

A comparative study on fentanyl, morphine and nalbuphine in attenuating stress response and serum cortisol levels during endotracheal intubation

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Abstract

Background: The process of Laryngoscopy & Intubation is a noxious stimulus, therefore constituting a period of intense sympathetic activity. Various non-pharmacological & pharmacological methods have been used to attenuate this hemodynamic response. Opioids are potent agents that can attenuate pressor response by maintaining the proper depth of anaesthesia. Although there are few studies comparing opioids in attenuating hemodynamic response during intubation, none of them incorporated measuring serum cortisol levels during intubation. Henceforth, in our study, we have compared the efficacy of bolus administration of intravenous(IV) fentanyl, IV morphine, and IV nalbuphine to suppress the pressor response and serum cortisol level during laryngoscopy and endotracheal intubation. **Objectives:** 1) To evaluate the efficacy of Intravenous(IV)opioids in attenuating the stress response and serum cortisol levels during endotracheal intubation. **Materials And Methods:** In our study, 60 ASA I and II patients, aged between 20 to 60 years were enrolled and randomly divided into three groups. Of the three groups group I (received Fentanyl 2 mcg/kg), group II (received Morphine 0.1mg/kg), and group III (received Nalbuphine 0.2mg/kg). Patients who are pregnant, lactating or illicitly abusing centrally acting drugs, or allergic to the drug under study are excluded from the study. After random group allocation hemodynamic parameters like heart rate, blood pressure, and mean arterial pressure were monitored at baseline followed by a 1-minute interval up to 4 minutes after intubation. Furthermore, Blood sampling was done in the preoperative ward followed by a 5- and 10-minutes period after intubation intraoperatively for measuring serum cortisol levels. **Conclusion:** Comparatively, fentanyl caused a significant reduction in stress response during laryngoscopy and intubation followed by morphine and nalbuphine

Keywords: morphine, fentanyl, nalbuphine, laryngoscopy, serum cortisol.

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INTRODUCTION

Endotracheal intubation is one of the frequently performed procedure in the practice of anesthesia since the time of introduction of General anesthesia in the last quarter of 19th century. Endotracheal intubation is the placement of tube translaryngeally into trachea via nose or mouth. Glossopharyngeal and vagus carry the afferent and efferent stimuli from Infraglottic region and Epiglottic region and activate vasomotor centre to cause a peripheral sympathetic adrenal response to release adrenaline and nor adrenaline¹. Laryngoscopy and Intubation constitute a

period of extreme haemodynamic stress and associated with intense sympathetic activity manifested as Hypertension and Tachycardia.² Hemodynamic variations that occur during the process are usually unpredictable and transitory. Normal healthy person can tolerate this response, but in susceptible individuals, this transient sympathetic response can evoke life-threatening complications³ Various non-pharmacological and pharmacological methods have been used to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation. Some of the non-pharmacological methods that are in practice are usage of supraglottic airways which aids smooth intubation along with shorter duration of laryngoscopy. blocking Superior laryngeal and Glossopharyngeal nerve⁵ has been used to attenuate cardiovascular response to laryngoscopy and Endotracheal intubation. Pharmacological methods like use of β -blockers^{6,7,8}, Vasodilator^{9,10}, Inhalation agents.¹¹ Topical and Intravenous Lidocaine^{12,13,14}, Narcotics,^{15,16,17} Calcium channel blockers^{18,19,20} has been tried. Opioids are potent agents that can attenuate pressor response by maintaining adequate depth of anaesthesia. Analgesic effect of opioids suppresses the nociceptive stimulation caused by the intubation procedure. The centrally mediated decrease in sympathetic tone might partly be involved in pressor response attenuation. Although there are few studies comparing opioids in attenuating hemodynamic response during intubation,^{21,22,23} none of them incorporated measuring serum cortisol levels during intubation. Henceforth, In our study, we have compared the efficacy of bolus administration of IV fentanyl, IV morphine and IV nalbuphine to suppress the pressor response and serum cortisol level during laryngoscopy and endotracheal intubation

AIM: This study was done to compare the efficacy of bolus administration of IV Fentanyl 2mcg/Kg IV, Morphine 0.1mg/Kg and IV Nalbuphine 0.2mg/Kg in attenuating the cardiovascular stress responses accompanying laryngoscopy and endotracheal intubation by measuring heart rate, systolic blood pressure, diastolic blood pressure mean arterial pressure with serum cortisol Levels in each groups.

OBJECTIVE:

- 1) To evaluate the efficacy of IV Fentanyl 2mcg/Kg, IV Morphine 0.1mg/Kg and IV Nalbuphine 0.2mg/Kg in attenuating the stress response to laryngoscopy and endotracheal intubation.
- 2) To study any change in stress hormone before and after the induction of General Anesthesia by measuring blood levels of serum cortisol

MATERIALS AND METHODOLOGY

Design

This study “Comparative evaluation of Intravenous Fentanyl, Intravenous Morphine and Intravenous Nalbuphine in attenuating stress response to Laryngoscopy and Intubation” was carried out at Tagore medical college and hospital between December 2018 to March 2022. This study was undertaken after obtaining Ethical committee as well as written informed consent for all 60 patients. 60 patients, with 20 in each group, in different age group, either sex, belonging to ASA I and ASA II scheduled for elective surgical procedures under General Anesthesia were included.

Inclusion criteria: Patients of either sex - Patient with ASA grade I and II. Patients scheduled for Elective surgical procedures under General Anesthesia.

Exclusion criteria: Patient with anticipated difficult Airway. Hiatus Hernia. GERD. BMI > 30. Patients on sedative, Hypnotics, Anti-hypertensive. Pregnant, Lactating mothers

Pre-anesthetic evaluation: On the day prior to surgery pre anesthetic evaluation was done. A thorough clinical examination of the patient was performed including General examination and Systemic examination. Airway assessment was done by Mallampati grading to anticipate difficult intubation. All patients were explained about the Anesthetic technique and written informed consent taken. Patients were kept NPO for 8 hours prior to surgery. Routine investigation done Hb, RBS, Urea, Creatinine, BT, CT, HIV, HbsAg, Chest X-ray, ECG. No specific investigations were required preoperatively pertaining to the study.

Technique of Anesthesia/procedure: 60 patients belonging to ASA grade I and II were randomly divided into 3 groups, each group consist of 20 patients

GROUP I [FENTANYL group]

GROUP II [MORPHINE group]

GROUP III [NALBUPHINE group]

On the day of surgery, Anesthesia machines and circuits were checked, resuscitation equipments were kept ready. After explaining the procedure and the effects of the drug, informed consent was obtained. In Preoperative ward, Baseline blood samples collected for checking serum cortisol levels in all patients and after ensuring fasting status patient was shifted to the operation theatre and connected to ASA standard monitors and Baseline Heart Rate (HR), Systolic pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial pressure (MAP), SPO₂ were recorded. Intravenous access established and Serum Cortisol levels were sent after 5 min of settling in the OT. All patients were premedicated with Inj. Glycopyrrolate 0.2mg, Inj. Ondansetron 4mg administered Intravenously.

All patients were preoxygenated with 100% Oxygen for 3 minutes

GROUP I - patients received Intravenous Fentanyl 2mcg/kg over 1-2 minutes.

GROUP II - patients received Intravenous Morphine.0.1mg/kg over 1-2 minutes

GROUP III - patients received Intravenous Nalbuphine 0.2mg/kg over 1-2 minutes.

After 5 minutes of stabilization period SBP, DBP, MAP, Heart rate, SpO₂ (T₁) was recorded and Induction of anaesthesia done with Inj. Propofol 2mg/kg. After ensuring achievement of adequate depth of anaesthesia and ease of ventilation with bag and mask, Inj. Vecuronium 0.1mg/Kg bolus given unless there is no contraindication to facilitate laryngoscopy and intubation. Oxygenation continued by positive pressure mask ventilation using Bain's circuit. At 2 minutes after induction SBP, DBP, MAP, Heart rate, SpO₂ was recorded. At 3 minutes after induction, using

laryngoscope with a Macintosh blade intubation was done with well lubricated, appropriate sized cuffed, disposable oral Endotracheal Tube. After confirmation of the tube position by capnography tracing and Bilateral auscultation, cuff inflated and tube fixed and connected to anaesthesia machine for controlled ventilation. Anesthesia maintained with 50/50 % of O₂ and N₂O. Sevoflurane MAC titrated according to hemodynamic variables. SBP, DBP, MAP, Heart rate, SpO₂ were recorded at 1 minute interval after laryngoscopy and Intubation and blood sample collected after 5 min, 10 min followed by intubation for checking serum cortisol level

STATISTIC METHOD EMPLOYED

All data presented as mean±SD. Demographic data were analysed by student's T test. STATISTICAL SOFTWARE The statistical software SPSS FOR WINDOWS (V 17) was used for the analysis of the data and Microsoft word and Excel have been used to Generate Tables etc.

Table 1

		Groups			Total
		Fentanyl Group	Morphine Group	Nalbuphine Group	
Sex	Male	10	10	10	30
	Female	10	10	10	30
Total		20	20	20	60

Table 2

Age	N	Mean	SD	95% CI		Mini	Maxi
				Lower	Upper		
Fentanyl Group	20	32.00	6.61	28.90	35.10	22	44
Morphine Group	20	32.05	8.61	28.02	36.08	20	48
Nalbuphine Group	20	28.15	5.24	25.71	30.59	21	45
Total	60	30.73	7.00	28.90	32.56	20	48

Table 3

AGE	Sex	N	Fentanyl		Morphine		Nalbuphine	
			Mean	SD	Mean	SD	Mean	SD
	Male	10	33.90	6.52	34.30	8.34	27.40	3.4
	Female	10	30.10	6.47	29.80	8.70	28.90	6.657

Table 4

	N	Mean	SD	95% CI		Mini	Maxi	ANOVA	P Value	
				Lower	Upper					
HR_0	Fentanyl	20	81.40	7.89	77.70	85.10	68	92	3.289	0.044
	Morphine	20	75.90	7.24	72.51	79.29	64	88		
	Nalbuphine	20	76.50	7.16	73.15	79.85	66	90		
	Total	60	77.93	7.72	75.94	79.93	64	92		
HR_1	Fentanyl	20	88.30	7.90	84.60	92.00	74	100	1.338	0.270
	Morphine	20	86.70	7.49	83.19	90.21	74	98		
	Nalbuphine	20	90.50	6.69	87.37	93.63	80	104		
	Total	60	88.50	7.42	86.58	90.42	74	104		
HR_2	Fentanyl	20	79.70	7.98	75.96	83.44	64	92	3.776	0.029
	Morphine	20	80.60	7.32	77.18	84.02	70	90		

	Nalbuphine	20	85.65	6.80	82.47	88.83	74	100		*
	Total	60	81.98	7.72	79.99	83.98	64	100		
HR_3	Fentanyl	20	73.40	7.17	70.04	76.76	60	86	7.390	0.001
	Morphine	20	74.30	7.44	70.82	77.78	62	84		
	Nalbuphine	20	81.30	6.72	78.15	84.45	72	96		
	Total	60	76.33	7.85	74.31	78.36	60	96		
HR_4	Fentanyl	20	67.40	6.72	64.26	70.54	54	80	11.556	0.001
	Morphine	20	67.80	7.11	64.47	71.13	58	78		
	Nalbuphine	20	76.80	7.15	73.45	80.15	66	92		
	Total	60	70.67	8.15	68.56	72.77	54	92		

* - There is a **Statistical Significance** difference between the Groups at 95% (P < 0.05)

** - There is a **Highly Statistical Significance** difference between the Groups at 99% (P < 0.01)

*** - There is a **Very Highly Statistical Significance** difference between the Groups at 99.9% (P < 0.001)

NS - **Not Statistical Significance** Difference between the Groups at 95% (P > 0.05)

Table shows rise in Heart rate much less in fentanyl group,as compared with morphine and nalbuphine group at all measured time intervals

Table 5

		N	Mean	SD	95% CI		Mini	Maxi	ANOVA	P Value
					Lower	Upper				
SBP_0	Fentanyl	20	121.70	7.35	118.26	125.14	108	132	1.446	0.244
	Morphine	20	117.60	7.58	114.05	121.15	106	130		
	Nalbuphine	20	120.50	8.53	116.51	124.49	108	134		
	Total	60	119.93	7.90	117.89	121.97	106	134		
SBP_1	Fentanyl	20	128.10	6.76	124.94	131.26	116	138	7.117	0.002
	Morphine	20	129.10	7.75	125.48	132.72	120	140		
	Nalbuphine	20	136.10	7.38	132.64	139.56	124	150		
	Total	60	131.10	8.03	129.03	133.17	116	150		
SBP_2	Fentanyl	20	118.70	6.56	115.63	121.77	108	128	16.425	0.001
	Morphine	20	122.50	7.10	119.17	125.83	112	134		
	Nalbuphine	20	131.30	7.69	127.70	134.90	120	146		
	Total	60	124.17	8.80	121.89	126.44	108	146		
SBP_3	Fentanyl	20	108.60	6.16	105.72	111.48	98	118	35.545	0.001
	Morphine	20	114.00	6.90	110.77	117.23	104	126		
	Nalbuphine	20	126.50	7.54	122.97	130.03	114	140		
	Total	60	116.37	10.15	113.75	118.99	98	140		
SBP_4	Fentanyl	20	97.10	6.17	94.21	99.99	88	106	57.832	0.001
	Morphine	20	105.00	6.51	101.96	108.04	94	118		
	Nalbuphine	20	121.30	8.81	117.18	125.42	108	142		
	Total	60	107.80	12.42	104.59	111.01	88	142		

Table shows rise in blood pressure is much less in fentanyl group,as compared with morphine and nalbuphine group at all measured time intervals

Table 6

		N	Mean	SD	95% CI		Mini	Maxi	ANOVA	P Value
					Lower	Upper				
DBP_0	Fentanyl	20	72.70	5.16	70.28	75.12	64	80	2.940	0.061
	Morphine	20	75.50	5.87	72.75	78.25	66	88		
	Nalbuphine	20	77.70	8.19	73.87	81.53	62	90		
	Total	60	75.30	6.75	73.56	77.04	62	90		
DBP_1	Fentanyl	20	77.30	5.67	74.65	79.95	66	86	23.158	0.001
	Morphine	20	84.40	5.93	81.62	87.18	74	94		
	Nalbuphine	20	91.20	7.61	87.64	94.76	80	110		
	Total	60	84.30	8.55	82.09	86.51	66	110		
DBP_2	Fentanyl	20	70.60	5.03	68.25	72.95	60	78	38.477	0.001
	Morphine	20	78.40	5.72	75.72	81.08	70	90		
	Nalbuphine	20	86.80	6.66	83.68	89.92	76	100		
DBP_3	Fentanyl	20	63.70	5.00	61.36	66.04	54	70		

DBP_4	Morphine	20	71.60	4.93	69.30	73.90	62	82	59.949	0.001 ***
	Nalbuphine	20	83.30	6.94	80.05	86.55	72	98		
	Total	60	72.87	9.86	70.32	75.41	54	98		
	Fentanyl	20	56.00	4.77	53.77	58.23	48	62	80.700	0.001 ***
	Morphine	20	63.50	5.27	61.04	65.96	52	70		
	Nalbuphine	20	78.60	6.93	75.36	81.84	70	94		
	Total	60	66.03	11.03	63.19	68.88	48	94		

Table shows rise in Diastolic blood pressure is much less in fentanyl group, as compared with morphine and nalbuphine group at all measured time intervals

Table 7

		N	Mean	SD	95% CI		Mini	Maxi	ANOVA	P Value
					Lower	Upper				
MAP_0	Fentanyl	20	88.75	5.58	86.14	91.36	81	99	0.944	0.395 NS
	Morphine	20	89.40	6.02	86.58	92.22	80	101		
	Nalbuphine	20	91.50	7.99	87.76	95.24	77	104		
	Total	60	89.88	6.61	88.18	91.59	77	104		
MAP_1	Fentanyl	20	93.70	5.87	90.95	96.45	85	102	17.412	0.001 ***
	Morphine	20	98.95	6.22	96.04	101.86	89	109		
	Nalbuphine	20	105.80	7.33	102.37	109.23	94	123		
MAP_2	Total	60	99.48	8.11	97.39	101.58	85	123	31.261	0.001 ***
	Fentanyl	20	86.55	5.24	84.10	89.00	80	94		
	Morphine	20	92.35	5.72	89.68	95.02	84	100		
MAP_3	Nalbuphine	20	101.35	6.83	98.15	104.55	90	115	51.319	0.001 ***
	Total	60	93.42	8.49	91.22	95.61	80	115		
	Fentanyl	20	78.00	4.69	75.80	80.20	69	84		
MAP_4	Morphine	20	85.30	5.08	82.92	87.68	76	94	78.921	0.001 ***
	Nalbuphine	20	96.90	7.64	93.32	100.48	80	110		
	Total	60	86.73	9.79	84.20	89.26	69	110		
MAP_4	Fentanyl	20	69.45	4.71	67.25	71.65	61	76	78.921	0.001 ***
	Morphine	20	76.80	5.42	74.27	79.33	67	84		
	Nalbuphine	20	92.35	7.24	88.96	95.74	82	107		
Total		60	79.53	11.23	76.63	82.43	61	107		

Table shows rise in Mean arterial blood pressure is much less in fentanyl group, as compared with morphine and nalbuphine group at all measured time intervals

Table 8

		N	Mean	SD	95% CI		Mini	Maxi	ANOVA	P Value
					Lower	Upper				
SCL_0	Fentanyl	20	22.90	5.08	20.52	25.27	17	32	2.415	0.098 NS
	Morphine	20	26.35	5.57	23.74	28.96	18	36		
	Nalbuphine	20	25.46	4.81	23.21	27.71	19	34		
	Total	60	24.90	5.29	23.54	26.27	17	36		
SCL_1	Fentanyl	20	11.150	1.57	10.415	11.885	8.7	13.8	73.316	0.001 ***
	Morphine	20	16.000	2.55	14.806	17.194	10.8	21.0		
	Nalbuphine	20	20.555	3.02	19.141	21.969	16.6	27.8		
SCL_2	Total	60	15.902	4.56	14.723	17.081	8.7	27.8	365.646	0.001 ***
	Fentanyl	20	7.980	1.07	7.481	8.479	6.2	10.4		
	Morphine	20	11.365	1.34	10.736	11.994	8.8	14.2		
	Nalbuphine	20	20.335	1.93	19.430	21.240	17.1	24.0		
Total		60	13.227	5.46	11.817	14.637	6.2	24.0		

Table shows no statistical significance in serum cortisol levels between the three groups SCL_0. Serum cortisol level are statistically significantly lower at SCL_1 and SCL_2 among all the three groups

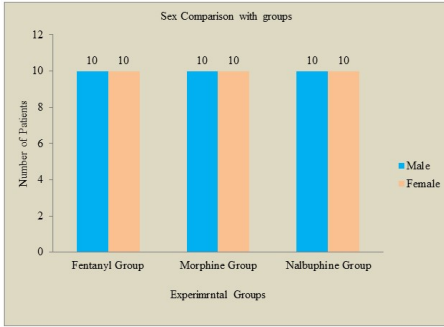


Figure 1

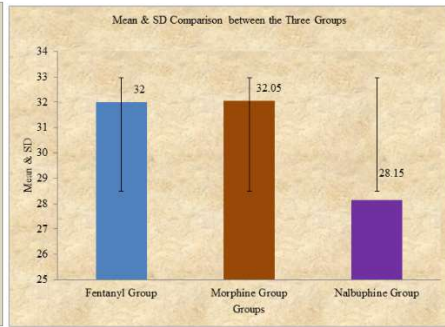


Figure 2

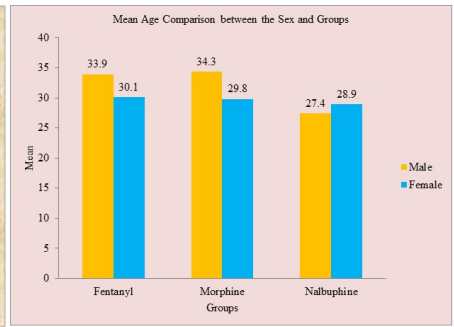


Figure 3

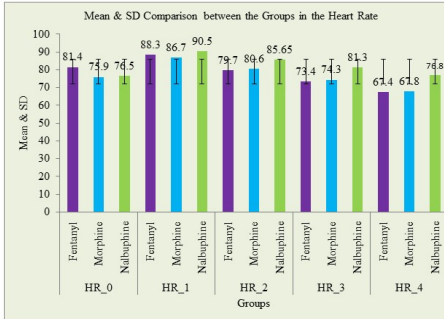


Figure 4

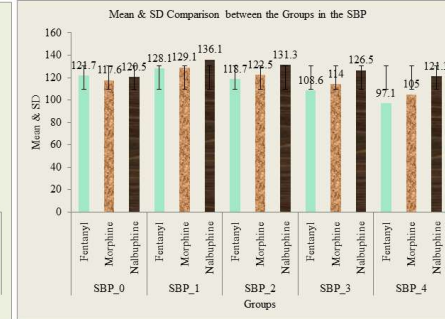


Figure 5

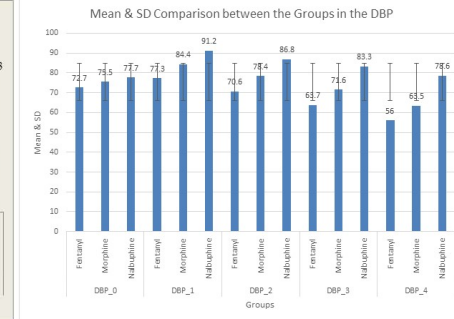


Figure 6

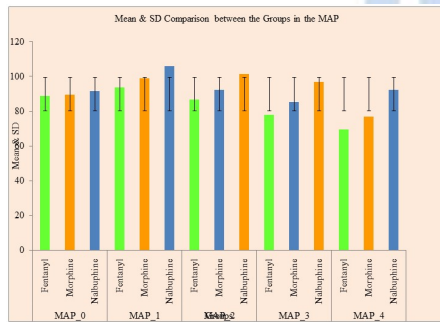


Figure 7

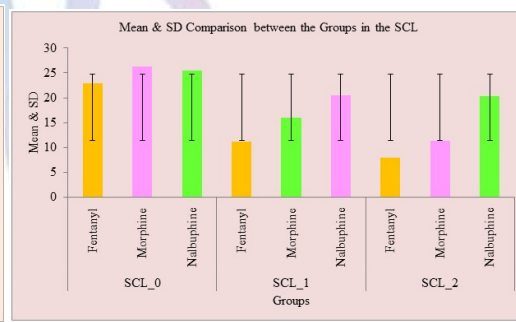


Figure 8

Figure 1: Sex ratio in all three group are comparable; Figure 2: Mean age and range of age in all three groups are comparable; Figure 3: Mean age comparison between the sex and groups are comparable; Figure 4: Heart rate between three groups at HR_0 has no statistical significance; Figure 5: Systolic blood pressure between three groups at SBP_0 has no statistical significance; Figure 6: Diastolic blood pressure between three groups at DBP_0 has no statistical significance; Figure 7: Mean arterial blood pressure between three groups at MAP_0 has no statistical significance; Figure 8: Serum cortisol level at SCL_1, SCL_2 for fentanyl group is significantly lower when compared with morphine, nalbuphine groups.

DISCUSSION

In this study, laryngoscopy response to intravenous opioid agents fentanyl was compared with morphine and nalbuphine. The results obtained showed a stable haemodynamic with the patient who received fentanyl as compared to other two groups. As well as, stress response was assessed using serum cortisol levels where the subjects assessed before the surgery (in waiting area) and intra operatively (5minutes and 10 minutes after intubation). Blood sample were collected in waiting area before induction, after intubation (5 minutes and 8 minutes). There were significant changes in serum cortisol level. Therefore, it appears to be significant decreased in serum

cortisol levels after intubation. Other indirect methods of determining anxiety or stress reduction are to examine changes in heart rate and blood pressure. With increasing anxiety or stress, a subject's heart rate and blood pressure (especially systolic) tend to increase as well, and vice versa. This is because fear and anxiety elicit the sympathetic nervous system, or the so-called "fight or flight" system response. One of the effects of sympathetic nervous system is to increase heart rate and systolic blood pressure. In fact, increase in heart rate and blood pressures are among the signs used to detect inadequate depth of Anesthesia by Anesthesiologists. Therefore, the difference in heart rate, systolic and diastolic blood pressure and

mean arterial pressure at four time intervals of the study compared to before tablet intake would be an indication of a subject's level of anxiety or stress, with higher levels being related to higher degrees of anxiety or stress. So this study was done to compare the effects of single bolus fentanyl, morphine and Nalbuphine versus control group in attenuating the haemo dynamic response to intubation. Bolus injection of fentanyl (2mcg/kg) given 3 minutes prior to intubation provided consistent and reliable protection against increases in mean heart rate, systolic pressure, diastolic pressure, and mean arterial pressure during laryngoscopy and endotracheal intubation and there after. Bolus injection of morphine (0.1mg/kg) given 3 minutes prior to intubation failed to attenuate the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure to the same extent as fentanyl during laryngoscopy and endotracheal intubation and thereafter Bolus injection of nalbuphine (0.2mg/kg) given 3 minutes prior to intubation failed to attenuate the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood to the same extent as fentanyl and morphine during laryngoscopy and endotracheal intubation and thereafter At each level the rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure is much less in Fentanyl group followed by Morphine and Fentanyl groups With Fentanyl group heart rate, mean systolic and diastolic blood pressure returned to baseline value within 3minutes after intubation, but it was 5 minutes with morphine groups, whereas with nalbuphine groups it was 7 to 8 minutes In Fentanyl group, HR, SBP, DBP, MAP showed significant decrease through the study period, compare to Morphine and Nalbuphine

CONCLUSION

At the dose used in this study, fentanyl was significantly reducing stress response during laryngoscopy and intubation followed by morphine and nalbuphine Hence Intravenous Fentanyl given at the dose of 2 mcg/kg effectively attenuates the stress response after laryngoscopy and intubation. Compare to Morphine 0.1mg/kg and nalbuphine 0.2mg/kg in that respective order

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