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Attenuation of pressor response and dose sparing effect on opioids with the use of dexmedetomidine in spine surgeries

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ABSTRACT

Background: The pressor response, which is part of a huge spectrum of stress response, results from the increase in sympathetic and sympathoadrenal activity, as evidenced by increased plasma catecholamines concentrations in patients undergoing surgery under general anaesthesia. Various drug regimens and techniques have been used from time to time for attenuating the stress response to laryngoscopy and intubation, including opioids, barbiturates, benzodiazepines, beta blockers, calcium channel blockers, vasodilators, etc. The dose of opioids required for effective attenuation of stress response is fairly high and numerous drugs have been used as adjuncts in decreasing the dose of opioids with a varied level of success, but are not absolutely free from side-effects. This study was conducted to investigate the ability of pre-operative intravenous dexmedetomidine in decreasing the dose of opioids and anaesthetics for attenuation of haemodynamic responses during laryngoscopy and tracheal intubation in spine surgery.**Methods:** Fifty patients belonging to ASA I and II physical status were included in this study. Twenty five patients received 1µg/kg each of dexmedetomidine and Fentanyl pre-operatively (group D) and other twenty five patients received 2microg/kg of Fentanyl preoperatively (group F). **Results:-** Statistically significant changes in heart rate, blood pressure, sedation score, reduction in dose of induction agent, opioids demonstrated.**Conclusion:** Dexmedetomidine is not only an excellent drug for attenuation of pressor response to laryngoscopy and intubation and during extubation, but also decreases the dose of opioids and propofol in achieving an adequate analgesia and anaesthesia, respectively.

Keywords: fentanyl, dexmedetomidine, pressor response, analgesia

Introduction

The pressor response, which is part of a huge spectrum of stress response, results from the increase in sympathetic and sympathoadrenal activity, as evidenced by increased plasma catecholamines concentrations in patients undergoing surgery under general anaesthesia [1-5].Various drug regimens and techniques have been used from time to time for attenuating the stress response to laryngoscopy and intubation, including opioids, barbiturates, benzodiazepines, beta blockers, calcium channel blockers, vasodilators, etc[6-10]. The dose of opioids required for effective attenuation of stress response is fairly high and numerous drugs have been used as adjuncts in decreasing the dose of opioids with a varied level of success, but are not absolutely free from side-effects [10-12].Alpha-2 agonists like clonidine has been used extensively in the past for attenuation of sympathoadrenal stimulation caused by tracheal intubation and surgery[4,13]. Dexmedetomidine is the new alpha-2 agonist having eight-times more affinity for alpha-2 adrenoceptors as compared with clonidine, which has shown only partial agonist activity and is known to decrease the plasma catecholamines levels and suppressing the release of catecholamines also [5, 13-15].

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With an emphasis on multidimensional features of Dexmedetomidine, we designed a randomized, prospective, double-blinded study to determine whether the addition of dexmedetomidine would decrease the dose of opioids and anaesthetics for attenuation of haemodynamic response during laryngoscopy, tracheal intubation, surgery and extubation.In 1999, FDA approved Dexmedetomidine for sedation use in ICU in mechanically ventilated patients. Unlike most anesthetics that affect the GABA receptor, its mechanism of action is to activate the alpha-2 adrenergic receptor. The consequence is a reduction in noradrenergic neurotransmitter release and depression of adrenergic pathways. The action of Dexmedetomidine is unique in that it produces sedation in a manner similar to natural sleep maintaining patient arousability and respiratory function. There are two mechanisms by which Dexmedetomidine produces analgesia involving activation of presynaptic alpha 2 receptors in the spinal cord. One is by direct activation of the descending inhibitory pain pathway, the other is by inhibiting the release of substance P.

Aims and objectives

To investigate the ability of pre-operative intravenous dexmedetomidine in decreasing the dose of opioids and anaesthetics for attenuation of haemodynamic responses during laryngoscopy and tracheal intubation in spine surgery.

Objectives

1. To assess and compare effect of infusion of study drug in both the groups.
2. To compare the hemodynamic responses following infusion, during laryngoscopy, intubation and during extubation.
3. To compare the requirement of total dose of propofol during induction and additional dose of Fentanyl in either of the groups.

Physiology of Haemodynamic Response

Autonomic nervous system does the biological housekeeping of the internal environment of the body. Sympatho-adrenal system regulates the body response to combat any stress. The neurotransmitters of the sympathoadrenal system are noradrenaline and adrenaline. Normal basal secretion by adrenal medulla of adrenaline is 0.2µg/kg/minute and that of noradrenaline is 0.05µg/kg/minute which are adequate to maintain the body physiology. In situations of stress the sympathoadrenal system is stimulated by hypothalamus resulting in an increase in the catecholamine secretion. This reaction is closely correlated with endocrine system in combating stress. The sympathetic system in response to stress acts to increase heart rate, blood pressure, cardiac output, dilates bronchial tree and shunts blood away from skin and viscera to muscles.A powerful noxious stimulus like laryngoscopy and tracheal intubation induces hypothalamic activity and results in an increased outflow in the sympathetic tracts. Consequently norepinephrine is released by post ganglionic sympathetic fibers and increased secretion from adrenal medulla. Attempts have been made to assess sympathetic activity directly by measurement of plasma catecholamine concentrations with the use of radio enzymatic assays and high pressure liquid chromatography, by various workers.It was concluded by the study of changes of plasma catecholamine concentration during laryngoscopy and endotracheal intubation by Russell WJ and Mortis RG[16] that a positive correlation existed between arterial pressure and plasma noradrenaline concentration. The magnitude of increase in blood pressure paralleled the increase in plasma noradrenaline concentration. Plasma adrenaline did not change significantly.This was further confirmed by Derbyshire[17] and Smith [18]who showed that the plasma noradrenaline concentration increased by 34% in samples obtained from central venous line and by 74% in samples obtained from radial artery. This can be explained by uptake of noradrenaline in lungs. The adrenergic response was maximum by one minute and had diminished by 5 minutes. Thus heart rate and blood pressure have been used as indirect indices to measure levels of sympathetic activity clinically. In addition to activation of the autonomic nervous system, endotracheal intubation also stimulates central nervous system activity as evidenced by increase in electroencephalographic activity and basal metabolic rate. In patients with compromised intracranial compliance, the increase in CBF may result in elevated intra cranial pressure which in turn may result in herniation of brain contents and severe neurologic compromise.

Materials and methods

50 patients scheduled for elective spine surgery were randomized into two groups: D and F (n=25 in each group).

25 patients were administered 1µg/kg each of Dexmedetomidine and Fentanyl pre-operatively.

25 patients were administered 2ug/kg of Fentanyl preoperatively

Inclusion criteria:

1. ASA physical status class I or II.

2. Age between 20 to 60 years
3. Patients posted for surgeries under General Anaesthesia

Exclusion criteria:

1. Patients' refusal
2. ASA physical status III and IV
3. Co-morbid diseases (hypertension, cardiac, pulmonary , neurological disease).
4. Allergy to the drug to be used.
5. Pregnancy
6. Patient taking antipsychotic drugs
7. Difficult intubation

After obtaining approval by ethical committee and written informed patient consent, 25 ASA Grade I or II patients in each group were enrolled for the study. Appropriate patients were selected after preoperative assessment by eliciting proper history and physical examination. Thorough investigations included hemoglobin, complete blood count, bleeding time, clotting time, fasting blood sugar level, chest x-ray, urine routine and microscopic examination, renal function test, liver function tests and serum electrolytes. Patients were randomly divided into two groups as defined above. The drugs will be injected by an experienced anaesthetist blinded for the study. Patients were pre-medicated with tab alprazolam 0.25mg a night before and tab ranitidine 2 hours before on the morning of surgery with a sip of water. In the pre-op room, a good intravenous access was secured and baseline parameters were observed and recorded, which included heart rate (HR), mean arterial blood pressure (MAP), electrocardiogram respiratory rate and pulse oximetry (SpO_2). All patients were pre-hydrated with 500 mL of Ringer's lactate solution. Thereafter, group F received 100 mL of normal saline over 20 min pre-operatively and inj. Fentanyl 2µg/kg 3 min before induction, while group D received 1µg/kg of dexmedetomidine in 100 mL of normal saline over 20 min and 1µg/kg of Fentanyl 3 mins before the induction of anaesthesia., during which all the vital parameters of the patient were monitored. Induction of anaesthesia was carried out with propofol in a dose sufficient to abolish the verbal response followed by 0.1mg/kg of vecuronium bromide to provide neuromuscular blockade. The lungs were ventilated with 50% nitrous oxide in oxygen with Bains circuit for the next 3 min. Thereafter, laryngoscopy was performed with a Macintosh laryngoscope and intubation will be performed with a cuffed endotracheal tube of appropriate size with a strict and vigil monitoring of hemodynamic and respiratory parameters at regular intervals. Response to skin incision was observed and recorded in a similar manner. During surgery, anaesthesia was maintained with isoflurane and 66% nitrous oxide in oxygen. At the end of the surgical procedure, residual neuromuscular blockade was antagonized with neostigmine 2.5mg and glycopyrrolate 0.5mg intravenously (IV). Extubation was carried out as routine procedure and stress response to extubation was again observed and recorded in a similar manner as done during the intubation process, and patients were shifted to the post-operative care unit for further observation.

Demographic data was analyzed statistically.

We monitored the following parameters:

Preoperative sedation: following infusion of the study drug, patients were assessed for sedation on the basis of Ramsay sedation scale which is

1. Patient anxious or agitated or both
2. Patient co-operative, oriented and tranquil
3. Patient responds toverbal commands only.
4. Brisk response to light glabellar tap.
5. Sluggish response to light glabellar tap.
6. No response

Fall in oxygen saturation (SPO2) in the preoperative period after infusion <95%.Hemodynamic parameters. Requirement of the total dose of propofol. Need of additional intraoperative opioid dose.

Analysis plan

- Inclusion of cases after taking consent on a prescribed format.
- Systematic collection of data as per proforma.
- Observations and analysis of data obtained
- Clinical interpretation of the collected data

Statistical methods employed

Descriptive data presented as mean ± SD and percentage.Pair wise comparisons between the groups was done by repeated measures ANOVA test. Bonferroni test followed by student unpaired t-test. For all tests a p-value of ≤ 0.05 was considered as significant. Chi-square test is also used for some pair wise comparisons.

Observation and results

Z-test for proportion of two populations, suggests that there is no significant difference in the proportion of gender and ASA grading in two groups. Unpaired t-test suggests that there is no significant difference in the mean age, height, weight and the duration of surgery in two groups.The mean HR before induction was significantly lower in the group D after the administration of study drug as compared with group F ($p<0.05$). Just after the induction of anaesthesia mean HR decreased further in both the groups, and on analyzing the magnitude of decrease, it was found to be

highly significant in group D as compared to group F (P<0.001) .The laryngoscopy and intubation was associated with a significant rise of mean HR in group F as compared with group D (P<0.001). Mean HR after 3 and 5 min of intubation again returned to lower values, but on comparison of rate of decrease in the heart rate from the preoperative values, it was highly significant in group D (P<0.001). Thereafter, till the completion of surgery, no significant difference was noted in the mean heart rate in the two groups.

Table 1: Heart Rate (beats/min) at various durations

	Group D		Group F		p-value
	Mean ± SD	**%**	**Mean ± SD**	**%**	
Pre-operative	90.00±4.73	--	82.96±9.27	--	> 0.05 (NS)
after adm of study drug	85.12±3.87	5.4	79.88±8.95	3.71	< 0.05*
1 min after induction	70.40±4.06	6.3	78.16±7.60	1.8	< 0.01**
at laryngoscopy and intubation	92.88±6.48	3.2	90.52±5.57	9.1	< 0.01**
3 min after laryngoscopy and intubation	82.96±4.99	8.7	80.28±4.68	0.5	< 0.01**
5 min after laryngoscopy and intubation	81.80±4.78	12.7	79.40±4.43	1.2	< 0.01**
Just before extubation	92.72±3.70	12	100.20±1.78	20.7	< 0.01**
Immediately after extubation	93.44±4.24	11.8	105.44±2.52	23.7	< 0.01**

*****: Significant at 1% level of significance; *: Significant at 5% level of significance, NS: Not Significant***

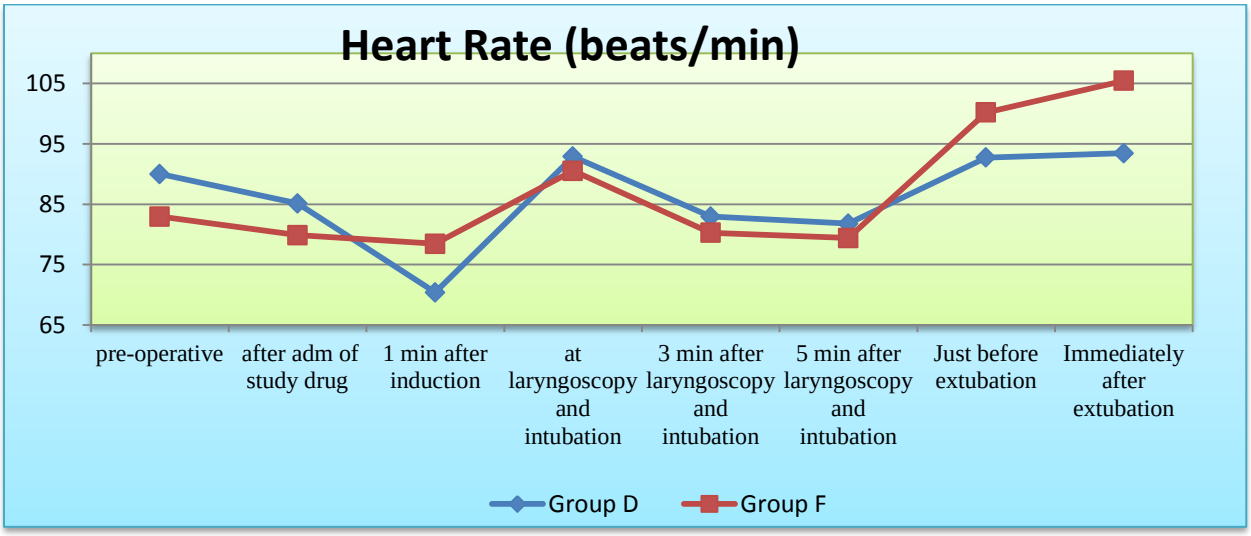

Fig 1: Heart Rate(beats/min) at various durations

After the administration of injection neostigmine and glycopyrolate for reversal of residual neuromuscular blockade, mean HR started increasing in patients of both the groups, but just before and immediately after the extubation, mean HR rose significantly high from the preoperative values in group F as compared to group D(P<0.05),which came to the normal values in 2–3 min after the extubation. The mean SBP was significantly lower in the group D after the administration of study drug before induction as compared in group F. Just after the induction of anaesthesia mean SBP decreased further in both the groups, and on analyzing the magnitude of decrease , it was found to be highly significant on statistical comparison in group D (P<0.001) .The laryngoscopy and intubation was associated with a highly significant rise of mean SBP in group F as compared with group D (P<0.001). Mean SBP after 3 and 5 min of intubation again returned to lower values, but on comparison of rate of decrease from the preoperative values , it was highly significant in group D as compared to group F (P<0.001). Thereafter, till the completion of surgery, no significant difference was noted in the systolic blood pressures.

Table 2: Systolic blood pressure (mm hg) at various durations

	Group D		Group F		p-value
	Mean ± SD	**%**	**Mean ± SD**	**%**	
pre-operative	127.12±10.068	--	125.76±11.215	--	> 0.05 (NS)
after adm of study drug	116.28±7.743	8.5	118.2±8.851	6.01	< 0.05*
1 min after induction	104.04±4.005	10.5	116.68±8.42	5.28	< 0.01**
at laryngoscopy and intubation	126.52±6.172	1.1	132.84±7.83	4.55	< 0.01**
3 min after laryngoscopy and intubation	110.0±3.789	13.47	122.48±5.69	3.69	< 0.01**
5 min after laryngoscopy and intubation	107.28±4.329	17.2	121.04±4.477	4.83	< 0.01**
Just before extubation	129.92±3.39	2.2	138.0±2.517	8.65	< 0.01**
Immediately after extubation	130.96±4.402	3.03	159.08±4.339	25.41	< 0.05*

***: Significant at 1% level of significance; *: Significant at 5% level of significance*

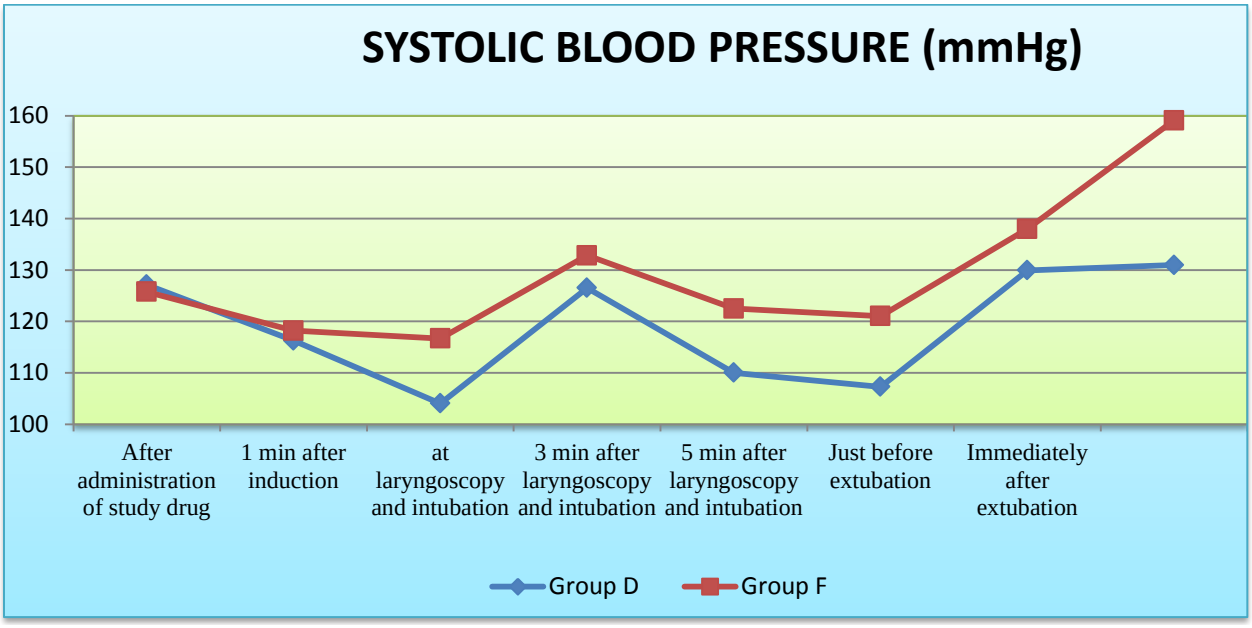

Fig 2: Systolic blood pressure (mmhg) at various durations

After the administration of injection neostigmine and glycopyrolate for reversal of residual neuromuscular blockade, mean SBP started increasing in patients of both the groups, but just before and immediately after the extubation, mean SBP rose significantly high from the preoperative values in group F as compared to group D (p <0.05),which came to the normal values in 2–3 min after the extubation.

Table 3: Total amount of Propofol required (mg/kg)

	N	Mean	SD	SEM	t-stat	p-value
Group D	25	1.552	0.192	0.038	-10.901	<.01**
Group F	25	2.356	0.315	0.063		

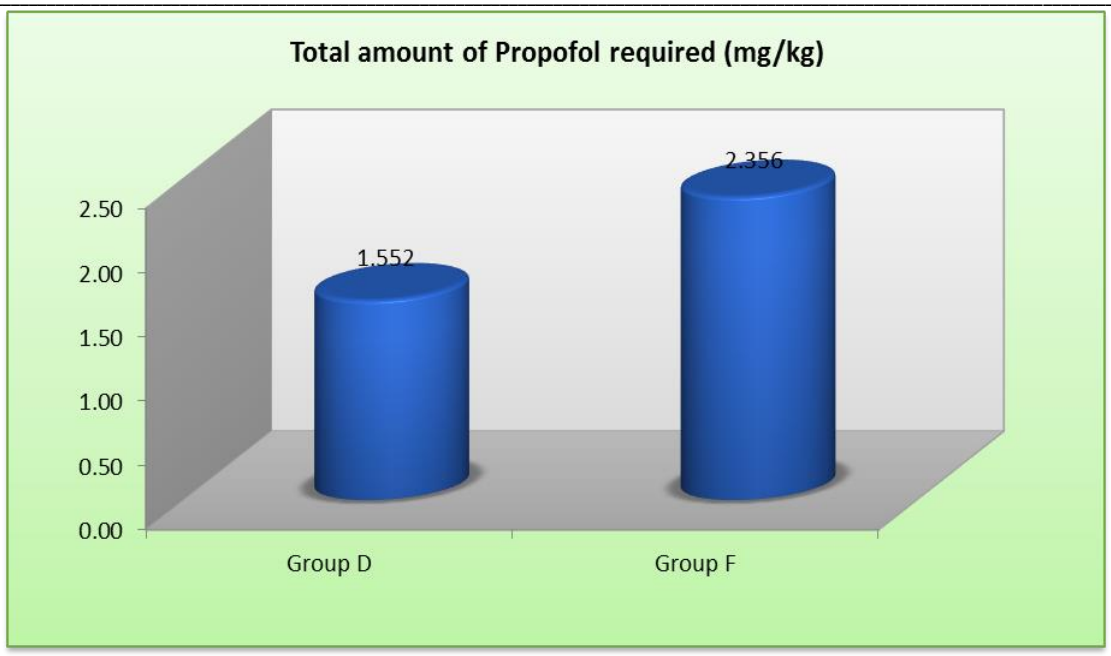

Fig 3: Total amount of Propofol required (mg/kg)

Total amount of propofol required was found to be significantly more in Group F as compared to Group D($p < 0.01$)

Table 4: Additional dose of Fentanyl required intra-operatively (microg/kg)

	N	Mean	SD	SEM	t-stat	p-value
Group D	25	.488	.088	.018	-13.107	<.01**
Group F	25	1.488	.371	.074		

****: Significant at 1% level of significance**

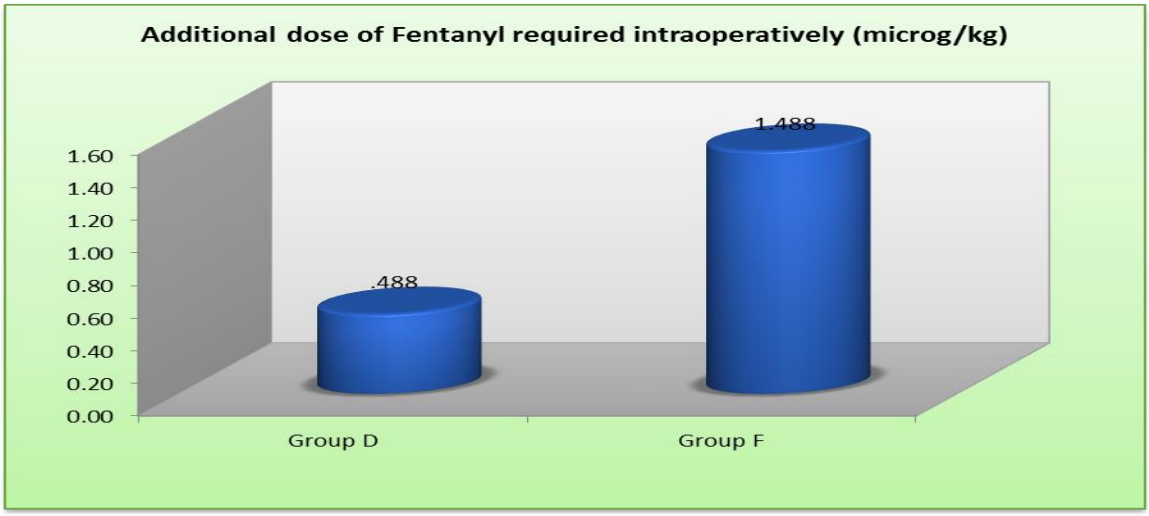

Fig 4: Additional dose of Fentanyl required intra-operatively (microg/kg)

Total amount of Fentanyl required was found to be significantly more in group F as compared to Group D ($p<0.01$)

Table 5: Pre-operative Sedation scale

	N	Mean	SD	SEM	t-stat	p-value
Group D	25	2.000	0.000	0.000	9.798	<.01**
Group F	25	1.200	0.408	0.082		
****: Significant at 1% level of significance**						

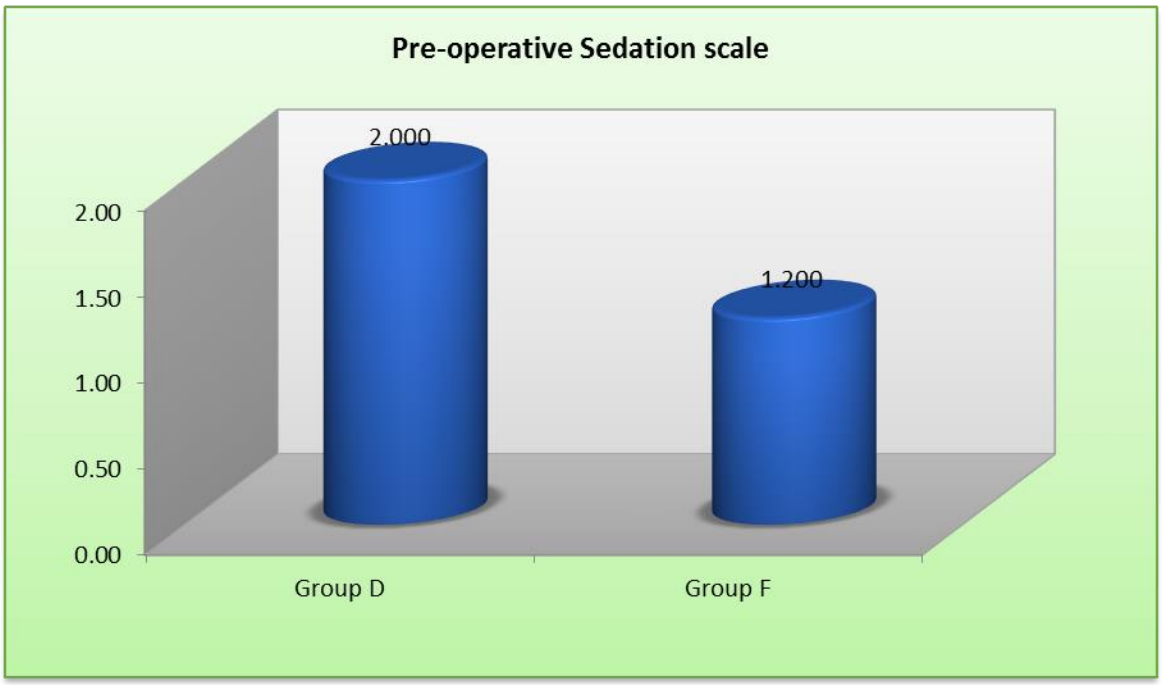

Fig 6:Pre-operative sedation score was found to be significantly higher in Group D as compared to that of Group F (p<0.01)

Discussion

One of the important contributions of the anaesthesiologist to patient care is his ability to perform laryngoscopy and intubation. To date numerous efforts have been made to make the procedure safe, full proof and devoid of any complications.Attenuation and blunting of pressor response during laryngoscopy and intubation has been one of the most researched topics in anaesthesia, but with only a few positive established outcome[1-5]. Numerous drugs and their combinations have been tried in the past and studies have highlighted the use of these drugs in varying doses for suppression of stress response but not without the significant incidence of quite a few side-effects, especially with higher doses of opioids[5-10].Cardiovascular responses viz. changes in heart rate, blood pressure and wide variety of cardiac arrhythmias can occur because of afferent stimulation of vagus and a sympatho-adrenal response. The smaller magnitude of responses are better tolerated in healthy normotensive individuals, but if exaggerated they can be detrimental even in this patients and definitely so in individuals having systemic illness, culminating in various perioperative complications. Sympatho-adrenal stimulation with sudden rise in heart rate and blood pressure can also lead to left ventricular failure, myocardial ischaemia, cerebral haemorrhage, pulmonary edema, increase in intracranial pressure and its complications; for example, convulsions in pre-eclamptic patients.The analgesic, sedatives, anxiolytic, sympatholytic and blunting of exaggerated haemodynamic responses by administration of dexmedetomidine are being extensively studied and are mainly mediated by the activation of alpha-2 receptors located in the postsynaptic terminals in the central nervous system (CNS), which causes decreased neuronal activity and augmentation of the vagal activity[4,19-21].

The role of alpha-2 agonists in regulating the autonomic and cardiovascular responses is well

understood, whereby they inhibit release of catecholamines (norepinephrine) from the sympathetic nerve terminals by augmentation of a vasoconstrictive effect[1,22-23].In the present study, we have tried to evaluate the efficacy of intravenous dexmedetomidine in attenuation of pressor response to laryngoscopy and intubation and also minimising the requirement of induction agent and opioids in patients undergoing spine surgeries[24].The mean age, weight, height and sex distribution in both groups was comparable ('P' > 0.05).The method of administration of study drugs over 20 minutes in our study, is similar to the studies conducted by Mowafi et al[25]. Basar et al[26] and Kunisawa et al [34].

Comparison of heart rate: While analysing the changes in heart rate in our study it was seen that the preoperative baseline heart rates were comparable in both the groups ('p' value >0.05).In our study, it was observed that there was a statistically significant fall in the mean HR before induction after the administration of study drug in group D (5.4%) as compared to group F (3.71 %) ($p< 0.05$). The same thing has also been observed in the studies conducted by Martina Aho et al., Kunisawa et al[27]and Sagiroglu et al[28]who have found that Dexmedetomidine produce decrease in the HR.This is due to the activation of alpha-2 adrenoreceptors, imidazoline-preferring receptors or both in the ventrolateral medulla and especially in solitaries nucleus tract by dexmedetomidine .After induction of anaesthesia, compared to pre-induction values, it was found that in group D there is a significantly greater fall in the mean heart rate(6.3%) as compared to group F(1.8%) ($p<0.01$). In both the groups there was a decrease in the HR after the administration on propofol due to the potentiation of $GABA_A$ receptor activity, thereby slowing the channel-closing time and also acting as a sodium channel blocker.In our study at laryngoscopy and intubation, there is a rise in heart rate from the basal values which was statistically highly significant in group F as compared to group D.($p<0.001$).There was a decrease in mean HR by and at 3rd and 5th min respectively after intubation in group D and decrease in mean HR by and at 3^{rd} and 5^{th} min after intubation respectively in group F compared to the preoperative values. This decrease was statistically highly significant in group D than in group F. Menda F et al [7] similarly in their study showed that dexmedetomidine as an adjunct to anaesthetic induction attenuated hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG.In the present study, just before extubation and immediately after extubation, mean heart rate increased from the preoperative values by in group F when compared to in group D. Guler G et al similarly in their study showed that a single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation.

Comparison of SBP: While analysing the changes in systolic blood pressure in our study it was seen that the preoperative baseline systolic blood pressures were comparable in both the groups ('p' value >0.05).In our study it was observed that there was a significant fall in mean systolic blood pressure after administration of the study drug before induction in group D was (8.5%) as compared to in group F(6.01%) ('p' value < 0.05). This may be due to the stimulation of alpha 2 receptors which reduces central sympathetic output, resulting in increased firing of inhibitory neurons. After induction of anaesthesia compared to the pre-induction value, the fall in the mean systolic blood pressure was highly significant in group D as compared to group('p' value <0.01). Similar observations were made by Kunisawa et al [27] where in there was a decrease in SBP in dexmedetomidine group. They divided the patients into three groups, one was given dexmedetomidine 1ug/kg as infusion intravenous and 0.7ug/kg bolus before anaesthetic induction, second group was given Fentanyl 2ug/kg and third group was given Fentanyl 4ug/kg intravenously. They concluded that dexmedetomidine suppresses the decrease in blood pressure due to anaesthetic induction.The laryngoscopy and intubation was associated with a highly significant rise in the mean systolic blood pressure from the basal values in group F(1.1%) compared to group D(4.55%). There was a decrease in SBP by, and at 3^{rd} and 5th min respectively after intubation in group D and decrease in SBP by, and at 3^{rd} and 5^{th} min in group F compared to the preoperative values. The fall in SBP was statistically highly significant in group D compared to the fall in group F. Menda F et al [7] similarly in his study showed that dexmedetomidine as an adjunct to anaesthetic induction attenuated hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. They divided the patients in two groups, one group received dexedetomidine infusion (1ug/kg) intravenously and the other group received normal saline infusion intravenous(placebo group) before induction. They found that the SBP after tracheal intubation significantly increased in the placebo group. Thereafter, till the completion of surgery, no significant difference was noted in the mean systolic blood pressure in both the groups. ($p>0.05$). Just before and immediately after the extubation, mean SBP ($p<0.05$) rose significantly high from the preoperative values in group F (as compared to group D, which came to the normal values in 2–3 min after the extubation. Guler G et al [15] similarly in their study showed that a single-dose

Dexmedetomidine attenuates airway and circulatory reflexes during extubation.

Dose of propofol required for induction

We studied the total dose of propofol required for induction in each group. In group D mean dose required was 1.552 mg/kg and in group F mean dose required was 2.356 mg/kg showing reduction in the total dose of propofol required for induction in group D which was statistically highly significant ($p<0.01$). Various authors have studied the effect of Dexmedetomidine on propofol requirements for induction of anaesthesia. This may be due to the effect of Dexmedetomidine mediated through both pre and post synaptic alpha receptor activation in the central nervous system. Demir G et al[29] similarly in their study showed that the amount of propofol required for induction was reduced with the use of intravenous dexmedetomidine.

Additional requirement of intraoperative fentanyl

We studied the requirement of additional fentanyl intra-operatively in each group. In group D mean dose required was 0.488ug/kg and in group F mean dose required 1.488ug/kg was showing statistically highly significant reduction in the requirement of additional fentanyl intraoperatively in group D ($p <0.01$). Similarly, Scheinin Bet al [24] showed in his study that dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for perioperative fentanyl. The study was carried out in two groups, first being isofluorane-opioid-saline anaesthesia and second being isoflurane-opioid-dexmedetomidine anaesthesia. They concluded that dexmedetomidine has a significant opioid and anaesthetic sparing property.

Sedation scoring

In group D mean sedation score was 2 and in group F was 1.2 just before induction, showing that the preoperative sedation in group D is significantly higher than in group F (p value<0.01) .This is due to central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from locus cerulus which plays an important role in sedation and anxiolysis produced by dexmedetomidine. Similarly, Cheung CW et al[30] in their study showed that dexmedetomidine produces a comparable sedation to midazolam in third molar surgery in which sixty patients received either dexmedetomidine(upto 1ug/kg) or midazolam(upto 5mg), which was infused until the Ramsay sedation score was four.

Conclusion

Dexmedetomidine is an excellent drug when used as an adjunct to general anaesthesia for attenuation of pressor response to laryngoscopy and intubation and during extubation. It not only decreased the magnitude of stress response to laryngoscopy, intubation and extubation but also decreased the dose of opioids and propofol in achieving an adequate analgesia and anaesthesia respectively.

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