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COMPARISON OF LOADING DOSE OF DEXMEDETOMIDINE WITH PLACEBO FOR ATTENUATION OF HAEMODYNAMIC RESPONSES DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

Anaesthesiology

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ABSTRACT

BACKGROUND: Various pharmacological agents have been used for attenuation of sympathoadrenal surge response to Laryngoscopy & endo tracheal intubation(LETI), with significant drawbacks. Dexmedetomidine, a selective alpha2-adrenoceptor agonist is gaining interest in this field and the current study is being undertaken to evaluate the efficacy of bolus dose of Dexmedetomidine in attenuation of stress response to LETI.

METHODS: This prospective randomized double blind study was conducted on 68 patients of either sex ,ASAI or II scheduled to undergo elective surgery under general anaesthesia. Patients in Group A received normal saline placebo , while in Group B got loading dose of Dexmedetomidine(1µgm/Kg), prior to induction of anaesthesia. Mean heart rate(HR) and mean systolic,diastolic and mean blood pressure(SBP,DBP,MAP) were recorded at specified time intervals prior to and after LETI and comparison was done using Student's –t test and Fisher's exact test with p-value < 0.05 considered statistically significant

RESULTS: At all points of time after LETI mean Heart rate in Group B was significantly lower than Group A. On Intergroup comparison, mean SBP,DBP & MAP after 1,3,5 mins of LETI was significanty lower in Group B compared to A. Mean HR,SBP,DBP & MAP were increased in both Group A & B on comparison to intragroup baseline values, however significantly more in Group A. Haemodynamic perturbations were minimal with few adverse effects.

CONCLUSION: Dexmedetomidine infusion is safe &effective in attenuating haemodynamic surge following LETI compared to placebo.

KEYWORDS

Laryngoscopy & endo tracheal intubation(LETI), alpha2-adrenoceptor. Dexmeditomidine, haemodynamic.

INTRODUCTION

Laryngoscopy and endotracheal intubation (LETI) is the mainstay of securing an airway for administering general anaesthesia[1]. Airway manipulation causes increase in heart rate and blood pressure, due to release of noradrenaline and to a lesser extent, of adrenaline[2]and the magnitude of these changes were dependent on the depth of anaesthesia.[3]

Laryngoscopy and endotracheal intubation is associated with some occasional disturbances in cardiac rhythm [4,5] which is initiated by stimulation of upper airway during laryngoscopy. While in normal subjects these hemodynamic changes are short lived and of little significance[6], they may be hazardous to the patients with cardiac or cerebrovascular disease and may precipitate rupture of intracranial vessels or dissecting aneurysm[7].

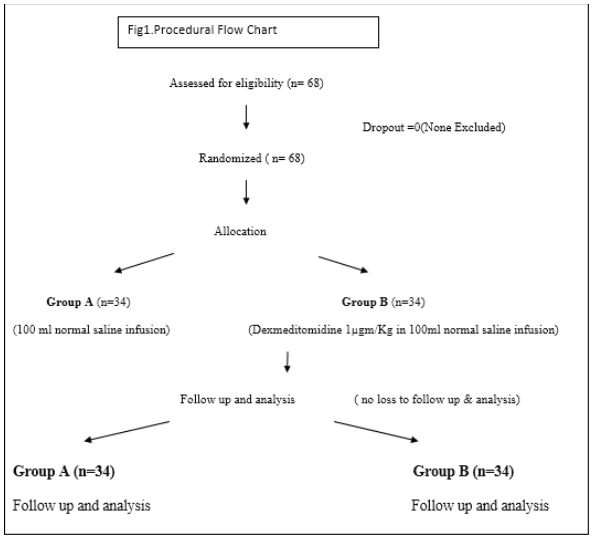
To attenuate these hemodynamic responses due to laryngoscopy and intubation various methods like topical and/or intravenous lignocaine, opioids, deep inhalational anaesthesia, ganglion blocking agents, calcium channel blocker, vasodilator like sodium nitroprusside, magnesium have been tried[8] but no pharmacological agents till date, has been considered to be free of complications, in part due to their interaction with the biological system of each patient.

Alpha 2 adrenergic agonist like clonidine and dexmedetomidine are gaining interest in this field. They reduce sympathetic outflow via alpha adrenergic receptor activation in the presynaptic membrane mostly in locus ceruleus which modulates the stimuli arriving at the CNS. Dexmedetomidine compared to Clonidine is a much more selective alpha2-adrenoceptor agonist, thus avoiding the unwanted vascular effects from activation of alpha1-receptors. Dexmedetomidine is shorter-acting drug than clonidine and has a reversal drug for its sedative effect, Atipamezole[8,9,10].

The present study was thus formulated with the primary objective of evaluation of the efficacy of loading dose of 1 µgm/Kg dexmedetomidine over placebo for attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation. The secondary objectives were documentation of adverse effects or complications in either groups.

METHODOLOGY

This prospective randomized double blinded study was carried out in a tertiary care teaching hospital on sixty eight(68) ASAI&II patients of either sex , aged between 18 and 60 years, undergoing elective surgery under general anaesthesia (Fig1) after obtaining institutional ethics committee clearance(Order no:BMC/PG/3724) and written informed consent from each patient. Patients with advanced hepatic, renal, cardiovascular, cerebrovascular, respiratory disorders and those on beta blockers, endocrine dysfunction, with anticipated difficult airway, grossly obese, who strained or took more than 15 seconds for intubation, with history of abuse potential and with history of allergy to study drug were excluded from the study.



A detailed history of all patients awaiting surgery was taken during the pre-operative visit , they were examined thorougly and relevant investigations were done. All patients received tablet Diazepam 10mg orally on the night before surgery and remained fasting for at least 6 hours before surgery. Inj. Glycopyrrolate 0.2mg intravenously and inj ranitidine50mg i.v and Inj Midazolam 1mg i.v were given half an hour before induction of anaesthesia. On the operation table patients were connected to all the essential monitor – pusle oxymeter, non-invasive blood pressure monitor (NIBP), electrocardiography (ECG), and capnometer. Before infusion of study drugs baseline parameters were recorded [heart rate, noninvasive blood pressure (systolic, diastolc and mean), ECG finding and SPO_2].

The sixty eight patients to be studied were divided randomly by

computerised randomisation table into two groups of 34 each(Fig-1), according to the study solution to be received on operation table.

Group-A: control group- received 100ml of normal saline (0.9%)
Group-B: study group- received 1µg/kg injection Dexmedetomidine, which was made 100ml by adding normal saline.

The study solution was prepared by an anaesthesiologist who was not the part of the study. The patient and the investigator were unaware of the assigned drugs. The study solution was infused with an infusion pump for15 minutes as per randomisation table. After completion of infusion , preoxygenation with 100% oxygen was done for 5 minutes by a Boyle's apparatus through Mapleson A system. Inj Fentanyl citrate 2µg/kg was given to every patient. All the patients were induced with Thiopentone sodium (2.5%) in a dose sufficient to abolish eyelash reflex. After confirmation of manual ventilation injection rocuronium bromide in a dose of 1mg/kg was given for facilitation of laryngoscopy and endotracheal intubation. The endotracheal tube was connected to the Boyle's apparatus with Bain circuit (Mapleson D system). Anaesthesia was maintained with 33% oxygen and 66% nitrous oxide for the study period, during that period no surgical stimulus and change in position of the patient were allowed.

The haemodynamic variables [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)] were recorded on arrival to operating room, 5 minutes after saline placebo or Dexmedetomidine infusion ,after administration of induction agent,1 minutes after intubation,3 minutes after intubation and 5 minutes after intubation.

After completion of the study period anaesthesia was maintained with intravenous injection rocuronium Bromide (0.3mg/kg), paracetamol 1gm i.v infusion, N_2O, O_2 and inhalation anaesthetics (Isoflourane) as per requirement of surgery. Any untoward event resulting due to injection of study drugs on patients was noted and treated accordingly. The patients who required use of any drug to treat this untoward event resulting alteration in heart rate and blood pressure in initial study period , those with more than 15 seconds for LETI, coughing, bucking after intubation, and having unanticipated difficult intubation were excluded from the study. Hypotension (reduction in arterial pressure of 20% or more from the baseline) was treated primarily by increasing the i.v. infusion rate or with 3 mg bolus dose of mephentermine. Bradycardia (definied as heart rate less than 50beats/min) was treated with 0.5 mg bolus i.v dose of atropine. Sedation scores using Ramsay sedation score were recorded in both groups at 1 and 3 minutes after infusion of the study drug or placebo.

Towards the end of surgery Inj ondansetron 4mg i.v was administered. After completion of surgery ,reversal was done with appropriate doses of intravenous injection Neostigmine 0.05 mg/kg to antagonize the effects of neuromuscular blocking agents and injection glycopyrolate 0.01mg/kg to counteract muscarinic actions.

Results obtained in this study were tabulated and compared statistically (MedCalc and Microsoft Office Excel software) by using different test. Numerical data were compared between groups by student's t test and categorical variables for intergroup were compared by using Fischer's exact test. All analysis were two tailed, $p<0.05$ was considered statistically significant.

A sample size of 62 patients was required for this study, calculated at 80% power and Type 1 error of 0.05 using hemodynamic parameters like heart rate and mean arterial pressure as primary outcome measure from a previous study.[11] Assuming 10% dropouts a sample size of 68 (34 patients in each group) was chosen for this study.

RESULTS AND ANALYSIS

The demographic profile of the the groups like mean age , body weight and sex distribution were comparable as shown in Table 1.

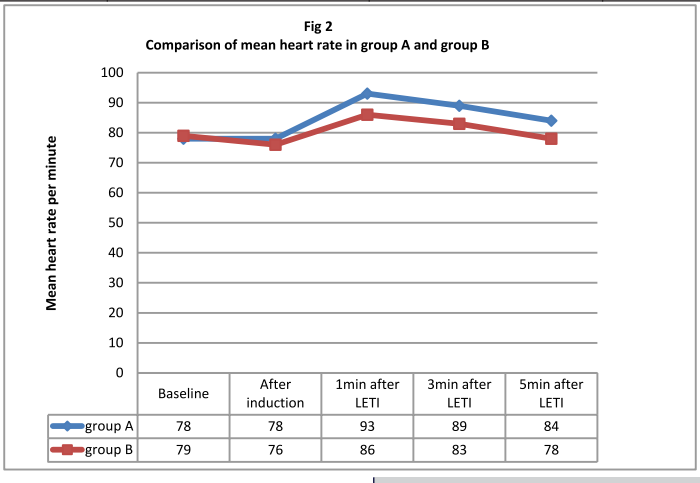
Table1.DEMOGRAPHIC CHARACTERISTICS OF THE TWO GROUPS

	GROUP A	GROUP B	p value
MEAN AGE±SD IN YEARS	29.74±7.84	32±9.45	0.15
SEX(MALE:FEMALE)	16:18	14:20	0.09
MEAN BODY WEIGHT±SD IN KG	56±4.46	56.73±8.96	0.67

Regarding the heart rate response in case of intra-group comparison, the rise in mean heart rate at 1 ,3&5 mins after LETI(laryngoscopy and endo tracheal intubation) was statistically significant compared to baseline in both the group A(placebo) (Table-2) but in Group B it was significant only after 1 min of LETI. At five minutes the rise in mean heart rate in group-A was statistically significant compared to baseline, whereas in group-B the heart rate returned to baseline value. Inter-group comparison revealed that mean heart rate was significantly lower in Group B at 1min , 3min and 5min after LETI (Fig-2) compared to Group A.

Table 2
INTRAGROUP COMPARISON OF MEAN HEART RATE (beats/min) ± STANDARD DEVIATION WITH BASELINE VALUES

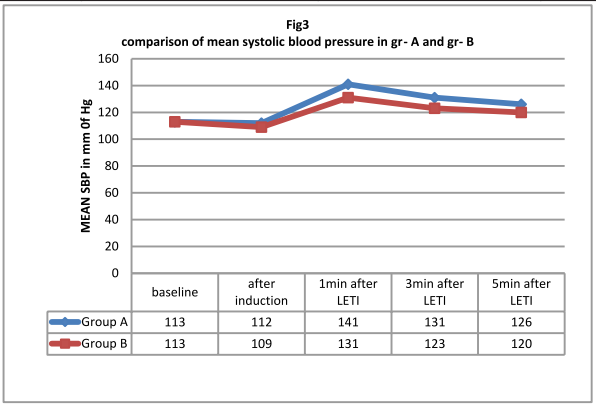
	ON ARRIVAL TO OPERATING ROOM (baseline)	**AFTER ADMINISTRATION OF PLACEBO /STUDY DRUG**	AFTER ADMINISTRATION OF INDUCTION AGENT	AFTER LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION		
				1 min	**3 mins**	**5 mins**
GROUP A	78.97± 9.33	78.38± 9.02	78.61± 9.40	93.32±9.90	89.12± 9.53	83.58± 7.19
	'p' (when compared with baseline by using Student's 't' test)	P = 0.7918	P = 0.8746	P< 0.0001	*P< 0.0001*	*P= 0.0257*
GROUP B	79.14± 9.58	75.20± 9.23	76.29± 9.12	86.35±7.76	83± 8.24	78.38± 7.57
	'p' (when compared with baseline by using Student's 't' test)	*P = 0.0888*	*P = 0.2134*	*P= 0.0011*	*P= 0.0795*	*P= 0.7178*



On intra-group comparison(Table3) in both the groups there was a statistically significant increase **(p< 0.001)** in mean systolic blood pressure(SBP) from the baseline after 1, 3 and 5 minutes after LETI.

But on inter group comparison (Fig-3) it was observed that after1,3and5 minutes of LETI mean SBP in Group B was significantly lower compared to Group A(p<0.05).

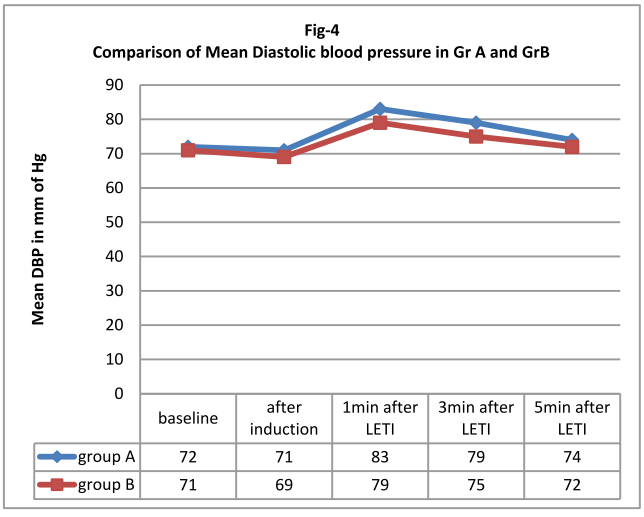
Table3	INTRAGROUP COMPARISON OF MEAN SYSTOLIC BLOOD PRESSURE (mm Hg) ± STANDARD DEVIATION WITH BASELINE VALUES					
	ON ARRIVAL TO OPERATING ROOM (baseline)	AFTER ADMINISTRATION OF PLACEBO /STUDY DRUG	AFTER ADMINISTRATION OF INDUCTION AGENT	AFTER LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION		
				1 min	3 mins	5 mins
GROUP A	113.35±10.49	114.35± 10.08	112.76± 10.53	140.64±11.24	130.41±10.59	126±9.09
	'p' (when compared with baseline by using **Student's 't' test**)	P = 0.6899	P = 0.8177	P< 0.0001	P< 0.0001	P< 0.0001
GROUP B	113.47± 10.43	111.64± 10.12	109.23± 9.87	131.05±8.67	123.58± 8.53	120.64± 8.48
	'p' (when compared with baseline by using **Student's 't' test**)	P= 0.0028	P = 0.4654	P = 0.0898	P< 0.0001	P< 0.0001



On intra-group comparison(Table3) in both the groups there was a statistically significant increase **(p< 0.001)** in mean sysztolic blood pressure(SBP) from the baseline after 1, 3 and 5 minutes after LETI.

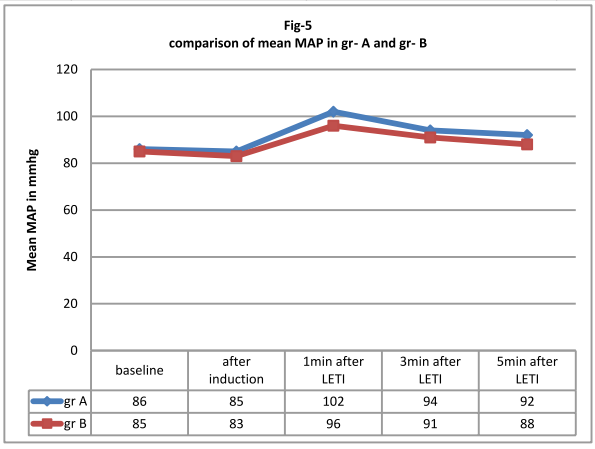
But on inter group comparison (Fig-3) it was observed that after1,3and5 minutes of LETI mean SBP in Group B was significantly lower compared to Group A(p<0.05).

Table4	INTRAGROUP COMPARISON OF MEAN DIASTOLIC BLOOD PRESSURE (mm Hg) ± STANDARD DEVIATION WITH BASELINE VALUES					
	ON ARRIVAL TO OPERATING ROOM (baseline)	AFTER ADMINISTRATION OF PLACEBO /STUDY DRUG	AFTER ADMINISTRATION OF INDUCTION AGENT	AFTER LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION		
				1 min	3 mins	5 mins
GROUP A	72.61± 10.57	72.82± 10.03	71.88± 10.29	83.35± 8.73	79.76± 8.17	74.79± 7.24
	'p' (when compared with baseline by using **Student's 't' test**)	P = 0.9333	P = 0.7738	P< 0.0001	P= 0.0027	P= 0.3247
GROUP B	71.64± 8.86	70.94± 8.82	69.82± 8.72	79.29±7.93	75.76± 7.18	72.41± 7.08
	'p' (when compared with baseline by using **Student's 't' test**)	P= 0.7451	P= 0.3964	P = 0.0004	P = 0.0390	P = 0.6935



Intra-group mean MAP(mean arterial pressure) showed statistically significant rise from baseline at all the point of measurement after LETI in both the groups(Table-5). This rise was significantly less in study group(B) only immediately after LETI. Inter-group comparison(Fig-5) showed significant lowering of mean MAP 1 minute after LETI (p <0.05) but at 3 minute and 5 minutes after LETI the changes were not significant (p>0.05)

TABLE-5	INTRAGROUP COMPARISON OF MEAN MAP (mm Hg) ± STANDARD DEVIATION WITH BASELINE VALUES					
	ON ARRIVAL TO OPERATING ROOM (baseline)	AFTER ADMINISTRATION OF PLACEBO /STUDY DRUG	AFTER ADMINISTRATION OF INDUCTION AGENT	AFTER LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION		
				1 minutes	3 minutes	5 minutes
GROUP-A	86.55± 9.67	86.67± 9.28	85.52± 9.52	102.23± 8.64	94.11± 8.74	92± 6.99
	'p' (when compared with baseline by using **Student's 't' test**)	P = 0.9584	P = 0.6580	P< 0.0001	P = 0.0011	P = 0.0094
GROUP B	85.52± 8.36	84.38± 8.29	83.05± 8.01	96.5±7.42	91.67± 6.83	88.5± 6.50
	'p' (when compared with baseline by using **Student's 't' test**)	P = 0.5729	P = 0.2159	P< 0.0001	P = 0.0014	P = 0. 041



Mean sedation scores using Ramsay sedation score were 1.47±0.34(1 min after infusion) and 1.14±0.23(3 mins after infusion) in Group A , while it was 2.44±0.27(after 1 min)and 2.75± 0.33(after3 mins)in Group B.Thus, in group B sedation was significantly more than Group A.($p<0.05$)

Certain dysrhythmias were noted on continuous ECG monitoring in the initial five minutes following airway instrumentation in both the groups, however none of them required treatment. There were no episodes of haemodynamic perturbations like hypotension, hypertension or bradycardia in either group during study period.

Dryness of mouth occurred in 8(23.52%) patients of Group B ,which was significantly more compared to only 1(2.94%) in group-A. In 2 patients(5.88%) in group-A and 1(2.94%) patient in group-B shivering was observed. Hypoxia and apnoea were not encountered in either group. 2 patients in each group had post operative nausea and vomiting(PONV) and treated with injection Ondansetron. There were no episodes of haemodynamic perturbations like hypotension, hypertension or bradycardia in either group during study period.

DISCUSSION

Endotracheal intubation is associated with increase in heart rate, blood pressure and plasma catecholamine concentrations.[12] Whereas this stress response is well tolerated by patients with no cardiovascular comorbidities ,it might have harmful consequences like, myocardial ischemia[13], ventricular arrhythmias ,left ventricular failure, pulmonary oedema and cerebral haemorrhage[3] in patients with hypertension, coronary artery disease, intracranial aneurysms and cerebrovascular diseases. In various studies Opioids, adrenergic blocking agents,vasodilating agents and local anesthetics have been used to attenuate the hemodynamic effects of endotracheal intubation.[14] The drugs which were used were either partially effective or they produced other undesirable effects on the patients.[15]

α-2 agonists in the perioperative period have been associated with attenuated heart rate and blood pressure responses to stressful events and decreased anaesthetic requirements.[16] Clonidine has been used by various authors to blunt the haemodynamic response for laryngoscopy and intubation.[17] Recently however, dexmedetomidine, a highly selective α-2 agonist has become more popular than clonidine due to titratable sedation, sympatholysis ,analgesia and minimum respiratory depression.[13] Preoperative administration of a single dose of dexmedetomidine blunted the hemodynamic responses more than clonidine or placebo during laryngoscopy, and reduced anesthetic requirements.[18]

Dexmedetomidine was used and compared for premedication alone or with other drugs to attenuate pressure response to laryngoscopy and intubation by various authors. While a bolus dose of 0.3 µg/kg was not effective in attenuating pressure responses,[19]higher dose of 2 µg/kg or rapid infusion over a short duration resulted in severe hypertension followed by reflex bradycardia ,sudden hypotension and episodes of apnoea.[20,21] 1 µg/kg dexmedetomidine was found to be more effective compared to dosage of 0.5 µg/kg.[16,22,23] Distribution half-life of i.v. Dexmedetomidine being 6 minutes and onset of action 10 to 15 minutes.[24] Thus ,the present study was formulated with the primary objective of evaluation of the efficacy of loading dose of 1 µgm/Kg dexmedetomidine as an infusion over 15 minutes over placebo for attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation. The secondary objectives were documentation of adverse effects or complications in either group.

Baseline mean HR, SBP,DBP AND MAP were comparable between the two groups.

On intra-group comparison, the rise in mean heart rate at one minute after LETI was statistically significant compared to baseline in both the groups,however it returned to baseline values in Group B after five minutes of LETI(Table2), similar to findings of LahaA et al[14]. Although the mean HR was more than baseline value after LETI in the dexmedetomidine group, it was clinically within acceptable limits most probably due to preserved baroreceptor reflex. In contrast mean HR was significantly higher in Group A at all time points after LETI compared to baseline very much similar to findings of Varshali M Keniya[25] and Laha.A et al[14]. At all points of time after LETI mean Heart rate in Group B was significantly lower than Group A(Fig-2) similar to findings of Menda.F[11] and Laha.A et al[14].

Mean SBP was significantly increased **($p< 0.05$)** from the baseline after infusion of placebo and at 1,3&5 minutes after LETI in Group A(Table3). In Group B after infusion of dexmedetomidine the Mean SBP was significantly lower than baseline value similar to findings of Modh.D.B et al[26] probably due to hyperpolarization of noradrenergic neurons and suppression of neuronal firing in the locus ceruleus resulting in decreased noradrenaline release. After LETI mean SBP was more than baseline value in Group B, although within clinically acceptable limits similar to observation of Laha.A et al[14]. On Intergroup comparison(Fig3) , mean SBP after 1,3,5 mins of LETI was significanty lower in Group B compared to A similar to findings of Laha.A[14] & Modh.D.B et al[26].

After infusion of Dexmedetomidine in Group B mean DBP was lower

than baseline(Table4), although not statistically significant. This is contrary to findings of Laha.A[14] &Bloor et al[21], who found transient but significant rise in DBP immediately after infusion. Thus our findings showed that a dose of 1 µg/kg of dexmedetomidine was safe similar to findings of Mondal S[18] & Sagiroglu AE et al[16]. During intra-group comparison mean DBP in both group showed statistically significant rise above baseline at first three point of measurement after LETI compared to baseline as also observed by LAHA et al[14]. (Fig-4). Inter-group comparison showed significant difference in fall of diastolic blood pressure in study group compared to placebo group after one minute of LETI.

Intra-group mean MAP showed statistically significant rise from baseline at after 1 &3 mins of LETI in both the groups(Table5) compared to baseline, which was contrary to findings of Modh et al[26] probably be due to propofol being used as an induction agent compared to thiopentone in our study. On inter group comparison mean MAP was lower in Group B compared to placebo group at all points(Fig5), however statistically significant at only one minute after LETI. The above finding is corroborating with the findings of Keniya.V.M[25], Sagiroglu AE[16] and Sulaiman.S et al.[27]

Certain transient dysrhythmias like sinus tachycardia and ventricular premature contractions were noted on continuous ECG monitoring in both groups, although not requiring anytreatment . Shibman AJ et al[12] showed that reflex autonomic responses provoked by laryngoscopy and endotracheal intubation could cause various types of dysrhythmias. Dexmedetomidine infusion provided stable haemodynamics as there was no episode of hypotension or bradycardia during study period similar to findings of Bekker A[28] and Sagiroglu AE et al[16].

Sedation was significantly more in dexmedetomidine group at 1 min and 3 min after infusion of the drug similar to findings of Sagiroglu AE and Laha A et al, but no hypoxia was observed probably due to sparing of respiration centre by α-2 adrenergic agonists. Sagiroglu AE and Ebert et al[29] didn't observe any apnea, airway obstruction or hypoxemia with bolus doses of dexmedetomidine similar to our study , while Bloor et al[21], contrary to our study, found that a bolus dose of 1-2 µg/kg intravenously within two minutes, causes irregular ventilation and apnea episodes. It is an established fact that dexmedetomidine causes dryness of mouth[30]. In group-B there was significant dryness of mouth (in23.52% patients) compared to group-A(only2.94%) probably due to the effect of drug on presynaptic alpha adrenoceptors in the brain stem and parasympathetic nerves which supplies the salivary glands.

Limitations

The most significant limitation of this study was that intraoperative anaesthetic and analgesic drug requirements were not measured. It was not possible to measure the plasma levels of catecholamines due to laboratory constraints. Fentanyl was used in either group ,which itself blunts surge response to LETI. While the study was mainly focused in the laryngoscopy and intubation response , changes in the haemodynamics post extubation as well as post operative sedation scores were not recorded.

CONCLUSION

Thus, a pre induction loading dose (1ug/kg) of dexmedetomidine infusion is a reasonable, safe and useful option to attenuate haemodynamic surge following laryngoscopy and endotracheal intubation compared to placebo. Although it blunts the sympathoadrenal responses to airway instrumentation it does not completely abolish it. Furthur studies may be undertaken in the future with even lower doses of dexmedetomidine or combination with other agents and in elderly population with cardiac comorbidities in order to get a better idea about its safety and efficacy .

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