Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(9A):3203-3210 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Laryngoscopy and intubation induced stress response – Dexemedetomidine a safer alternative

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Abstract: Laryngoscopy and endotracheal intubation are strong noxious stimuli which cause sympathetic stimulation leading to marked increase in release of catecholamine. There occurs increase in heart rate and blood pressure within 5 seconds of the procedure, peak effect observed in 1 to 2 minutes and returns to baseline with in 5 to 10 minutes. In this context, the present study was undertaken, to compare two doses of Dexemedetomidine in attenuating the hemodynamic response, observe the level of sedation and any untoward effect. 90 patients aged 30 to 50years, were divided into two groups of 45each. Before induction of anaesthesia both the groups received Dexemedetomidine 0.5 mcg/kg and 1.0 mcg/kg body weight respectively in 10 ml of normal saline over a period of 10 minutes. Patients were observed for 5 minutes during which sedation level was recorded at 3rd& 5th minute. Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, Rate pressure product were recorded at different times like before administration of test drug, 5 minutes after injecting the test drugs, immediately after intubation and at 1, 3, 5,8,10 minutes. Data obtained were statistically analyzed& compared. There was significant decrease in all observed hemodynamic parameters in both groups at different times from baseline, However patients receiving Dexemedetomidine higher dose (1.0mcg/kg) the change was more significant compared to the other Group. Therefore it can be concluded that, Dexemedetomidine prior to induction of anaesthesia attenuates the cardiovascular response to laryngoscopy & intubation in a dose dependent manner.
Keywords: Dexemedetomidine, laryngoscopy, intubation, hemodynamic response, sedation

INTRODUCTION

Laryngoscopy and intubation results in reflex sympathetic changes leading to tachycardia , severe hypertension depending on different factors like depth of anaesthesia [1], analgesic and anaesthetic agent used, duration of laryngoscopy and intubation along with measures taken prior to airway manipulation . Though exact mechanism is not known, main cause of hypertension and tachycardia is sympathetic stimulation leading to increased sympathoadrenal activity [2].

Different studies show norepinephrine levels may double from 160 to 300pg/ml and epinephrine levels increase 4 times from 70 to 280pgm/ml and continue for 4 to 8 minutes. Various drugs and techniques have been in use to suppress the stress response to laryngoscopy and intubation like opioids, benzodiazepines, beta blockers, calcium channel blockers, vasodilators, high dose of inducing and inhalational agents with varied level of success and their own limitations. Along with their effect on minimizing cardiovascular response they should have certain additional properties like no effect on recovery, cerebral blood flow and awareness. Hence there is a need to find a drug with proper dosage which can suppress such stress response. α2- agonists like clonidine and Dexemedetomidine are very much useful having better pharmacodynamic profile [3]. Dexemedetomidine is highly specific and selective α2 adrenergic receptor agonist with α 2:α1 selectivity of 1620:1 compared to 220:1 of clonidine[4]. Because of additional beneficial properties like sedation, analgesia, anxiolysis and better hemodynamic stability this study was designed to see the efficacy of IV dexemedetomidine in attenuation of cardiovascular response in two different doses.

Aim:

1. To evaluate and compare the efficacy of IV Dexemedetomidine 0.5mcg/kg with

Dexemedetomidine 1.0mcg/kg body weight in attenuating the haemodynamic response to laryngoscopy and intubation.
2. To observe the level of sedation.
3. To look for any untoward effects.

MATERIAL AND METHODS:

It was a single centered, randomized, single blind study conducted among 90 patients of either sex aged between 30 to 50 years and belonging to American Society of Anaesthesiologists (ASA) Physical status I and II. Approval from the Institutional Ethics Committee and written informed consent from each patient was obtained prior to their enrolment into this study. Patients who were suitable candidates for elective laparoscopic surgery were selected and randomly segregated into 2 different groups of 45 each using a computer generated randomization programme. They received two different doses Dexemedetomidine, 0.5mcg/kg and 1.0 mcg/kg respectively.

Complete preanasethetic evaluation of each patient was done. Patients with allergy to study medication, on other drug therapy, pregnancy, any cardiovascular, pulmonary, renal, hepatic, endocrine, neurological disease and anticipated difficulty in airway were excluded from the study. Also patient s that required more than 20 sec for laryngoscopy and intubation were excluded from the study.

Patients were premedicated with tablet Rabeprazole 40 mg and alprazolam 0.5mg on night before surgery and were advised for overnight fasting. On the day of surgery an i.v line was secured in the preoperative room, injection glycopyrrolate 0.2mg given i.m and ringer lactate solution 10ml/kg body weight was preloaded over a period of one hour. Inside the operation theatre pulse oxymeter, ECG monitor was attached and arterial line was secured in radial artery under local anesthesia. Baseline hemodynamics like Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Rate pressure product (RPP) were recorded.

After recording the baseline parameters patients in Group D1 received Dexemedetomidine 0.5mcg/kg diluted in 10ml normal saline and patients in Group D2 received Dexemedetomidine 1.0mcg/kg diluted in 10ml normal saline intravenously over a period of 10minutesutes with a syringe pump. Patients were observed and preoxygenated for 5 minutes during which the depth of sedation was assessed at 3rd and 5thminutes in accordance to Ramsay sedation scale [Table – 1]. At the end of 5minutesutess vitals were recorded and patients were induced anaesthesia with propofol 1% injected slowly until loss of response and intubation was facilitated with 0.1mg/kg vecuronium prior to laryngoscopy. Maintenance of anaesthesia was done with isoflurane (0.5 to 1%) in 66% nitrous oxide and 33% oxygen on intermittent positive pressure ventilation (IPPV).

The HR and BP were recorded before administration of the study drug (B), 5minutesutes after the drug is injected i.e. just before induction (PD), immediately after intubation (inflation of cuff taken as t0), also at the end of 1minutes (t1), 3minutesutes (t3), 5minutesutes (t5), 8minutesutes (t8) and 10minutesutes (t10) following direct laryngoscopy and intubation.

After study period of 10minutesutes injection Butrophanol 1mg given IV and surgery was allowed to start. Intraoperative muscle relaxation was maintained with intermittent vecuronium 1mg. At the end of surgery injection diclofenac sodium 1.5mg/kg was administered intragluteal for post-operative analgesia. Inhalational agent was stopped, patients were assessed for spontaneous recovery and residual blockade was reversed with neostigmine 2.5mg and glycopyrrolate 0.4mg. Following fulfilment of recovery criteria, they were shifted to recovery room. Any fluctuation of haemodynamic parameter in the intraoperative and postoperative period was managed as per standard guidelines.

Table 1: Ramsey Sedation Scale

Score	Responsiveness
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds to command only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patients exhibits no response

RESULTS

All data expressed as Mean ± standard deviation. Both the study groups were comparable with respect to age, weight, sex and ASA physical status (Table 2). HR, SBP, DBP, MAP were noted in both groups at different times i.e., before administration of

study drug (B), 5minutes after the drug is injected (PD), immediately after intubation (t0), after end of 1minutes (t1), 3minutes (t3), 5minutes (t5), 8 minutes (t8) and 10minutes (t10) of intubation. RPP was also calculated by multiplying HR with SBP.

Statistics

For the purpose of sample size calculation the difference in heart rate following intubation was considered the primary outcome measure which estimated that 45 subjects to be required per group (Group D1 for those receiving 0.5 µg/kg drug dose and Group D2 for those receiving the 1.0 µg/kg drug dose) in order to detect a difference of 8 beats/ minutes in this parameter between groups with 90% power and 5% probability of type 1 error.

Patient details and study data were recorded in individual case record forms and were considered for analysis. All raw data were entered into MS Excel spread sheet and analysed using standard statistical software. All analysis were two tailed and P<0.05 was considered statistically significant.

Changes in HR:-

Table 3, summarizes descriptive statistics of both groups, Baseline HR were comparable (figure 1). HR was significantly less in Group D2 patients at PD (5minutes after test drug), t0, t1, t3 compared to Group D1 (Students unpaired t-test). Group D1 showed statistically significant changes in HR at various time points, similarly in Group D2 patients also serial changes in HR at various time points was significant and more marked.

Table 2: Comparison of Age, Weight, Sex

	Group D1 Mean ± SD	Group D2 Mean ± SD
Age	34.911 ± 10.606	36.393 ± 9.129
Weight (kg)	63.75±9.64	66.33±10.27
Sex(M:F)	18:27	16:29

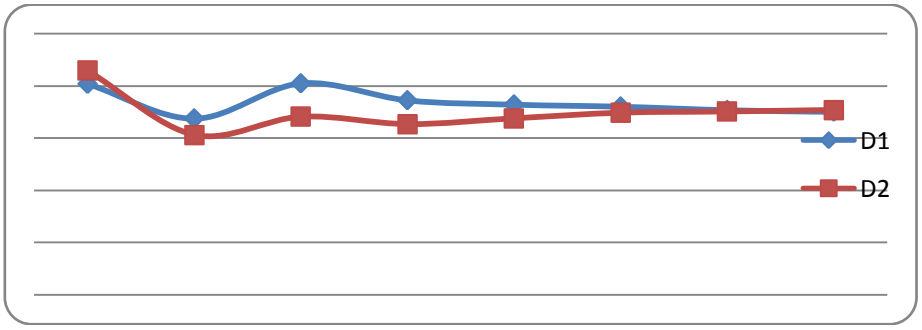

Fig-1: Comparison of Heart Rate (HR) between the two Groups

Table-3: Comparison of Heart Rates

Heart Rate	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
B	80.778 ± 10.623	85.911 ± 9.862	0.0197
PD	67.533 ± 10.217	61.222 ± 3.49	0.0003
0 MINUTES	80.978 ± 7.656	68.222 ± 3.41	0.0001
1 MINUTES	74.489 ± 6.771	65.356 ± 3.386	<0.0001
3 MINUTES	72.867 ± 7.537	67.6 ± 3.194	<0.0001
5 MINUTES	72.089 ± 7.597	69.756 ± 2.924	0.0596
8 MINUTES	70.756 ± 6.796	70.222 ± 3.183	0.6352
10 MINUTES	70.111 ± 5.843	70.822 ± 3.626	0.4901

Changes in SBP, DBP and MAP

Table 4, 5, 6 summarize descriptive statistics of both groups, Baseline values were comparable (figure 2, 3, 4). Intergroup comparison shows SBP, DBP, MAP were significantly less in Group D2 patients at PD(5 minutes after test drug), t0,t1,t3 compared to Group D1 (Students unpaired t-test).

Intragroup comparison shows serial changes in SBP, DBP, MAP were statistically significant at various time points, compare to baseline (Friedman's Analysis of Variance). Just after intubation t0 there was 13% rise in SBP from baseline in Group D1 where as it was only 6% rise in Group D2 patients.

Immediately after intubation (t0) there was 14% rise in DBP from baseline in Group D1 where as it was only 6% rise in Group D2 patients. Also immediately after intubation (t0) there was 14% rise in MAP from post drug time in Group D1 where as it was only 6% rise in Group D2 patients.

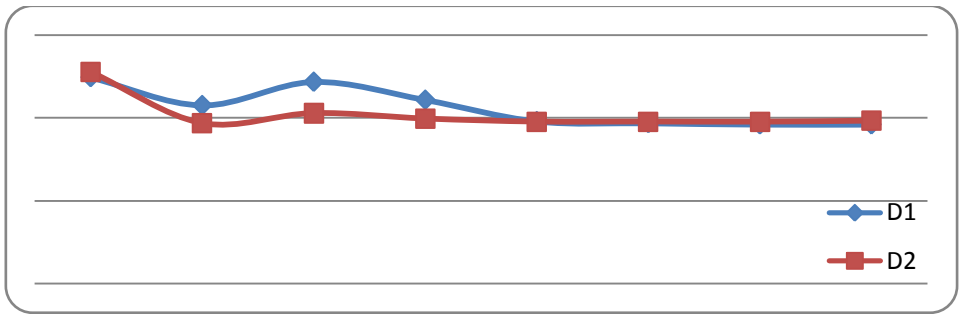

Fig-2: Comparison of Systolic Blood Pressure (SBP)

Table 4: Comparison of Systolic Blood Pressure

SBP	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
B	124.69 ± 8.19	128.02 ± 8.281	0.0581
PD	107.82 ± 9.48	97.155 ± 7.006	<0.0001
0 MINUTES	121.91 ± 6.546	103.13 ± 6.380	< 0.0001
1 MINUTES	111.07 ± 7.056	99.844 ± 6.263	<0.0001
3 MINUTES	98.111 ± 8.671	98.022 ± 5.837	0.9547
5 MINUTES	97.022 ± 8.861	98.044 ± 5.148	0.5056
8 MINUTES	96.222 ± 9.679	97. 956 ± 4.866	0.2872
10 MINUTES	96.2 ± 8.976	98.568 ± 4.697	0.1225

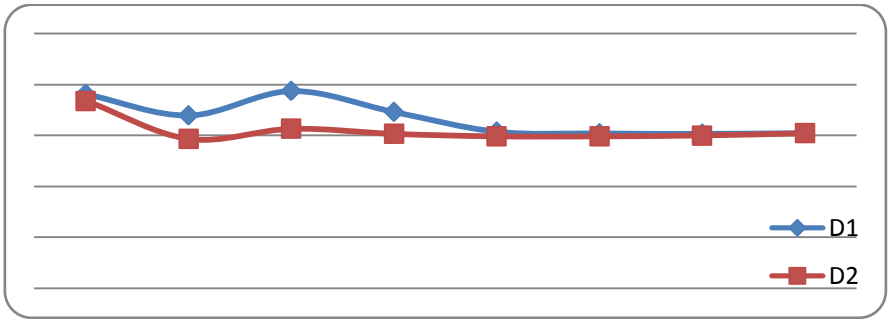

Fig-3: Comparison of Diastolic Blood Pressure (DBP)

Table-5: Comparison of Diastolic Blood Pressure

DBP	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
B	76.264 ± 7.998	73.556 ± 5.918	0.0713
PD	67.867 ± 8.903	58.677 ± 4.317	<0.0001
0 MINUTES	77.489 ± 5.476	62.622 ± 4.064	<0.0001
1 MINUTES	69.222 ± 4.832	60.644 ± 4.238	<0.0001
3 MINUTES	61.461 ± 4.897	59.677 ± 4.079	0.0615
5 MINUTES	60.854 ± 5.647	59.667 ± 3.925	0.2724
8 MINUTES	60.644 ± 6.004	60.044 ± 3.82	0.5734
10 MINUTES	60.911 ± 6.302	60.867 ± 4.159	0.9686

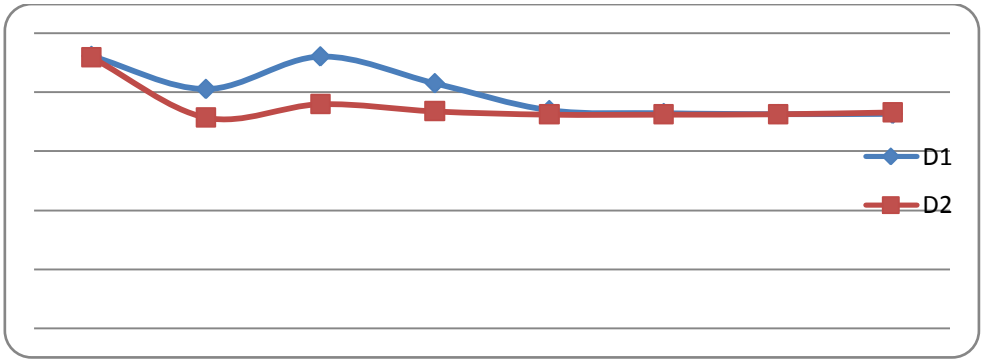

Fig-4: Comparison of Mean Arterial Pressure (MAP)

Table 6: Comparison of Mean Arterial Pressure

MAP	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
B	92.356 ± 7.702	91.822 ± 6.043	0.7157
PD	81.133 ± 8.735	71.467 ± 4.357	<0.0001
0 MINUTES	92.253 ± 5.379	76.482 ± 3.808	<0.0001
1 MINUTES	83.089 ± 5.178	73.556 ± 3.969	<0.0001
3 MINUTES	73.933 ± 5.626	72.467 ± 3.788	<0.1509
5 MINUTES	72.911 ± 6.452	72.467 ± 3.703	0.6898
8 MINUTES	72.566 ± 6.645	72.648 ± 3.538	0.9685
10 MINUTES	72.667 ± 6.759	73.222 ± 3.692	0.63

Changes in RPP (Rate Pressure Product):-

Table 7 summarizes descriptive statistics of both groups, Baseline values were comparable. Inter group comparison shows significant lower RPP in Group D2 patients at PD, t0, t1, t3, t5, t8 and t10 from baseline values.

Intragroup comparison shows serial changes in RPP were statistically significant at various time points, compare to baseline (Friedman's Analysis of Variance). Immediately after intubation (t0) there was 35% rise in RPP from post drug time inGroup D1 compared to 18% inGroup D2 patients.

Sedation and side effects

Level of sedation was recorded at 3rd and 5thminutes after administration of Dexmedetomidine (Table 8). Intergroup comparison shows sedation score was significantly more in Group D2 patients receiving Dexmedetomidine1.0 mcg/kg (students paired t-test). Also intragroup comparison shows sedation was more at 5thminutes than 3rdminutes in Group D2 patients (students paired t-test). There was no significant bradycardia or hypotension necessitating treatment at any time during the study period.

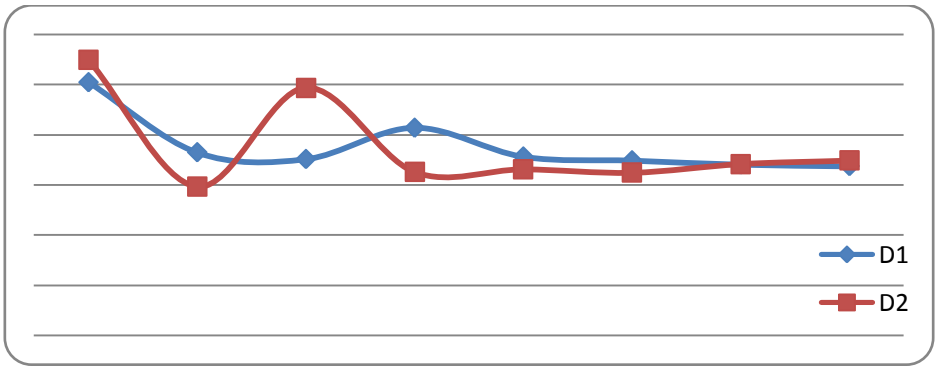

Fig-5: Comparison of Rate Pressure Product (RPP)

Table-7: Comparison of Rate Pressure Product

RPP	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
B	10720.84 ± 1707.6	10998.32 ± 1482.2	0.0095
PD	7281.48 ± 1419.6	5948.02 ± 543.01	<0.0001
0 MINUTES	9872.05 ±1198.1	7035.73 ± 553.88	<0.0001
1 MINUTES	8273.49 ± 1058	6525.46 ± 524.03	<0.0001
3 MINUTES	7149.06 ± 826.93	6626.28 ± 510.41	0.0007
5 MINUTES	6981 ± 832.63	6489.1 ± 507.33	0.3666
8 MINUTES	6808.28 ± 990.1	6878.66 ± 483.57	0.9265
10 MINUTES	6744.67 ± 879.74	6980.78± 445.17	0.1374

Table 8: Comparison of Ramsay Sedation Score

TIME	Group D1 Mean ± SD	Group D2 Mean ± SD	P VALUE
3MINUTES	2.00 ± 0.00	2.91 ± 1.08	0.000005
5 MINUTES	2.00 ± 0.00	3.05 ± 1.22	0.000004

DISCUSSION:

Laryngoscopy and intubation are two of the most consistent manoeuvres that lead to significant increases to blood pressure and heart rate. This had been attributed to a sympathetic response as evidenced by an increase in the circulating catecholamine levels [5, 6, 7]. These changes were reported to be greatest 60 seconds after intubation of the trachea that last for 5-10 minutes. It is for these reasons that numerous studies had been undertaken to search for effective and safe drugs to attenuate this sympathetic response. The α2 receptors are involved in regulating the autonomic and cardiovascular systems. α2 receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals where they inhibit norepinephrine release. α2 receptors are also located within the central nervous system and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow and an augmentation of cardiac-vagal activity. This can result in a decrease in heart rate and cardiac output. The use of α2 agonists in the perioperative period has been associated with reduced anaesthetic requirements and attenuated heart rate and blood pressure responses to stressful events. In addition, α2 receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia [8,9,10].

Dexmedetomidine offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability and with great advantage to avoid respiratory depression. Ramsay sedation score found to be more in the group receiving 1.0 µgm kg-1 of the drug.

It was observed that Dexmedetomidine used in premedication suppresses the sympathetic activation which is due to the endotracheal intubation[11]. This was found in this study using the two different doses of Dexmedetomidine, 1.0 µgm kg-1 found to be more effective in attenuation this hemodynamic response following laryngoscopy and intubation. It was found in the study by Jaakola *et al.;* that during the intubation blood pressure and heart rate were significantly reduced by 0.6 $\mu g.kg^{-1}$Dexmedetomidine[12]. In Scheinin's study these parameters were also reduced by equal doses of Dexmedetomidine. Similar response was seen with both the doses used in this study, 1.0 µgm.kg-1 being more effective in controlling this hemodynamic perturbation following laryngoscopy and intubation.

Lawrence [13] *et al.;* found that single dose of 2 µg/kg of Dexmedetomidine before induction of anesthesia attenuated the hemodynamic response to intubation as well as that to extubation. In the other study which was done by Tezer14et al, it was concluded that sympathetic responses during laryngoscopy and intubation were effectively reduced by Dexmedetomidine1 µg./kg and esmolol 250 µg/kg/minutes[15]. Similar outcome was noticed in this study when 1.0 µgm kg-1 of the drug was used. Khan [16] *et al.;*. demonstrated that heart rate, systolic and diastolic blood pressure were reduced by Dexmedetomidine. All the above parameters were reduced in this study with both the doses of test drug in a dose dependent fashion and 1.0 µg.kg-1 being more effective in controlling the hemodynamic perturbation.

Ebert [10] studied the autonomic, cardiovascular, and sedative responses to increasing plasma concentrations of Dexmedetomidine; he found that low plasma concentrations resulted in sedation, mild analgesia with preservation of recall and recognition. Subsequent higher doses resulted in increased sedation, analgesia and memory impairment, as well as an increase in BP. Even at higher doses, there was no respiratory compromise. In this present study dose dependent cooperative sedation was noticed in both the groups. Sedation was more in the group that received a dose of 1.0 µg kg-1 but memory impairment

was not noticed in this group. While comparing the Ramsey Sedation Score it was found higher in those who received 1.0 µg.kg-1 of the drug than those who received 0.5 µg.kg-1 of the drug that is a statistical significance was found between the two groups.

A. Sagiroglu *et al.;* [17], concluded in their study that patients who received 1 µg.kg-1 of dexmedetomidine showed better hemodynamic control during laryngoscopy and intubation than those who received 0.5 µg.kg-1 the drug. In the present study, HR, SBP, DBP, MAP and RPP were significantly lower just before induction that is after 5 minutes of intravenous administration of the test drug. Pretreatment with dexmedetomidine0.5µg.kg-1 and 1.0µg/kg attenuated, but did not totally obtund, the cardiovascular response to tracheal intubation. A rise in than the preinduction values immediately following intubation (0 minutes) in HR, SBP, DBP, MAP and RPP was noted in both the groups being less in those who received 1.0 µg.kg-1 of the drug. Group D1 experienced a rise of 19% rise in HR, 14% rise in SBP, 15% rise in DBP, 14% rise in MAP and 35% rise in RPP values while group D2 experienced a rise of 12% rise in HR, 7% rise in SBP, 7% rise in DBP, 7% rise in MAP and 18% rise in RPP values above the preinduction values. Rate pressure product is calculated by multiplying systolic arterial pressure and the heart rate and is an index of myocardial oxygen consumption18. Rate pressure product exceeding 22,000 is commonly associated with myocardial ischaemia and angina 19. In this study, in both the groups, the rate pressure product did not reach 22,000 at any point of time. Thus it was found that the rise in these parameters in group D2 was almost half of that seen in Group D1 immediately post intubation that is at 0 minutes. In this study pre-treatment with both the doses of Dexmedetomidine, successfully attenuated but did not totally blunt the cardiovascular response to laryngoscopy and tracheal intubation after induction of anaesthesia. This study was thus in accordance with the findings of the study done by A. Sagiroglu *et al.*[17].

CONCLUSION:

From this study, it may be concluded that pre-treatment with Dexmedetomidine attenuated, but did not totally blunt, the cardiovascular response to tracheal intubation in a dose dependent manner& 1.0 mcg/kg of the test drug was more effective in this regard with better sedation and without increasing risk of side effects.

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