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COMPARISON OF DEXMEDETOMIDINE, LIDOCAINE AND FENTANYL IN ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION IN CARDIAC SURGERY PATIENTS

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ABSTRACT

Objective: Laryngoscopy and intubation produce sympathoadrenal response posing risk especially in cardiac patients due to arrhythmias, myocardial ischemia increasing morbidity and mortality. Our aim is to compare lidocaine, fentanyl and dexmedetomidine in attenuation of this response in cardiac surgery patients. **Material and Methods*:*** Ninety patients were allocated into 3 groups of 30 participants each. Group A obtained 1µg/kg Dexmedetomidine for 10 minutes before laryngoscopy. Group B 1.5mg/kg of Lidocaine and Group C 2µg/kg Fentanyl 90 seconds before intubation. Hemodynamic parameters like Heart rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Rate Pressure Product (RPP) were noted before intubation and 1,3,5,10 and 15 minutes after intubation. Statistical analysis was done using Epi info version 7.2.1.0 statistical software (Chi square test, ANOVA test). **Results*:*** Dexmedetomidine had significant reduction in SBP at 1st (p-value=0.003), 5th, 10th and 15th (p-value<0.001) minute and in DBP at 3rd, 5th, 10th and 15th (p-value< 0.001). MAP was significantly reduced with dexmedetomidine at 1st, 3rd, 5th, 10th and 15th minute (p-value</ = 0.001) and RPP at 1st (p-value=0.040), 3rd (p-value=0.001), 5th (p-value=0.001), 10th (p-value<0.001) and 15th(p-value=0.002) minute. Dexmedetomidine had higher fall in HR at 1st, 3rd, 5th, 10th mins which was not statistically significant(p-value>0.05). **Conclusion*:*** Dexmedetomidine 1µg/kg given as 10 min infusion before laryngoscopy was more effective than fentanyl and lidocaine in blunting hemodynamic response to laryngoscopy and intubation in cardiac surgery patients. However due to significant hypotension associated with dexmedetomidine, it has to be used with caution in these patients.

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INTRODUCTION

Endotracheal intubation is the best and efficient method for securing airway during surgery. Laryngoscopy and intubation provide an intense noxious stimulus via vagal and glossopharyngeal afferent nerves to nervous system and also cause catecholamine release leading to marked sympathetic response such as tachycardia and hypertension [1,2].

This poses a risk especially in patients with preexisting cardiovascular or cerebrovascular disease and may increase the morbidity and mortality in these patients due to cardiac arrhythmias, myocardial ischemia and other complications [3]. To control the fluctuations in hemodynamic parameters during laryngoscopy and intubation several techniques can be used such as deepening of anaesthesia, limiting the laryngoscopy time to less than 15 seconds and use of many pharmacological agents like intravenous and topical lignocaine, opioids, beta blocking drugs, calcium channel blocking drugs and also drugs like magnesium sulphate, nitroglycerine. The technique or the drug chosen depends upon the length of the surgery, choice of anaesthesia, route of administration and any associated comorbidities [2,4].

Dexmedetomidine is an alpha 2-adrenergic receptor agonist and causes dose-dependent sedation, anxiolysis, hypnosis and analgesia due to its action on the central adrenergic flow. It is also known to blunt the hemodynamic response to laryngoscopy as well as intubation resulting in a decrease in the incidence of myocardial ischemia during cardiac surgery [5].

Fentanyl is a synthetic μ-opioid receptor agonist which is highly potent, has a rapid onset of action and acts for a shorter duration. It is known to cause reduction of cardiovascular responses to direct laryngoscopy and intubation [6]. Lidocaine belongs to amide group of local anesthetics and found to be effective in blunting stress response to laryngocopy as well as tracheal intubation [7]. Even though many studies have researched effective agents for blunting hemodynamic alterations during laryngoscopy and intubation, but not many of them have measured the impact of lidocaine, fentanyl and dexmedetomidine in this regard in cardiac surgery patients. With this background, this study is designed for comparison of the effect of these three drugs in attenuation of sympathoadrenal response of laryngoscopy and intubation in patients posted for elective cardiac surgery.

MATERIALS AND METHODS

This prospective, randomized, double blinded study was conducted in Cardiac Surgery Operating room after obtaining Institutional Ethics Committee Approval.This study was done on 90 inpatients between 30-70 years with American Society of Anesthesiologists physical status grade (ASA) II and III with Body Mass Index (BMI) <30 posted for elective cardiac surgery under general anaesthesia. It was determined that at 95.0% confidence interval with 80.0% power, sample size of 30 for each group is adequate to verify minimum difference of 3.89±17.27 beats/mint in variation of mean heart rate at 5 minute after intubation in groups (intravenous dexmedetomidine, lidocaine and fentanyl). Patients with hypotension (SBP<90mmhg), bradycardia (HR<60/min), allergy to the medications under study, ejection fraction<35.0%, diabetes, asthma, pregnancy, chronic renal and liver disorders, long QT, any addiction, intubation attempt lasting more than 15s and any difficulties with intubation were not included in this trial.

Informed consent was acquired from all patients and pre anaesthetic checkup done. Any significant present/past medical/ surgical history and any drug allergy history was noted. On arrival in the operation room, nil per oral status and pre anaesthetic evaluation findings was confirmed. Standard routine monitors including Noninvasive blood pressure (NIBP), oxygen saturation (SpO_2) and Electrocardiogram (ECG) were attached and baseline parameters i.e. heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) and oxygen saturation (SpO_2) were noted. Femoral Arterial Cannulation for Invasive BP monitoring and Right Internal Jugular Vein Cannuation was done under local anaesthesia.

Randomization was done using sealed envelope method and inpatients were allocated into three groups each containing 30 participants. Group A obtained 1μg/kg of Intravenous Dexmedetomidine for 10 minutes before laryngoscopy. Group B obtained 1.5mg/kg of Intravenous Lidocaine and Group C obtained 2μg/kg of Intravenous Fentanyl 90 seconds before intubation. The anaesthetist who prepared and administered the drugs was different from anaesthetist who observed the study variables. Preoxygenation was performed with 100.0% oxygen for 3-5 minutes. Anaesthesia induction was done with Injection Etomidate 0.3mg/kg and Inj. Rocuronium Bromide 1mg/kg IV. Under direct laryngoscopy patient airway was secured with

proper size endotracheal tube placement. Position of tube was confirmed by 5-point auscultation and End tidal carbon dioxide ($EtCO_2$) readings and tube was fixed. Hemodynamic parameters (HR, SBP, DBP, MAP, SpO_2) were noted 1, 3, 5, 10 and 15 minutes after intubation (Primary Outcome). A 20% rise in HR and/or MAP above baseline was considered as a positive reaction for intubation. Neuromuscular monitoring was done to ensure adequate relaxation after rocuronium.

The surgery was permitted to proceed and anaesthesia maintenance done with oxygen, sevoflurane and Inj. Vecuronium 0.1mg/kg, Inj Midazolam and Inj. Fentanyl. Depth of anaesthesia was monitored by entropy monitoring and maintained between 40-60. Patient was shifted intubated to Cardiac Surgery Intensive Care Unit. In the recovery room, patient was observed for any adverse effects postoperatively (Secondary outcome).

STATISTICAL ANALYSIS

Frequency and percentage were used to assess Nominal/ categorical variables and were analyzed using Chi square test. Mean and standard deviation were used to assess Continuous variables and were analyzed using ANOVA test for comparison between multiple groups. A p-value≤ 0.05 was taken as statistically significant. All statistical analysis was done using Epi info version 7.2.1.0 statistical software.

Results

This study was done on 90 eligible inpatients between 30-70 years with ASA II and III with BMI<30 posted for elective cardiac surgery under general anaesthesia after obtaining informed written consent. They were allocated into 3 groups of 30 each. Age, gender distribution was matched in all 3 groups(p-value>0.05) as seen in Table 1. Weight distribution and ASA grading were also similar in all 3 groups(p-value >0.05) as seen in Table 1. Twenty patients in the dexmedetomidine group had Valvular Heart disease (VHD),5 patients were posted for Coronary artery bypass grafting (CABG) and 5 patients had adult congenital heart disease (Adult CHD). 20 patients in the lidocaine group had VHD, 8 patients underwent CABG and 2 patients had adult CHD. 12 patients in the fentanyl group had VHD, 14 underwent CABG and 4 patients had adult CHD.

Table 1: General characteristics of study groups

	Group A (n=30)	Group B (n=30)	Group C (n=30)	p-value	Significance
Age (years)	40.1 ± 14.97	43.8 ± 16.67	48.03 ± 16.67	0.168	NS
Gender					
Female	17 (56.7%)	12 (40%)	13 (43.3%)	0.392	NS
Male	13 (43.3%)	18 (60%)	17 (56.7%)		
Weight (Kg)	52.6 ± 6.44	52.2 ± 7.59	54.43 ± 7.64	0.448	NS
ASA					
Grade II	20 (66.7%)	21 (70%)	20 (66.7%)	0.950	NS
Grade III	10 (33.33%)	9 (30%)	10 (33.33%)		

S=Significant, NS=Non-Significant

Table 2: Difference of Heart rate (/min) between study groups

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p-value	Significance
Baseline	99.83 ± 21.55	94.93 ± 19.44	96.37 ± 15.69	0.594	NS
1 minute after intubation	94.27 ± 19.63	96.27 ± 18.67	95.73 ± 16.36	0.908	NS
3 minutes after intubation	87.33 ± 18.18	95.1 ± 18.67	89.83 ± 15.82	0.224	NS
5 minutes after intubation	83.37 ± 17.05	89.57 ± 18.24	84.93 ± 14.96	0.336	NS
10 minutes after intubation	79.2 ± 15.91	84.13 ± 17.61	82.7 ± 14.58	0.477	NS
15 minutes after intubation	82.73 ± 15.25	83.83 ± 16.39	83.03 ± 15.63	0.962	NS

S=Significant, NS=Non-Significant

Table 3: Difference of Systolic Blood Pressure (mmHg) between study groups

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p-value	Significance
Baseline	127.1 ± 17.52	133.77 ± 24.38	135.17 ± 21.26	0.296	NS
1 minute after intubation	124.03 ± 16.52	139.43 ± 23.4	140.27 ± 20.15	**0.003**	**S**
3 minutes after intubation	87.33 ± 18.18	95.1 ± 18.67	89.83 ± 15.82	0.224	NS
5 minutes after intubation	104.4 ± 17.89	123.73 ± 24.3	128.33 ± 19.57	**<0.001**	**S**
10 minutes after intubation	98.7 ± 16.72	118.9 ± 23.16	123.43 ± 18.32	**<0.001**	**S**
15 minutes after intubation	100.53 ± 18.07	120.8 ± 22.22	122.17 ± 17.17	**<0.001**	**NS**

S=Significant, NS=Non-Significant

Table 4: Difference of Diastolic Blood Pressure (mmHg) between study groups

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p-value	Significance
Baseline	72.47 ± 11.25	76.97 ± 11.93	74.8 ± 14.4	0.388	NS
1 minute after intubation	74.17 ± 10.29	85.13 ± 12.88	84.1 ± 13.61	**0.001**	**S**
3 minutes after intubation	68.2 ± 9.68	78.2 ± 12.66	81 ± 12.93	**<0.001**	**S**
5 minutes after intubation	63.3 ± 8.43	77.3 ± 13.07	75.6 ± 12.27	**<0.001**	**S**
10 minutes after intubation	60.57 ± 9.25	74.37 ± 13.96	72 ± 12.12	**<0.001**	**S**
15 minutes after intubation	62.3 ± 9.32	74.6 ± 13.97	71.4 ± 11.43	**<0.001**	**S**

S=Significant, NS=Non Significant

Table 5: Difference of Mean Arterial Pressure (mmHg) between study groups

Time	Group A	Group B	Group C	p-value	Significance
Baseline	92.07 ± 11.39	96.9 ± 15.82	96.17 ± 14.95	0.368	NS
1 minute after intubation	91.73 ± 11.39	104.07 ± 15.74	102.9 ± 14.16	**0.001**	**S**
3 minutes after intubation	83.93 ± 10.59	96.13 ± 16.04	100.17 ± 13.67	**<0.001**	**S**
5 minutes after intubation	77.23 ± 10.35	93.13 ± 16.28	93.37 ± 13.09	**<0.001**	**S**
10 minutes after intubation	73.63 ± 10.27	89.57 ± 16.07	89.83 ± 12.66	**<0.001**	**S**
15 minutes after intubation	75.43 ± 11.18	90.53 ± 15.96	88.97 ± 12.09	**<0.001**	**S**

S=Significant, NS=Non-Significant

Table 6: Difference of Rate Pressure Product between study groups

Time	Group A	Group B	Group C	p-value	Significance
Baseline	12635.1 ± 2986.7	12863.6 ± 4041.9	12927.9 ± 2514	0.935	NS
1 minute after intubation	11653.3 ± 2671.4	13525.4 ± 3861.9	13344.6 ± 2579.2	**0.040**	**S**
3 minutes after intubation	9821.1 ± 2216.9	12383.1 ± 3655	12092.4 ± 2256.1	**0.001**	**S**
5 minutes after intubation	8641.4 ± 1995.3	11177.5 ± 3447.7	10834.6 ± 2268.2	**0.001**	**S**
10 minutes after intubation	7761.5 ± 1747.9	10080.3 ± 3083.9	10112.4 ± 1902.8	**<0.001**	**S**
15 minutes after intubation	8241.6 ± 1746.1	10134.6 ± 2713.1	10117.1 ± 2346.4	**0.002**	**S**

S=Significant, NS=Non-Significant

The intergroup comparison of heart rate (HR) as seen in Table 2 showed that dexmedetomidine had higher fall in HR at 1st, 3rd, 5th and 10th min post intubation which was clinically significant although it was not statistically significant (p-value>0.05). Lidocaine group had a slight increase in HR at 1st and 3rd min post intubation above the baseline. The intergroup comparison of systolic blood pressure (SBP) as seen in Table 3 showed that dexmedetomidine had significant reduction at 1st (p-value= 0.003), 5th, 10th and 15th (p-value <0.001) minute after intubation compared to that of two other groups which was highly significant statistically. A slight increase in SBP was observed at 1st minute after intubation in lidocaine and fentanyl groups. The intergroup comparison of diastolic blood pressure (DBP) as seen in Table 4 showed that dexmedetomidine had significantly

greater fall at 3rd, 5th, 10th and 15th (p-value < 0.001) after intubation compared to the other two groups which was highly significant statistically. All three groups showed increase in DBP at 1st minute after intubation though the increase was significantly less in dexmedetomidine group (p-value=0.001).

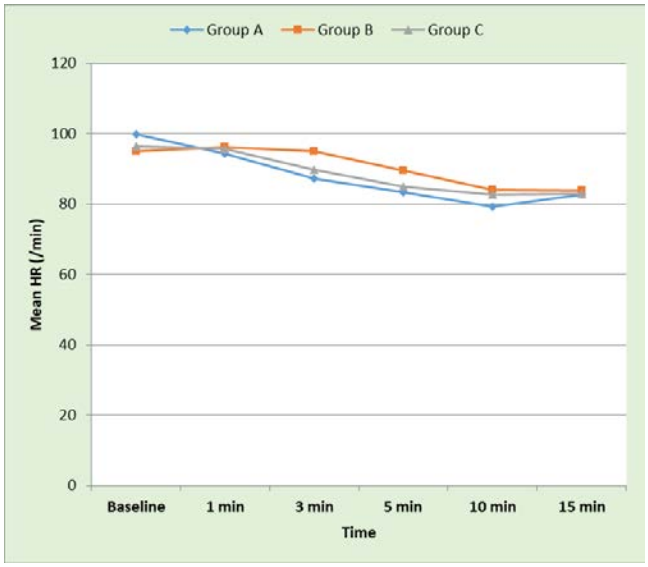

Fig 1: Difference of heart rate (/min) between study groups

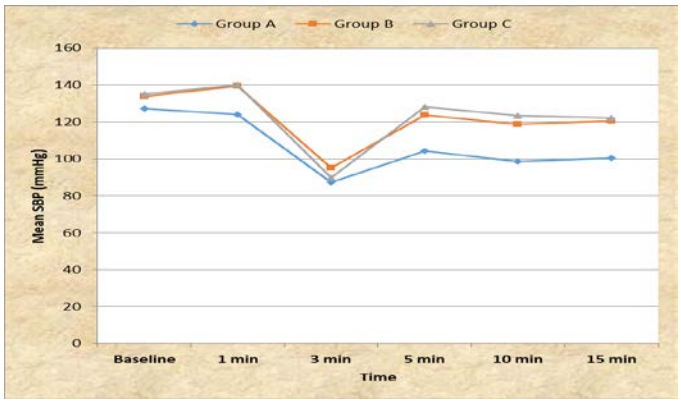

Fig 2: Difference of Systolic Blood Pressure (mmHg) between study groups

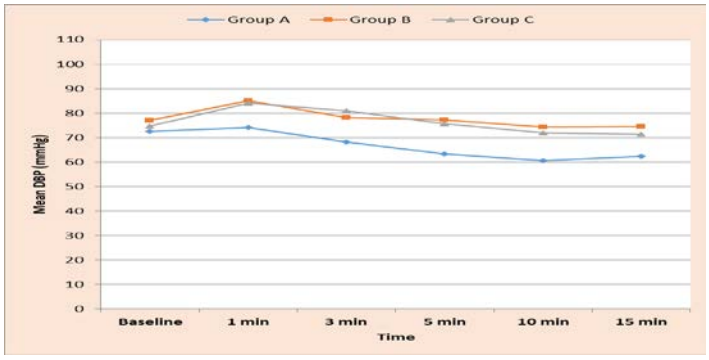

Fig 3: Difference of Diastolic Blood Pressure (mmHg) between study groups

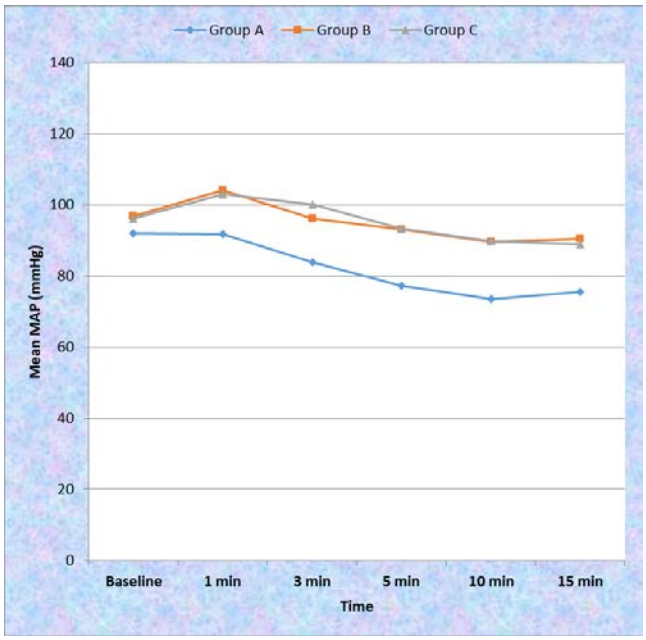

Fig 4: Difference of Mean arterial pressure (mmHg) between study groups

The intergroup comparison of mean arterial pressure (MAP) as seen in Table 5 showed that dexmedetomidine caused highly significant reduction than that of the other two groups at 1st, 3rd, 5th, 10th and 15th minute (p-value≤0.001) after intubation. MAP was higher compared to baseline at 1st minute after intubation in both lidocaine and fentanyl groups but was higher at 3rd minute in only fentanyl group.

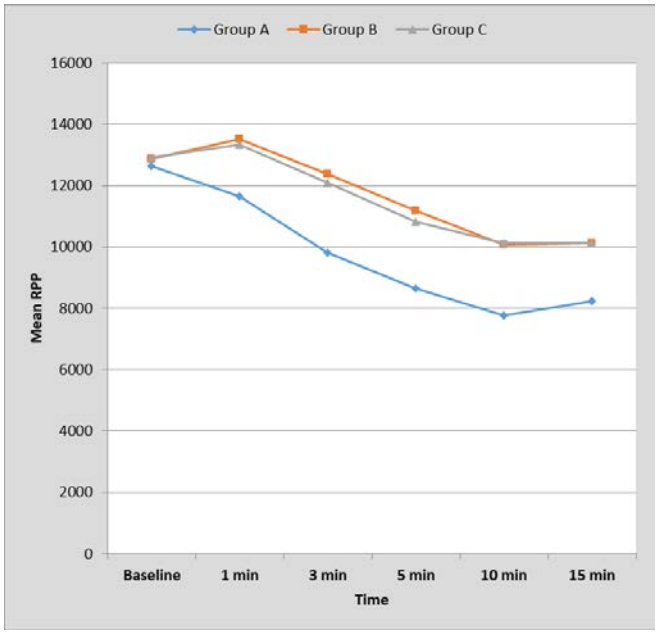

Fig 5: Difference of Rate pressure product between study groups

The intergroup comparison of Rate pressure product (which is a product of Heart rate and systolic blood pressure) as seen in

Table 6 demonstrated that dexmedetomidine was more efficient than the other two groups in decreasing Rate Pressure Product (RPP) at 1st (p-value=0.040), 3rd (p-value=0.001), 5th (p-value= 0.001), 10th (p-value<0.001) & 15th (p-value=0.002) minute after intubation which was highly statistically significant. Fentanyl and lidocaine groups demonstrated increase in RPP at 1st minute.

DISCUSSION

Laryngoscopy and tracheal intubation are regarded as the most crucial procedures during general anaesthesia, as they trigger a transient but significant sympathoadrenal responses [1,2]. This current study was conducted to compare the effect of dexmedetomidine, lignocaine and fentanyl in attenuation of hemodynamic responses to laryngoscopy and intubation in patients undergoing cardiac surgery as maintaining hemodynamic stability is of utmost importance in them [3]. Although there are many techniques and drugs available [2,4] for attenuating these responses, there are not many studies comparing these three medications in cardiac patients.

As per the results of this study, dexmedetomidine was found to cause significant decrease in SBP, DBP, MAP and RPP than fentanyl and lignocaine. It also showed a clinically significant decrease in HR in Dexmedetomidine group though it was statistically insignificant. Post operative complications were not observed with any of the three study drugs.

Dexmedetomidine had higher fall in heart rate at 1st ,3rd,5th and 10th min post intubation compared to fentanyl and lidocaine which was clinically significant although it was not statistically significant (p-value>0.05), most probably because the patients posted for cardiac surgery in our study were on beta blocker, calcium channel blocker or digitalis therapy prior to surgery. Jalonen et al. [8] used dexmedetomidine as an adjunct to anaesthesia in CABG patients receiving beta blockers and found that the occurrence of intraoperative bradycardia needing treatment was not more common in the dexmedetomidine group than in the placebo group. The authors suggested that with the β receptors already blocked in these patients, additional sympathetic blockade with dexmedetomidine did not tend to further decrease the heart rate as has been observed in our study. Lawrence et al. [9] found that a single dose of 2µg/kg of dexmedetomidine lead to diminished sympathoadrenal response to intubation as well as during extubation. There was bradycardia at 1st and 5th min after bolus administration. But the dosage of dexmedetomidine in our study was 1µg/kg as a slow infusion over 10 mins. Hence statistically significant bradycardia was not observed in our study compared to the other two groups. Mohsin et al. [10] conducted a meta-analysis of clinical trials which compared the effectiveness of dexmedetomidine and fentanyl in avoiding elevation in HR during intubation and found that HR was significantly lower at 1 min, 5min and 10 mins post intubation in dexmedetomidine group. Das et al. [11] compared fentanyl and dexmedetomidine in diminution of hemodynamic response to laryngoscopy and intubation and found that dexmedetomidine had significant fall in blood pressure than fentanyl (p-value=0.03) while there was no significant fall in heart rate between dexmedetomidine and fentanyl (p-value=0.19) which was in concordance with our study.

In our study dexmedetomidine had statistically significant reduction in systolic blood pressure at 1st (p-value =0.003), 5th, 10th and 15th (p-value<0.001) minute after intubation compared to that of two other groups. Dexmedetomidine also had significantly greater fall in diastolic blood pressure at 3rd, 5th, 10th and 15th (p-value < 0.001) after intubation and highly significant reduction in mean arterial pressure at 1st, 3rd, 5th,10th and 15th minute (p-value≤0.001) after intubation. Jain V et al. [12] observed that dexmedetomidine was better than fentanyl for attenuation in SBP at 2, 5, 10 mins and of DBP and MAP at 1, 2, 5, 10, 15 mins which was similar to our study. Kataria et al. [13] found dexmedetomidine to be superior to fentanyl in attenuation of MAP in laparoscopic cholecystectomy as seen in our study. Seangrung et al. [14] found that difference in mean values of SBP, DBP and MAP were significantly lesser with dexmedetomidine at 4-10 min (p-value<0.05) compared to lidocaine with propopfol which is similar to our study. Anandani DN et al. [15] observed that dexmedetomidine was better than lignocaine in attenuation of SBP and MAP after intubation as has been observed in our study. Samuel, H et al. [16], Gurulingappa et al. [6] and Thippeswamy RR et al. [17] compared fentanyl vs lignocaine in reduction of pressor response and found fentanyl was better than lignocaine which is similar to our study.

Rate Pressure Product is a good predictor of myocardial oxygen consumption and is important in defining the coronary circulatory changes to increased myocardial metabolic requirements [18]. In our study Dexmedetomidine was better

than the other two groups in decreasing RPP at 1st (p-value =0.040), 3rd (p-value=0.001), 5th (p-value =0.001), 10th (p-value <0.001) and 15th (p-value =0.002) minute which was highly statistically significant. Anandani DN and colleagues compared lignocaine and dexmedetomidine in reduction of sympathoadrenal response to intubation and concluded that dexmedetomidine had more significant reduction in RPP than lignocaine and hence has superior cardio-protection in patients against hemodynamic response than lignocaine [15] which was also seen in our study. Jain V et al. [12] observed that the highest elevation in RPP occurred at 1 min post intubation in the fentanyl group, with a figure of 9758.43, which was statistically higher than that of the dexmedetomidine group with mean RPP of 8185.96 at 1 min after laryngoscopy which was in concordance with our study.

There are several trials that studied the efficacy of dexmedetomidine in patients undergoing cardiac surgery. Sulaiman et al. [19] studied the efficacy of dexmedetomidine for diminution of pressor response to intubation in patients posted for elective off pump CABG & observed that dexmedetomidine caused statistically significant fall in HR, SBP, DBP and MAP compared to placebo and also found that dexmedetomidine can be considered before induction even if patients are receiving beta blockers. Menda F et al. [5] studied the use of dexmedetomidine as an add-on to anaesthesia induction to diminish sympathoadrenal response to intubation in patients posted for fast-track CABG and concluded that dexmedetomidine effectively blunts intubation response and is a safe add-on to anaesthesia induction, even among patients receiving beta blockers. Silpa A R et al. [20] compared the efficiency of 2 doses of dexmedetomidine in reducing cardiovascular response to intubation in patients posted for elective heart surgery and concluded that dexmedetomidine at a dosage of 1µg/kg was better than that of 0.5 µg/kg. Mahjoubifard M et al. [21] studied the effect of dexmedetomidine, lidocaine and fentanyl in attenuation of hemodynamic response to laryngoscopy and intubation in cardiac surgery patients and found that dexmedetomidine was not suitable for hemodynamic control as it led to hypotension and bradycardia. They concluded that fentanyl was more effective than the other two medications in cardiac surgery patients. In our study, dexmedetomidine didn't cause significant bradycardia but it was associated with significant reduction in mean arterial pressure and rate pressure product from 3rd minute post intubation which was more than 20-25% of baseline and maybe considered harmful.

CONCLUSION

Our study showed that dexmedetomidine at a dosage of 1µg/kg as a slow infusion over 10 mins before laryngoscopy and intubation was superior to fentanyl at a dosage of 2µg/kg and lignocaine at a dosage of 1.5mg/kg given 90 seconds before intubation in attenuation of hemodynamic responses to laryngoscopy and intubation in patients undergoing cardiac surgery. However, dexmedetomidine was associated with more than 20-25% reduction in mean arterial pressure and rate pressure product from 3rd minute post intubation onwards which may be harmful and hence the use of dexmedetomidine has to be done with caution in cardiac surgery patients. Our study was conducted on only 90 patients undergoing cardiac surgery and a larger study population may be needed to get a definitive result. Also, uniformity in the type of cardiac surgery cases couldn't be achieved among study groups because of shortage of patients.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Indu Verma contributed in conception of work and study design. Karthik K and Indu Verma performed experimental work, collected data and performed statistical analysis of data. Manbhavan Mahajan contributed in interpretation of collected data. All authors contributed in proofreading and reviewing the final manuscript.

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