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Comparative Study Between Intravenous Dexmedetomidine And Fentanyl For Attenuation Of Haemodynamic Response To Laryngoscopy And Endotracheal Intubation: A Randomized Control Trial

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Abstract:
Background*: The degree of haemodynamic changes that are observed may vary depending on a number of factors, including the level of anaesthesia, the kind of anaesthetic drug used, whether any safety measures are followed prior to airway manipulation, the duration of the laryngoscopy or intubation, and others The main mechanism generating hypertension and tachycardia, the sympathetic response, may be heightened by catecholamine activity. Pressor response has been linked to intraoperative myocardial infarction, abrupt left ventricular failure, dysrhythmias, or intracranial haemorrhage in patients with end organ decompensation. Dexmedetomidine is a highly selective and specific α-2 adrenoceptor agonist with an α2:α1 binding selectivity ratio of 20:1, whereas clonidine has a ratio of 220:1. Clonidine and dexmedetomidine bind to and activate α-1 and α-2 receptors, respectively.Additionally, a plethora of studies has shown that dexmedetomidine reduces the haemodynamic response to laryngoscopy and intubation. One of the most powerful analgesics is fentanyl, a synthetic opioid that, when given before induction, lowers the haemodynamic response to intubation. A comparative study between dexmedtomidine and fentanyl is necessary to determine whether medicine is more beneficial, as both medications have the ability to decrease the sympathetic response to endotracheal intubation and laryngoscopy.*
Materials and Methods*: A prospective randomized, and double-blind study was conducted in 60 ASA Grade I and II patients of either gender, aged between 18 and 65 years, undergoing various surgical procedure under spinal-anesthesia and developing shivering. The patients were randomized into two groups of n = 30 each to receive either dexmedetomidine - 0.6 µg/kg (Group D) Fenatnyl- 2 µg/kg (Group F) as an intravenous just before intubation. Blood pressures (systolic, diastolic and mean) recordings. Apart from general physical and systemic examination, routine investigations, blood urea, serum creatinine, serum electrolytes, ECG and X- Ray chest was performed in all patients SPSS-20 was used for statistical analysis, unpaired t-test for numerical data and chi-square test for categorical data.*
Results*: The mean age was between 39 to 40 years and mean BMI was around 26. Similarly, the mean duration of surgery was 70 minutes for both the groups. Total males in study were 29 and females were 31. There was statistically significant difference in Mean arterial blood pressure (MAP) in both study groups after intubation and at 1 minute. The mean MAP in F group was more than D group at all the time intervals. The mean heart rate was statistically higher in F group as compared to D group at all time after intubation. The frequency of bradycardia was nil in F group as compared to 20% in D group. Frequency of hypotension was13% in D group and nausea or vomiting was 20% in F group.*
Conclusion: *Our research shows that a single intravenous dose of Fentanyl (2µg/kg body weight) given over 2 minutes prior to induction and Dexmedetomedine 0.6µg/kg body weight infused over 10 minutes are both effective at obstructing the hemodynamic stress response to laryngoscopic endotracheal intubation without causing any appreciable side effects. On the other hand, when it comes to reducing the hemodynamic stress response following laryngoscopic endotracheal intubation, IV Dexmedetomidine works better and more efficiently than Fentanyl.*
Key Word*: Dexmedetomidine, Fentanyl, Hemodynamic response, laryngoscopy*

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I. Introduction

Anaesthesiologist skills in laryngoscopy & endotracheal intubation are the most important for preserving airway patency. However, people undergoing laryngoscopy and tracheal intubation usually experience an increase in blood pressure and heart rate [1]. The degree of haemodynamic changes that are observed may vary depending on a number of factors, including the level of anaesthesia, the kind of anaesthetic drug used, whether any safety

measures are followed prior to airway manipulation, the duration of the laryngoscopy or intubation, and others. Even now, it is unknown exactly what mechanism causes the haemodynamic responses to laryngoscopy and intubation. The main mechanism generating hypertension and tachycardia, the sympathetic response, may be heightened by catecholamine activity. Increases in blood pressure & pulse rate are usually sporadic, unpredictable, and variable. While momentary hypertension & tachycardia are usually safe in healthy individuals, they may pose a risk to those with heart failure, hypertension, or cerebrovascular diseases. In these situations, this laryngoscopic response may predispose the development of pulmonary oedema, cardiac insufficiency, and cerebrovascular disaster.[2–6] The pressor response is increased in hypertensive patients even when antihypertensive medication reduces their blood pressure to normotensive levels before surgery.[7] Pressor response has been linked to intraoperative myocardial infarction, abrupt left ventricular failure, dysrhythmias, or intracranial haemorrhage in patients with end organ decompensation. Intravenous anaesthetic induction medications do not effectively or consistently suppress the circulatory responses caused by endotracheal intubation.[8–10] Therefore, various authors have tried additional pharmacological measures such as using opioids, topical and intravenous lidocaine, volatile anaesthetics, calcium channel blockers, β blockers, sodium nitroprusside, nitroglycerine, and vasodilators like these before starting a laryngoscopy [11]. For patients who are at risk, anaesthesia induction must not only lower the cardiovascular response but also satisfy the following requirements: It needs to prevent cerebral blood flow impairment, be suitable for all patient groups, and keep the patient unaware of it; None of the medications on the previously mentioned list have been shown to be able to successfully reduce the sympathetic response to intubation while also meeting all the requirements. As such, it's vital to ascertain which medications might satisfy both conditions. Dexmedetomidine is a highly selective and specific α-2 adrenoceptor agonist with an α2:α1 binding selectivity ratio of 20:1, whereas clonidine has a ratio of 220:1. Clonidine and dexmedetomidine bind to and activate α-1 and α-2 receptors, respectively.[12] Additionally, a plethora of studies has shown that dexmedetomidine reduces the haemodynamic response to laryngoscopy and intubation.[13] One of the most powerful analgesics is fentanyl, a synthetic opioid that, when given before induction, lowers the haemodynamic response to intubation.[14] A comparative study between dexmedetomidine and fentanyl is necessary to determine whether medicine is more beneficial, as both medications have the ability to decrease the sympathetic response to endotracheal intubation and laryngoscopy. The purpose of the current investigation is to ascertain how the haemodynamic response to fentanyl and dexmedetomidine is affected during endotracheal intubation and laryngoscopy.

OBJECTIVES: Primary: 1. “To compare changes in Mean blood pressure in response to endotracheal intubation and laryangoscopy following administration of dexmedetomidine and fentnyl.” 2. “To compare changes in heart rate in response to endotracheal intubation and laryangoscopy following administration of dexmedetomidine and fentanyl.” Secondary: “To study side effects associated with use of Dexmedetomidine and Fentanyl for attenuation of stress response to endointubation and laryangoscopy.”

II. Material And Methods

This prospective randomized controlled double blind study was carried out on patients of Department of general anesthesia at Katihar Medical College, Katihar, Bihar for 1 year after the approval from ethical committee. A total 80 adult subjects (both male and females) of aged ≥ 18, years were enrolled for in this study.

Study Design: Prospective randomized controlled study

Study Location: This was a tertiary care teaching hospital based study done in Department of general anesthesia at Katihar Medical College, Katihar, Bihar.

Study Duration: 12 Months, March 2023- February 2024.

Sample size: 60 patients.

Sample size calculation: Sample size was calculated based on a study by Sellamuthu gunalan, rajagopalan vanketraman and paneerselvam Sundaretl in which mean arterial blood pressure just after intubation in dexmetomidine was 95.2+-16.92 and 109+-20.36 with alpha value of 5%, beta value of 20%(80%) and it was found to be 29 in each group so, 30 patients were included in each group.

Subjects & selection method: The study population was drawn from patients who presented to of general anesthesia at Katihar Medical College, Katihar, Bihar between from March 2023- February 2024. Patients were divided into two groups (each group had 40 patients).

The patients were randomized into two groups of n = 30 each to receive either dexmedetomidine - 0.6 µg/kg (Group D) Fenatnyl- 2 µg/kg (Group F) as an intravenous just before intubation. Allocation concealment was ensured using opaque sealed envelope method

Inclusion criteria:

The following criteria were included in the study:

1.Patients undergoing elective surgeries under general anaesthesia
2.Age >18years to 60 years
3.Those who gave informed and written consent to be part of the study
4.ASA Grade I
5. Mallampati garde 1 and 2

Exclusion criteria:

The following criteria were excluded from the study:

1.Those who refused consent
2.Age <18years
3.ASA Grade II or above
4.Patients allergic to any of the drug used.
5. Subjects with heart rate less than 60 beats per minutes.

Procedure methodology

After written informed consent was obtained, a well-designed questionnaire was used to collect the data of the recruited patients retrospectively. The questionnaire included socio-demographic characteristics such as age, gender, nationality, height, weight, and other clinical parameters.

Allocation concealment was ensured using opaque sealed envelope method for group allocation. Allocation was done by a person not involved directly in the research to avoid selection bias. Neither the anesthetist nor the patient was aware of the groups and the drugs used (Double blind). All patients were subjected to standard Pre anesthetic check-up before the surgery including detailed history, examination, vitals, routine investigations and markers. Patients heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), arterial oxygen saturation (SPO_2) were measured at the beginning and 0,5,10,15,20,25,30 minutes after anaesthesia and there after every 30 minutes. . The patients were randomized into two groups of n = 30 each to receive either dexmedetomidine - 0.6 µg/kg (Group D) Fenatnyl- 2 µg/kg (Group F) as an intravenous just before intubation.

Statistical analysis

The study compares time to shivering cessation, incidence of side effects, and severity of shivering using t-tests, chi-square, Fisher's exact, and nonparametric tests.

Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by nonparametric Mann-Whitney test. Chi-square and Fisher exact tests were performed to test for differences in proportions of categorical variables between two or more groups. The level $P < 0.05$ was considered as the cutoff value or significance.

III. Result

The baseline characteristics in both the study groups were comparable. The mean age was between 45 to 47 years and mean BMI was around 26. Similarly, the mean height was 1.62m for both the groups. The mean age of study participants in Dexmedetomidine group was lower than Tramadol group being 45.4 as compared to 47.3 years. But the difference was not statistically significant. The mean weight of D group was 68 kg as opposed to T group which was 69.9 kg. However, the difference was not statistically significant. The male and females were distributed unequally across the groups. Total males in study were 37 and females were 43. However, the distribution was similar across the groups. The mean BMI was 25.9 in D group and 26.68 in T group which was similar. The BMI in D group followed a normal distribution with maximum ranging between 25-30. The BMI in T group followed a normal distribution with maximum ranging between 27-31. The mean duration of surgery was 74.18 minutes in D group and 78.55 minutes in T group.

Table no 1: Descriptive statistics showing Mean, Standard Deviation and Comparison of means between both groups' baseline findings

Baseline parameters	Group	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
Age (years)	F	30	39.13	12.993	2.372	.757
	D	30	40.10	11.040	2.016	
Height (m2)	F	30	1.62	.070	.012	.728

	D	30	1.63	.076	.014	
Weight (kg)	F	30	68.37	10.374	1.894	.358
	D	30	70.73	9.399	1.716	
BMI (kg/m^2)	F	30	26.03	4.57	.834	.539
	D	30	26.74	4.24	.774	
Duration of surgery (min)	F	30	70.37	9.633	1.759	.944
	D	30	70.17	12.208	2.229	

The grade and temperature at the onset of shivering was similar in both the groups. The time of onset of shivering was higher in T group being 73 minutes as compared to D group being 72.4 minutes. Also, time take to cessation of shivering was much lower in D group being 177 minutes as compared to 275 minutes in T group. (Table 1)

The mean heart rate was comparable in both the study groups at all the time intervals. (Figure 4)

Table no 2: Gender and ASA distribution of both study groups

		Group		Total	P-value	95% CI
		Dexmedetomidine	Fentanyl			
Gender	Female	16	15	31	0.796	0.41-3.1
	Male	14	15	29		
ASA	1	14	15	29	0.79	0.31-2.41
	2	16	15	31		
Total		30	30	60		

The male and females were distributed equally across the groups. Total males in study were 29 and females were 31.

Similar to gender distribution, ASA distribution for class 1 was 29 and for class 2 was 31 distributed equally in both the groups. (Table 2)

Table no 3: Descriptive statistics comparing mean of Mean arterial blood pressure (MAP) in both study groups at different time intervals

Variation of Mean Arterial Pressure (MAP)	Group	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
ON ARRIVAL IN OT MAP (mm Hg)	F	30	85.63	7.554	1.379	.278
	D	30	87.47	5.184	.947	
AFTER INTUBATION MAP	F	30	95.70	7.442	1.359	.027
	D	30	91.97	5.055	.923	
1M MAP	F	30	96.23	7.281	1.329	.064
	D	30	93.13	5.283	.965	
3M MAP	F	30	90.93	7.652	1.397	.434
	D	30	89.60	5.236	.956	
5M MAP	F	30	91.13	7.385	1.348	.375
	D	30	89.63	5.461	.997	
10M MAP	F	30	92.13	7.385	1.348	.375
	D	30	90.63	5.461	.997	
15M MAP	F	30	93.13	7.385	1.348	.375
	D	30	91.63	5.461	.997	.

There was statistically significant difference in Mean arterial blood pressure (MAP) in both study groups after intubation and at 1 minute. The mean MAP in F group was more than D group at all the time intervals. (Table 3)

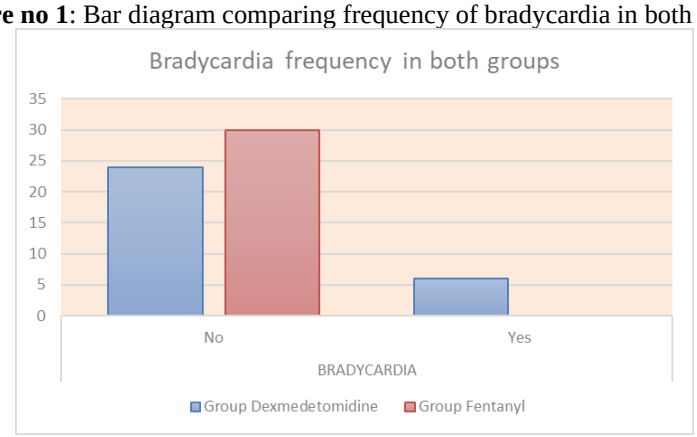
Table no 4: Descriptive statistics comparing mean of Heart rate (HR) in both study groups at different time intervals

Variation of Heart Rate (HR)	Group	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
ON ARRIVAL IN OT HR (BPM)	F	30	72.50	6.318	1.153	.918
	D	30	72.33	6.099	1.113	
AFTER INTUBATION HR	F	30	92.17	7.571	1.382	.000
	D	30	78.07	8.769	1.601	
1M HR	F	30	93.53	7.473	1.364	.000
	D	30	79.63	8.560	1.563	
3M HR	F	30	86.57	7.384	1.348	.006
	D	30	81.33	6.723	1.227	
5M HR	F	30	86.87	7.487	1.367	.031

	D	30	82.83	6.644	1.213	
10M HR	F	30	88.87	7.487	1.367	.031
	D	30	84.83	6.644	1.213	
15M HR	F	30	87.87	7.487	1.367	.031
	D	30	83.83	6.644	1.213	

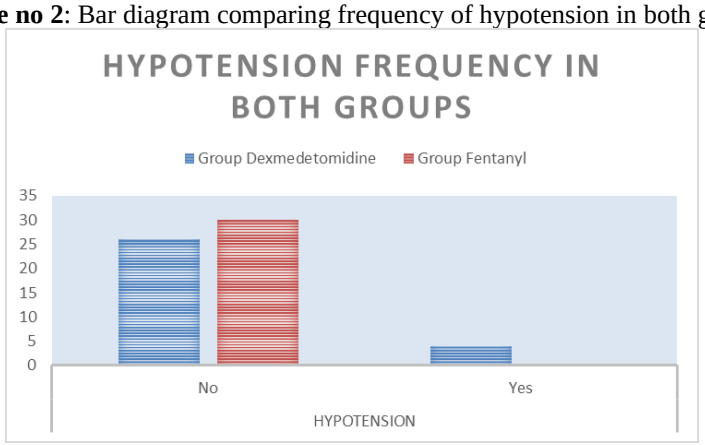
The mean heart rate was statistically higher in F group as compared to D group at all time after intubation. (Table 4)

Figure no 1: Bar diagram comparing frequency of bradycardia in both groups



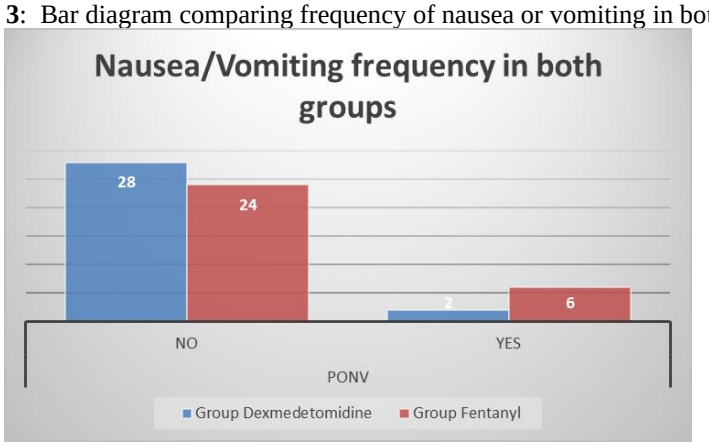
The frequency of bradycardia was nil in F group as compared to 20% in D group. (Figure 1)

Figure no 2: Bar diagram comparing frequency of hypotension in both groups



The frequency of hypotension was also nil in F group as compared to 13% in D group. (Figure 2)

Figure no 3: Bar diagram comparing frequency of nausea or vomiting in both groups



The frequency of nausea or vomiting was 20% in F group as compared to 8% in D group. (Figure 3)

IV. Discussion

Laryngoscopy and intubation are accompanied by sympathetic responses. These transient responses appear as an increase in blood pressure and heart rate. In patients with cardiovascular problems, the hemodynamic changes may lead to life-threatening risks, such as heart ischemia, acute heart failure, and cerebrovascular events. Dexmedetomidine can effectively decrease the stress response, reducing a hemodynamic response after intubation and laryngoscopy (1). Fentanyl is considered a synthetic opioid agonist phenyl pyridine derivative that has been used to reduce the hemodynamic response to intubation and laryngoscopy (2). It also has various other benefits, including intraoperative analgesics. However, because opioids are categorized as narcotic substances, obtaining fentanyl is not without difficult. Because of this, the usage of fentanyl is regulated by national drug control policy and international treaties. Since both Fentanyl and Dexmedetomidine can suppress the sympathetic response to laryngoscopy and endotracheal intubation, present study is undertaken to compare the effectiveness of Dexmedetomidine and Fentanyl in attenuating stress response to laryngoscopy and endotracheal intubation. Sixty American Society of Anesthesiologists grade I-II patients undergoing elective surgeries were recruited and randomized to receive Dexmedetomidine dose 0.6 microgram/kg body weight just before intubation in group A and received Fentanyl 2 microgram/kg body weight just before intubation in group B.

The baseline characteristics in both the study groups were comparable. The mean age of study participants in Dexmedetomidine group was higher than Fentanyl group being 40.1 as compared to 39.1 years. The mean height was 1.63 m in D group and 1.62 m in F group. The mean weight of D group was 70.7 kg as opposed to F group which was 68.37 kg. The mean BMI was 26.7 in D group and 26.03 in F group which was similar.

There was statistically significant difference in Systolic blood pressure (SBP) in both study groups after intubation, at 1 minute, at 5 minutes and at 10 minutes. The mean SBP in F group was more than D group at these intervals. There was no statistically significant difference in Diastolic blood pressure (DBP) in both study groups after intubation till 15 minutes. The mean DBP in F group was however more than D group at these intervals. There was statistically significant difference in Mean arterial blood pressure (MAP) in both study groups after intubation and at 1 minute. The mean MAP in F group was more than D group at all the time intervals. The mean heart rate was statistically higher in F group as compared to D group at all time after intubation.

The frequency of bradycardia was nil in F group as compared to 20% in D group. The frequency of hypotension was also nil in F group as compared to 13% in D group. The frequency of nausea or vomiting was 20% in F group as compared to 8% in D group.

Different writers have utilized Dexmedetomidine at different IV doses, ranging from 0.5 µg/kg to 2 µg/kg. In comparison to 0.5µg/kg, higher dosages of 1-2µg/kg demonstrated a superior attenuation of the hemodynamic response to laryngoscopy and intubation; nevertheless, they also caused significant drowsiness and were linked to an increased risk of cardiovascular compromise, including bradycardia and hypotension. Therefore, we followed the methodology of Jakola et al (15), and Gandhi et al (17) and employed 0.6 µg/kg IV in our investigation.

When a rapid bolus of dexmedetomidine is administered, the peripheral vasculature's vascular smooth muscle α2 receptors are activated, resulting in a brief rise in blood pressure and a reflex drop in heart rate.

Dexmedetomidine has a half-life of distribution of around 6 minutes. Therefore, the drug's action is sufficient to reduce CNS sympathetic activity during the direct laryngoscopic intubation process after 10 minutes of gradual infusion. An IV analgesic that is frequently used is fentanyl, a synthetic, lipophilic, phenylpiperidine opioid agonist. It is frequently employed as a stand-alone anesthetic as well as a part of balanced anesthesia, inhalational anesthesia, and neurolept analgesia. As an analgesic, it has 100 times the potency of morphine. Analogous analgesia is produced by 100µg of fentanyl and 10mg of morphine. It mostly causes analgesia by acting on µ receptors (7). Naloxone, a specific ε receptor antagonist, can counteract its effects; the FDA has allowed its use in suspected or confirmed cases of opioid overdose.

Fentanyl has hemodynamic stabilizing property during perioperative period by its action on autonomic regulatory area and cardiovascular system. Is also inhibits pituitary adrenal response via hypothalamus acting directly or indirectly. It attenuates the sympathetic adrenal response at 2µg/kg IV given before laryngoscopy and intubation (17,19).

In our study, we have given IV Fentanyl 2min before induction as its onset of action is 1-2min and by 5min when we do laryngoscopy and intubation, drug has reached its peak effect. In our study, Dexmedetomidine group showed better attenuation of HR response compared to Fentanyl group. The HR remained below the basal value at all the time intervals after laryngoscopic intubation which was statistically highly significant ($p<0.05$). This is in line with the research conducted by Scheinin et al (13), Jakola et al (15), Menda et al(16), Gandhi et al (17), Das et al (18) and Gunalan et al (19). The attenuation of the rise in the SBP was highly significant in the Dexmedetomidine group as compared to Fentanyl group. The SBP decreased and remained below the baseline value at all the time intervals in Dexmedetomidine group whereas there was a little rise in SBP during intubation in Fentanyl group and returned to basal value by 3 min. The findings of SBP from our study results correlated

with the studies done by Scheinin et al (27), Jakola et al (15), Menda et al(16), Gandhi et al (17), Das et al (18), Gunalan et al (19), Kunisawa et al (20) and Basar et al (21).

Compared to the Fentanyl group, the Dexmedetomidine group showed a highly significant attenuation of the rise in the DBP. When compared to the Fentanyl group, there is a small decline in DBP, while the DBP in the Dexmedetomidine group decreases and stays below the baseline value at all time intervals. The same results were reported in the studies done by by Scheinin et al (13), Jakola et al (15), Menda et al(16), Gandhi et al (17), Das et al (18), Gunalan et al (19), Kunisawa et al (20) and Basar et al (21).

The rise in the MAP was significantly attenuated in both the fentanyl and dexmedetomidine groups at the time of intubation. In the Dexmedetomidine group, there was a highly significant decrease in MAP. MAP at 1 min in fentanyl Fentanyl group showed insignificant increase but then decreased below the baseline after 3min. Our study results matched with studies conducted by by Scheinin et al (13), Jakola et al (15), Menda et al(16), Gandhi et al (17), Das et al (18), Gunalan et al (19), Kunisawa et al (15) and Basar et al (14).

Studies by Jakola et al (15) and Mowfi et al (22) had shown that when Dexmedetomidine is given before induction of anaesthesia, it decreased the intraocular pressure, HR and BP after intubation in patients undergoing ophthalmic surgeries. Jakola et al (15) also measured the plasma catecholamine levels and they noted the decrease in levels after Dexmedetomidine infusion which didn't rise even after intubation.

In our study, the plasma catecholamine levels and the changes in intraocular pressure were not measured. No cardiovascular side effects like hypotension and bradycardia were noted after fentanyl administration. Dexmedetomidine at a dose of 0.6 µg/kg when given slowly over 10 minutes caused hypertension/hypotension and bradycardia in around 10-15% patients. Nausea and vomiting were seen with 20% in F group as compared to 8% in D group.

We have conducted the study on healthy ASA grade 1 patients. So, further studies are needed to be conducted on ASA grade 2, 3 and 4 patients to know the efficacy of the study drugs on these high risk patients.

Strengths of the study

The study was conducted as per protocol. The sample size, sampling technique and procedure was followed for internal validation.

It was conducted by single researcher to rule out biases.

It seconded the findings of previous studies

Limitations of the study:

The study was a single centric study conducted over limited sample. A large study is needed which should also be multicentric for external validity of the study.

Further studies are needed to be conducted on ASA grade 3 and 4 patients to know the efficacy of the study drugs on these high risk patients.

The plasma catecholamine levels and the changes in intraocular pressure should also be measured as a part of study for sympathetic response.

V. Conclusion

Our research shows that a single intravenous dose of Fentanyl (2µg/kg body weight) given over 2 minutes prior to induction and Dexmedetomedine 0.6µg/kg body weight infused over 10 minutes are both effective at obstructing the hemodynamic stress response to laryngoscopic endotracheal intubation without causing any appreciable side effects. On the other hand, when it comes to reducing the hemodynamic stress response following laryngoscopic endotracheal intubation, IV Dexmedetomidine works better and more efficiently than Fentanyl.

For this function, it could be seen as an alternative to opioids. Compared to fentanyl, dexmedetomidine was more effective at preventing tachycardia after endotracheal intubation. HR was considerably lower in the dexmedetomidine group compared to the fentanyl group at one, five, and ten minutes following intubation. Dexmedetomidine may therefore be suggested for improved HR stability following intubation.

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