A/Placebo group (30 patients) – received 20 ml NaCl 0.9% over 10 min.

Group C/Clonidine group (30 patients) – received clonidine (2 μ g/kg) diluted in 20 ml NaCl 0.9% over 10 min.

Group D/Dexmedetomidine group (30 patients) – received dexmedetomidine (1 μ g/kg) diluted in 20 ml NaCl 0.9% over 10 min.

All patients were premedicated with oral lorazepam 2 mg and ranitidine 150 mg night before and 2 hrs prior to surgery. Inside the OT after giving the study drug, glycopyrrolate 0.2 mg was given intravenously. Patient was induced with fentanyl 2 μ g/kg, propofol 2 mg/kg and intubated after paralyzing with vecuronium 0.1 mg/kg. Intraoperatively maintenance of anaesthesia done with sevoflurane, Oxygen: nitrous oxide 50:50, vecuronium and fentanyl. End of surgery patient was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and extubated. Patient was then kept in recovery room for 2 hours and then shifted to ward.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded baseline, after study drug administration, after

induction and 1, 2, 3, 5, and 10 min after intubation. Sedation level was assessed using Ramsay sedation score 10 minutes post extubation.

Hypotension (reduction in arterial blood pressure of 20% or more from baseline) was treated by fluid bolus and followed 6 mg of ephedrine. Bradycardia (HR <45 beats/minute or 20% decrease from baseline) was treated with 0.6 mg bolus of atropine.

Statistical analysis was done using Excel Data Plugin. Data is represented as mean $\pm$ standard deviation. Chi-square test (for sex and ASA status) and two-way analysis of variance test were used. $p < 0.05$ was considered significant.

Comparison of the three study groups for age, weight, height, gender ratio and ASA status revealed no statistically significant intergroup difference ($p > 0.05$) [Table 1].

There was no difference in baseline HR among the groups ($p > 0.05$). After administration of the drug, changes in HR occurred in group C and D compared to group A, but it was not statistically significant. But after intubation to till 10 minutes after intubation, the HR in group C and D were lower compared to group A. Also, when comparing group C and group D the fall in heart rate was statistically significant after intubation to till 6 mins after intubation ($p < 0.05$). At 8th and 10th minute the fall in HR in group D was not statistically significant. [Table 2]

Baseline MAP among the groups were similar ($p > 0.05$). After drug infusion and intubation, the changes in MAP in group C was not statistically significant ($p > 0.05$) compared to group A, but the changes in MAP in group D compared to group A was significant. Thereafter there was significant difference in MAP in group C and D compared to group A. Between group C and D, the difference in MAP was significant ($p < 0.05$) in group D compared to group C after drug infusion to till 6th minute after intubation. Thereafter the fall in group D was not statistically significant compared to group C. [Table 3]

Baseline SBP among the groups were identical ($p > 0.05$). After drug infusion and intubation, the difference in SBP in group C was not statistically significant ($p > 0.05$) compared to group A, but the changes in SBP in group D compared to group A was significant ($p < 0.001$). Thereafter there was significant difference in SBP in group C and D compared to group A ($p < 0.001$). Between group C and D, the changes in SBP was significant ($p < 0.05$) in group D compared to group C after drug infusion to till 4th min after intubation. Thereafter the changes in group D was not statistically significant compared to group C. [Figure 1]

There was no difference in baseline DBP among the groups ($p > 0.05$). After drug infusion the fall in DBP in group C was not statistically significant ($p > 0.05$) compared to group A, but the fall in DBP in group D compared to group A was significant ($p < 0.05$). Thereafter there was significant difference in DBP in group C and D compared to group A ($p < 0.001$). Between group C and D, the changes in DBP was significant ($p < 0.05$) in group D compared to group C after drug infusion to till 4th minute after intubation. [Figure 2]

None of the patient in group A and group C had a sedation score of more than 3. In group D six patients (20%) had sedation score of 4 and none of the patients had score of more than 4. Sedation scores of group C and D were statistically significant compared to group A ($p < 0.001$). Also,

between group C and D higher sedation score was found in group D compared to group C. ($p < 0.001$). [Table 4]

DISCUSSION

Laryngoscopy and intubation activate the sympathoadrenal system resulting in hypertension, tachycardia, cardiac arrhythmia and increased myocardial oxygen consumption. Also, there is an acute increase in plasma concentration of epinephrine and norepinephrine.^[5]

Various factors like age, used medications, duration of intubation, depth of anaesthesia affect the cardiovascular responses during endotracheal intubation and laryngoscopy. Of these the duration of laryngoscopy and depth of anaesthesia are the most important factors.^[6] In our study the duration of laryngoscopy was kept less than 15 seconds. And patients with anticipated difficult airway were excluded from the study. Neuromuscular monitoring and depth of anaesthesia monitors were not used in our study. Laryngoscopy was done after 3 minutes of giving 0.1 mg/kg of vecuronium.

Centrally acting alpha 2 agonists like clonidine and dexmedetomidine offer a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability and with a great advantage of minimal respiratory depression. It maintains the hemodynamic stability by blunting the stress induced sympathoadrenal responses to intubation during surgery and during emergence from anaesthesia.^[7] Number of studies has been done using clonidine and dexmedetomidine in varying doses for blunting the intubation response. Zalunardo et al.,^[8] Altan et al.,^[9] and Ray et al.^[10] have successfully used 2 $\mu\text{g}/\text{kg}$ of clonidine for attenuating hemodynamic response to tracheal intubation. Arora et al., in his study comparing two doses of clonidine (1 $\mu\text{g}/\text{kg}$ and 2 $\mu\text{g}/\text{kg}$) for obtunding the laryngoscopic response has found that both the doses are helpful in blunting the laryngoscopic response but patients receiving clonidine 2 $\mu\text{g}/\text{kg}$ were more sedated. Hence, he concluded that minimal dose of IV clonidine 1 $\mu\text{g}/\text{kg}$ cause maximum attenuation of pressor response with minimal side effects like hypotension and sedation.^[2]

Menda et al.,^[11] Keniya et al.,^[12] and Bajwa et al.^[13] in their studies have used dexmedetomidine 1 $\mu\text{g}/\text{kg}$ IV and found it to be effective in attenuating the pressor response during laryngoscopy. Studies comparing different doses of dexmedetomidine has produced varying results. Smitha et al. compared the effect of 0.5 and 1 $\mu\text{g}/\text{kg}$ of dexmedetomidine with normal saline in attenuating stress response and found out that dexmedetomidine 1 $\mu\text{g}/\text{kg}$ was more effective than dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ in controlling haemodynamic responses to tracheal intubation.^[14] But Jarineshin et al., has found no significant difference between 0.5 – 1 $\mu\text{g}/\text{kg}$ of dexmedetomidine in reducing HR and MAP during intubation.^[15] Sebastian, et al studied 0.5 and 0.75 $\mu\text{g}/\text{kg}$ of dexmedetomidine and said dexmedetomidine 0.75 $\mu\text{g}/\text{kg}$ attenuated the haemodynamic stress response to laryngoscopy and endotracheal intubation completely compared to 0.5 $\mu\text{g}/\text{kg}$.^[16]

Most studies comparing the effect of clonidine and dexmedetomidine in different doses e.g. clonidine 2 $\mu\text{g}/\text{kg}$ and dexmedetomidine 1 $\mu\text{g}/\text{kg}$,^[1] clonidine 3 $\mu\text{g}/\text{kg}$ and dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$,^[17] clonidine 1 $\mu\text{g}/\text{kg}$ and dexmedetomidine 1 $\mu\text{g}/\text{kg}$,^[18] clonidine 1 $\mu\text{g}/\text{kg}$ and

dexmedetomidine 0.5 µg/kg and 1 µg/kg^[19] showed varying results. Based on these studies we decided to compare the effect of clonidine 2 µg/kg and dexmedetomidine 1 µg/kg in blunting the laryngoscopic response.

The baseline parameters for demography and hemodynamic variables were matched in the three groups.

In our study we found the mean SBP, DBP and MAP in the dexmedetomidine group remained close to the baseline throughout the study period showing a statistically significant difference from both the placebo and clonidine groups. In the clonidine group, the mean SBP, DBP and MAP were significantly lower compared to placebo group at all-time intervals, but the extent of the difference between placebo and dexmedetomidine group was higher as compared to that of the clonidine group. Similar trends were obtained for HR too.

In the placebo group, maximum mean SBP was observed to be 153.59 ± 8.73 mm of Hg after intubation which was significantly higher compared to both clonidine (148.44 ± 8.54 mm of Hg) as well as dexmedetomidine (124.51 ± 8.1 mm of Hg) group at the corresponding time interval. In the placebo group and dexmedetomidine group, the minimum mean SBP at any post intubation interval was 134.32 ± 5.77 mm of Hg and 116.61±6.99 mm of Hg at 10 min whereas in clonidine group the minimum value was at 6th minute (126.56 ± 7.21 mm of Hg).

As regards the hike in mean SBP between induction to intubation intervals, the change was distinctly sharp in the placebo group (from 122.54 ± 7.66 to 153.59 ± 8.73 mm of Hg) as compared to clonidine group (119.82±8.46 to 148.44 ± 8.54 mm of Hg) and dexmedetomidine group (110.83±7.7 to 124.51±8.1 mm of Hg). The minimum to a maximum range of SBP was between 120.53 ± 6.71 and 153.59 ± 8.73 mm of Hg in the placebo group, from 119.82±8.46 to 148.44±8.54 mm Hg in clonidine group and from 110.96±7.7 to 124.51±8.1 mm of Hg in the dexmedetomidine group.

Similar pattern of hemodynamic changes was observed in studies comparing clonidine and dexmedetomidine. But the doses they used was different comparing to our studies. Hussain et al also compared clonidine 2 µg/kg and dexmedetomidine 1 µg/kg and found the results same as our study.^[1] Sarkar et al used a higher dose of clonidine in their study and compared clonidine 3 µg/kg and dexmedetomidine 0.5 µg/kg and found results similar to our study.^[17]

In placebo and clonidine group, none of the patient developed hypotension or bradycardia. One patient in group D had developed hypotension after drug infusion which was managed by infusing intravenous fluid without inotropes.

Sedation levels in group D and C were significantly higher compared to group A. But both in group C and D none of the patients required supplemental oxygen. Arora et al in his study comparing clonidine 1 µg/kg and 2 µg/kg found that 2 µg/kg to cause more hypotension and sedation.^[2] But in our study we found that clonidine did not cause any hypotension. But clonidine group were more sedated compared to saline group. But there was no desaturation or requirement of supplemental oxygen.

Our study results are in contradiction to study by Kakkar A et al., who compared clonidine 1 µg/kg and dexmedetomidine 0.5 µg/kg and 1 µg/kg and concluded that all three groups were good in attenuating the laryngoscopic

response, but clonidine was associated with less side effects.^[19]

Our study had few limitations like invasive blood pressure was not monitored, plasma catecholamines level were not quantified, anaesthesia depth was not monitored, intraoperative usage of fentanyl and inhalational agents were not compared.

CONCLUSIONS

Dexmedetomidine 1 µg/kg and clonidine 2 µg/kg used in blunting the laryngoscopic response produces significant reduction in HR and BP compared to placebo. But dexmedetomidine produced better attenuation of intubation response compared to clonidine with no major side effects.

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