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COMPARISON OF TWO DIFFERENT DOSES OF FENTANYL i.e. 2µg/kg AND 4µg/kg IN ATTENUATING HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION

Dr. Anand G .Isarka, Dr.Megha Kunte Gupta,

mbbs, MD,Specialist Anaesthesia, department of Anaesthesilogy,Ain AL Khaleej Hopital, Abu Dhabi.

mbbs,MD.Specialist Anaesthesia, department of Anaesthesilogy,Sheikh Shakh bout Medical city , Abu Dhabi.

Corresponding author: Dr. Anand G .Isarka, mbbs, MD,

Specialist Anaesthesia, department of Anaesthesilogy,Ain AL Khaleej Hopital, Abu Dhabi.

ABSTRACT

Aims and objective-The purpose of this open comparative trial was to compare the efficacy of two different doses of fentanyl, 2ug/kg and 4µg/kg, to attenuate the haemodynamic response to laryngoscopy and intubation. **Mateterial and methods**-One hundred and fifty ASA-I patients 18-50 years of either sex were divided into three equal groups (Control group, F2 group and F4 group). All patients had standard protocol for premedication and induction. Pulse, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product were recorded at different time intervals and values were expressed as mean ± standard deviation.**conclusion-** Our study confirms previous reports that laryngoscopy and intubation are accompanied by a considerable increase in arterial blood pressure significantly attenuated by intravenous administration of fentanyl.

Key words- fentanyl,hemodynamic response, laryngoscope,intubation.

INTRODUCTION

General anaesthesia poses the problem of pressor response to laryngoscopy and intubation well recognised sipée 1951. Laryngoscopy and intubation provoke sympatheticoadrenal responses[1], afferent vagal stimulation and endorphin release which may cause tachycardia, hypertension, dysrhythinia and bradycardia (children).

These responses are usually transient and innocuous and of little significance in young healthy subjects. However, in susceptible patients, for example, coronary artery disease, systemic hypertension, cardiovascular disease, intracerebral aneurysm, these responses can result in potentially deleterious effects such as left ventricular failure, arrythmia, myocardial infarction, cerebral haemorrhage, rupture of cerebral aneurysm[2,3,4], etc. and even sudden death has been reported.

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Since long various techniques and drugs have been used to attenuate these responses including lidocaine, deepening planes of anaesthesia with inhalational agents, antihypertensives (B-blockers, phentolamine, nitroprusside, clonidine, captopril, nitroglycerine and hydralazine), calcium channel blockers (nicardipine, diltiazem, verapamil), narcotics (fentanyl, sufentanil, alfentanil, remifentanil), fibreoptic nasotracheal intubation, etc. All of these have their own disadvantages and an optimal agent is difficult to recommend for a given patient. Fentanyl has been used in dose range 2-20ug/kg intravenous to attenuate pressor response with varied results. We compared two different doses of fentanyl Le 2µg/kg and 4pg/kg in attenuating the pressor response.

AIMS AND OBJECTIVES

To study and compare two different doses of fentanyl Le 2ug/kg and /kg in attenuating haemodynamic response to laryngoscopy and intubation with respect to:

- Adequacy of suppression of response.
- Side effects/complications.

MATERIAL AND METHODS

Type of study

The present study was an open comparative clinical trial to compare the efficacy of two different doses of fentanyl, 2ug/kg and 4pg/kg, to attenuate the pressor response to laryngoscopy and intubation.

Study area and period

This study was done in Shri KMJ Hospital and Research Centre(Gondia) , Gondia City Hospital and Sai Siddhi Hospital (Mumbai)in the year 2012

Patient group

18-50 years ASA 1 patients without previous history suggestive of arterial hypertension, intracranial hypertension, cerebral aneurysm, cardio- pulmonary disease or any other associated systemic illness with normal preoperative X-ray chest and ECG

After obtaining thorough history, general and systemic examination and relevant investigations, a total population of 150 ASA I patients scheduled for elective surgery were randomly assigned to one of the following three equal groups:

Control Group: 50 patients received normal saline as placebo.

F2 Group : 50 patients received Inj. fentanyl 2µg/kg intravenous

F4 Group : 50 patients received Inj. fentanyl 4ug/kg intravenous.

Inclusion criteria

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- ASA I patients posted for elective surgery requiring general anaesthesia with endotracheal intubation and controlled ventilation.

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- Age group 18-50 years of either sex.
- ASA I

Exclusion criteria:

- Patient refusal.
- Patients with any other associated systemic illness like hypertension, diabetes mellitus, cardiac disease, pulmonary disease, neurological disease etc. Le. ASA II onwards.
- Patients with respiratory complaints, bradycardia (heart rate< 60/min). hypotension (systolic blood pressure < 90mmHg).
- Patients with anticipated difficult intubation. Duration of laryngoscopy > 15 seconds.
- More than one attempt for laryngoscopy and intubation.
- Pregnant patients.

Methodology:

One hundred and fifty ASA I patients who satisfied inclusion criteria weredivided into 3 equal groups of 50 patients each as already mentioned. Starvation and written informed consent for participation in trial were confirmed.

At zero time, study drug was given i.e

- Fentanyl 2ug/kg Lv. to F2 group.
- Fentanyl 4ug/kg i.v. to Fl group.
- Equal volume normal saline (placebo) i.v. to control group.

OBSERVATIONS

All three groups were comparable with respect to age, weight, sex and duration of surgery (p>0.05).

TABLE – 1 **PULSE RATE**

	Control group		F2 Group			F4 Group			
	Mean±S.D. (Beats/mi	% change from	Mean+/S.D. (Beats/min)	% change from	'p' Value	Mean±S.D. (Beats/	% change from	'p' Value	'p' Value

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	n)	base line		base line	w.r.t. control	min)	base line	w.r.t. control	w.r.t. F2
Baseline	80.70±14.71		80.32±15.77		NS	80.56±15.74		NS	NS
After pre medication	88.40±15.44	9.70±2.14	88.00±16.55	9.74±2.16	NS	88.22±16.60	9.68±2.71	NS	NS
After fentanyl	88.52±15.23	9.89±2.37	84.20±15.73	2.83±9.02	NS	82.82±15.48	3.02±3.58	NS	NS
After thiopentone Na	93.58±14.87	16.57±6.08	89.30±14.87	11.93±6.33	NS	85.14±16.33	5.78±2.23	<0.01	NS
Just before laryngoscopy	88.84±14.58	10.51±4.45	89.32±15.62	11.83±6.54	NS	87.78±17.17	8.98±1.64	NS	NS
Immediately after intubation	117.88±21.67	46.15±4.36	106.86±21.14	33.06±4.29	<0.01	97.72±19.09	21.36±2.95	<0.01	<0.05
1 min after intubation	118.86±21.88	47.41±5.89	103.96±20.48	29.44±2.90	<0.01	90.36±21.82	12.37±18.30	<0.01	<0.01
2 min after intubation	111.64±20.99	38.48±7.22	101.16±19.89	25.97±3.10	<0.01	86.64±16.63	7.68±1.96	<0.01	<0.01
3 min after intubation	107.28±19.81	32.95±2.94	98.44±19.40	22.58±3.28	<0.05	85.20±16.18	5.89±1.76	<0.01	<0.01
5 min after intubation	94.96±18.85	17.03±6.61	92.22±17.75	14.94±3.95	NS	80.86±15.32	0.53±2.30	<0.01	<0.01
10 min after intubation	82.60±13.38	2.74±3.73	86.54±15.56	7.91±4.62	NS	76.84±14.64	-4.49±2.31	NS	<0.01

TABLE – 2 **SYSTOLIC BLOOD PRESSURE**

	Control group		F2 Group			F4 Group			
	Mean±S.D. (mmHg)	% change from base line	Mean+/S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	Mean±S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	'p' Value w.r.t. F2
Baseline	125.20±1		125.12±1		NS	124.04±10.		NS	NS

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	0.24		1.28			97			
After pre medication	132.52±10.37	5.88±1.66	132.48±11.37	5.93±1.69	NS	132.44±11.00	5.97±1.94	NS	NS
After fentanyl	132.48±10.16	5.87±1.84	126.64±10.33	1.33±3.16	<0.01	120.04±10.33	-3.96±1.81	<0.01	<0.01
After thiopentone Na	117.60±9.99	-5.96±5.15	118.68±10.21	-4.86±7.01	NS	111.28±9.40	-10.95±2.06	<0.01	<0.01
Just before laryngoscopy	122.44±9.58	-2.01±5.64	117.56±12.35	-6.10±3.78	<0.05	100.64±9.81	-19.54±2.64	<0.01	<0.01
Immediately after intubation	176.12±13.26	40.70±2.89	161.60±15.19	29.12±1.77	<0.01	150.92±14.75	20.64±3.81	<0.01	<0.01
1 min after intubation	168.72±11.98	34.99±3.78	150.56±13.88	20.33±2.45	<0.01	136.00±12.24	8.77±2.20	<0.01	<0.01
2 min after intubation	160.16±13.04	28.00±4.61	141.88±13.64	13.38±3.14	<0.01	125.16±11.38	0.09±2.37	<0.01	<0.01
3 min after intubation	143.76±12.00	14.82±1.58	133.80±13.42	6.92±4.57	<0.01	114.84±10.62	-8.17±1.89	<0.01	<0.01
5 min after intubation	132.84±10.72	6.15±3.29	125.44±13.45	0.08±5.71	<0.01	107.38±9.73	-14.19±2.38	<0.01	<0.01
10 min after intubation	126.24±10.04	0.89±3.18	118.04±13.69	-5.66±6.67	<0.01	101.40±11.24	-18.85±6.34	<0.01	<0.01

TABLE 3 **DIASTOLIC BLOOD PRESSURE**

	Control group		F2 Group			F4 Group			
	Mean±S.D. (mmHg)	% change from base line	Mean+/S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	Mean±S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	'p' Value w.r.t. F2
Baseline	80.92±5.		80.80±5.		NS	81.48±5.53		NS	NS

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	57		45						
After pre medication	85.08±5.33	5.21±2..68	85.00±5.22	5.27±2.65	NS	85.32±5.33	4.80±3.30	NS	NS
After fentanyl	85.04±5.45	5.18±3.45	82.08±5.54	1.64±3.56	<0.01	80.40±5.06	-1.22±3.89	<0.01	NS
After thiopentone Na	83.92±5.77	3.75±3.20	77.92±5.36	-3.51±3.33	<0.01	78.32±5.00	-3.81±2.61	<0.01	NS
Just before laryngoscopy	85.84±5.82	6.13±3.32	78.36±6.28	-3.04±3.56	<0.01	76.32±5.33	-6.30±2.63	<0.01	NS
Immediately after intubation	109.80±8.02	31.92±8.47	99.76±7.30	23.45±3.22	<0.01	97.84±6.72	20.17±4.81	<0.01	NS
1 min after intubation	108.56±7.44	31.95±8.39	93.16±6.64	15.28±2.18	<0.01	89.72±5.55	10.21±3.35	<0.01	<0.05
2 min after intubation	99.68±6.54	23.44±7.39	89.52±6.40	10.78±2.55	<0.01	83.08±5.57	2.00±2.71	<0.01	<0.01
3 min after intubation	92.80±6.00	14.74±2.42	85.96±6.17	6.39±2.93	<0.01	76.48±5.00	-6.08±2.53	<0.01	<0.01
5 min after intubation	86.72±6.32	7.23±4.36	80.52±6.12	-0.30±4.47	<0.01	73.13±4.74	-10.13±3.22	<0.01	<0.01
10 min after intubation	82.96±5.74	2.57±3.35	75.16±6.18	-6.91±5.68	<0.01	69.96±4.66	-14.05±3.58	<0.01	<0.01

TABLE 4 **MEAN ARTERIAL PRESSURE**

	Control group		F2 Group			F4 Group			
	Mean±S.D. (mmHg)	% change from base line	Mean+/S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	Mean±S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	'p' Value w.r.t. F2
Baseline	95.68±6.		95.57±6.		NS	96.00±6.47		NS	NS

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	41		60						
After pre medication	100.69±6.17	5.49±1.55	100.82±6.33	5.54±1.55	NS	101.02±6.29	5.28±1.87	NS	NS
After fentanyl	100.85±6.06	5.46±1.97	96.93±6.07	1.49±2.46	<0.01	93.61±5.78	-2.42±2.39	<0.01	<0.01
After thiopentone Na	95.14±5.93	-0.48±2.94	91.50±5.79	-4.14±3.81	<0.01	89.30±5.64	-6.93±1.72	<0.01	NS
Just before laryngoscopy	98.04±5.83	2.57±3.34	91.42±7.29	-4.36±2.92	<0.01	84.42±6.14	-12.05±2.23	<0.01	<0.01
Immediately after intubation	131.90±9.23	37.94±5.29	120.37±8.64	25.94±1.99	<0.01	115.53±8.36	20.37±3.98	<0.01	0.01<
1 min after intubation	127.28±7.83	33.16±4.81	112.29±8.05	17.49±2.13	<0.01	105.14±6.83	9.56±2.25	<0.01	<0.01
2 min after intubation	119.84±7.84	25.36±5.01	106.97±7.83	11.92±2.75	<0.01	97.10±6.64	1.16±2.00	<0.01	<0.01
3 min after intubation	109.78±7.05	14.77±1.50	101.90±7.79	6.62±3.56	<0.01	89.26±6.18	-7.70±1.86	<0.01	<0.01
5 min after intubation	102.29±6.83	6.74±2.84	95.42±7.90	-0.14±4.88	<0.01	84.53±5.72	-7.91±2.44	<0.01	<0.01
10 min after intubation	97.38±3.36	1.82±2.41	89.45±8.11	-6.37±6.00	<0.01	80.44±5.56	-16.13±3.76	<0.01	<0.01

TABLE 5 **RATE PRESSURE PRODUCT**

	Control group		F2 Group			F4 Group			
	Mean±S.D. (mmHg)	% change from base line	Mean+/S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	Mean±S.D. (mmHg)	% change from base line	'p' Value w.r.t. control	'p' Value w.r.t. F2
Baseline	10134.80±		10098.16		NS	10115.52±23		NS	NS

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	2197.11		±2433.92			77.49			
After pre medication	11744.76± 2418.71	16.16±3. 19	11706.28 ±2682.77	16.26±3 .25	NS	11726.48±16 39.50	16.25±3. 89	NS	NS
After fentanyl	11758.20± 2398.49	16.35±3. 40	10682.00 ±2259.45	7.99±21 .78	<0. 05	9993.36±232 7.14	- 1.06±2.8 5	<0.0 1	NS
After thiopenton e Na	11033.32± 2209.41	9.67±8.8 5	10612.32 ±2055.38	6.53±10 .49	NS	9528.72±227 3.14	- 5.80±2.9 5	<0.0 1	<0. 05
Just before laryngosco py	10891.60± 2066.08	8.34±8.3 5	10573.52 ±2570.74	5.00±7. 26	NS	8877.52±215 3.86	- 12.30±3. 35	<0.0 1	<0. 01
Immediatel y after intubation	20817.68± 4521.73	105.63± 7.58	17353.72 ±4224.14	71.80±5 .85	<0. 01	14817.68±35 70.29	46.49±7. 25	<0.0 1	<0. 01
1 min after intubation	20091.84± 4193.08	98.89±1 0.00	15734.08 ±3805.09	55.80±5 .99	<0. 01	12322.30±32 58.30	22.28±2 0.69	<0.0 1	<0. 01
2 min after intubation	17666.00± 4593.82	74.62±2 5.98	14428.40 ±3533.64	42.90±7 .33	<0. 01	10889.48±25 54.16	7.77±3.5 6	<0.0 1	<0. 01
3 min after intubation	15458.72± 3344.93	52.65±4. 02	13239.84 ±3266.13	31.17±8 .57	<0. 01	9831.16±231 6.73	- 2.75±2.6 7	<0.0 1	<0. 01
5 min after intubation	12600.08± 3075.33	24.20±7. 30	11609.76 ±2850.28	15.20±1 0.09	NS	8716.12±204 8.69	- 13.72±3. 43	<0.0 1	<0. 01
10 min after intubation	10445.84± 2018.00	3.70±5.6 1	10270.20 ±2559.44	2.00±11 .09	NS	7808.44±179 4.49	- 22.46±6. 16	<0.0 1	<0. 01

TABLE 6 **ADVERSE EFFECTS**

Adverse effects	Number of patients with adverse effects					
	Control group (n=50)	F2 Group (n=50)	'p' w.r.t control	F4 Group (n=50)	'p' w.r.t control	'p' w.r.t F2
Chest wall rigidity with apnea	0	0	NS	3	NS	NS
Dysrhythmias	8	2	<0.05	3	NS	NS

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Hypotension	1	2	NS	6	NS	NS
Post operative vomiting	0	2	NS	6	<0.05	NS
Post operative respiratory depression	0	0	NS	2	NS	NS

DISCUSSION

Laryngoscopy and endotracheal intubation constitute a strong nociceptiye stimulus resulting in untoward effects like increase in heart rate, blood pressure, intracranial tension, intraocular tension and dysrhythmias which might prove hazardous in susceptible patients.

Various methods to attenuate these sympathetic response to laryngoscopy and intubation have been studied like:

- Deepening planes of anaesthesia.
- Topical anaesthesia of larynx. Regional nerve blocks (eg blockade of superior laryngeal and glossopharyngeal nerves).
- Vasoactive agents like ganglion blockers (trimethaphan), centrally acting drugs (clonidine), sympathetic blockade (metoprolol, esmolol, etc.) and vasodilators (hydralazine, sodium nitroprusside, nitroglycerine).
- Intravenous lignocaine, calcium channel blockers.

All of these have their own disadvantages and an optimal agent is difficult to recommend for a given patient.

Studies (eg Atweh and Kuhar, 1977) have shown high concentrations of opiate receptors in the solitary nucles and the nuclei of IX and X cranial nerves associated with visceral afferent fibres of these nerves which originate in pharynx and larynx. Further, vagal motor nuclei involved in monosynaptic pharyngeal and laryngeal motor reflexes also have a high concentration of opiate receptors. These receptors provide a possible mechanism for the effect of narcotics in blunting the response to laryngeal stimulation.

A number of opioids including fentanyl, eufentanil, alfentarul, refentanil are being extensively studied since then. Various studies have used fentanyl in a wide range ie. 2-20g/kg va adjuvant to blunt pressor response with varied results and complications We

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too chose fentanyl, a phenylpiperidine derivative and synthetic opioid agonist because of its intense analgesic potency, cost effectivity, short time of onset and duration of action and lack of direct myocardial depressant effect with minimum circulatory changes. Moreover it does not cause histamine release and does not increase intracranial pressure during controlled ventilation.

The present study was an open comparative trial to compare the efficacy of two different doses of fentanyl, 2ug/kg and 4ug/kg, to attenuate the pressor response.

The study population of 150 ASA-1 patients, 18-50 years of either sex was divided into three equal groups (Control Group, F2 Group and F4 Group). All patients had standard protocol for premedication (ie. Ing. glycopyrrolate 0.004mg/kg, Inj, ranitidine 1mg/kg, Inj metoclopramide 0.2mg/kg) and Induction. The study drug was administered at zero time and the subsequent standard protocol for induction was such that laryngoscopy was started at 3½-4 minutes after administration of fentanyl.

Pulse, systolic blood pressure, diastolic blood pressure were recorded at different time intervals. Mean arterial pressure and rate pressure product were also calculated. All values were expressed as mean ± SD. The results were calculated as percentage change w.r.t. baseline values at different time intervals.

Heart rate (HR)

The administration of study drug and thiopentone sodium was associated with increase in heart rate from baseline in all three groups Control (by 16.5726.08%), F2 (11.9316.33%) and F4 (5.7842.33%) However, the increase in heart rate was much less with F4 group and this was significant w.rt. Control group: $p<0.05$

Immediately after laryngoscopy and intubation, heart rate increased in all three groups. The maximum percentage change from baseline pulse in F2 and F4 groups (33.0614.27% and 21.33612.95% respectively) was significantly less than that in the Control group (46.14±4.36%), $p<0.01$

At the end of 5 minutes, there was a significant fall from maximum values in both F2 (14 9413.95%) and F4 (0.53+2.30%) as compared to Control group (17.0316.61%)

At the end of study i.e. after 10 minutes of intubation, the heart rate value was below baseline in F4 (-4.491231%) compared to F2 (-7.9114.62%) and Control groups (-2.74-3.73%).

At each of the above time periods except after the administration of thiopentone, the increase in heart rate after F4 was significantly less than F2. 'p'<0.05.

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Thus both F2 and F4 blunted tachycardia in response to intubation sequence, however F4 blunted it more effectively and rapidly. With F4, the heart rate approached baseline values after 5 minutes of intubation, however, with F2 it was still above baseline at the end of study period Le after 10 minutes of intubation.

Systolic blood pressure (SBP):

The administration of study drug and thiopentone sodium (just before laryngoscopy) was associated with greater fall in systolic blood pressure in both F2 (-6.10:13.78%) and F4 group (-19541264%) as compared to the Control group (-2.0115.64%), p<0.05 and 'p<0.01 respectively This difference between F2 and F4 was also highly significant with p<0.01

Following intubation, systolic blood pressure increased in all groups. The maximum percentage change from baseline systolic blood pressure in F2 and F4 groups (29.12±1.77% and 20.6413.81% respectively) was significantly less than that in Control group (40/7022.89%), 'p'<0.01. The intergroup difference between F2 and F4 at this time was also highly significant, p<0.01

At the end of 2 minutes after intubation, there was a significant fall from maximum values in both F2 (13.38341%) and F4 (0.97+2.37%) groups as compared to Control group (28.0014.61%), p <0.01. The difference between F2 and F4 was again highly significant, p <0.01

At the end of study, Le at 10 minutes after intubation, both F2 (-5.6616.67%) and F4 (-18.8416.34%) groups showed a significantly low systolic blood pressure compared to Control group (0.8923.18%), p<0.01 and this difference between F2 and F4 was also highly significant, p<0.01.

Thus both F2 and Ft were found to be effective in obtunding the stic blood pressure rise but Ft casing a thach greater and rapid fall t the above time periods p001 The systolic blood pr upproached near baseline values at 2 miratus after intubation with 4 but af 5 minutes after intubation with F2.

Diastolic Most presse (DB)

After giving study drug and thiopentone sodium and just below laryngoscopy there was a significant fall in diastolic blood pressure in both 12 (30413.56%) and F4 (-6.3012.63%) groups as compared to Control group (613132%), however the difference between F2 and F4 groups was not significant at this period of time

Immediately after laryngoscopy and, intubation, diastolic blood pressure increased in all three groups. The maximum percentage change from baseline diastolic blood pressure in F2 and F4 groups (23:45:3.22% and 20.174.81% respectively) was significantly less

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than Control group (35.9218.47%), p<0.01, however the difference between F2 and Fat this period was not significant.

At the end of 3 minutes, there was a significant fall from maximus valises in both F2 (6.3912.93%) and F4 groups (608:25%) than Control group (1474:242%) p001. In 14 group it is evident that diastolic blood pressure fell even below baseline. The difference betwem F2 and Ft groups was highly significant with p <0.01.

The end of study period showed diastolic blood pressure is be below baseline in both 12 (-69145.68%) and 14 (-14.0543.58%) groups as compared to Control group (2.5743.35%), p<0.01, the difference between 12 and 14 also again being highly significant

Thus except just before laryngoscopy and immediately after intubation, the increase in diastolic blood pressure at each of the above time periods was significantly less with F4 than with F2, p<0.01.

Mean arterial pressure (MAP)

After the administration of study drug and thiopentone sodium and just before laryngoscopy, there was a significant fall in mean arterial pre from baseline in both F2 (-4.3632.92%) and F4 (12.0512.23%) groups s compared to Control group (2.5713.34%), p<0.01 with the difference between F2 and F4 groups also highly significant with p<0.01

Immediately after intubation, mean arterial pressure incased in all 3 groups. The maximum percentage change from mean arterial pressure in both F2 (25.9411.99%) and F4 (20.3743.98%) groups were significantly less than Control group (37.9415.29%), p<0,01 Again the difference between F2 and F4 was highly significant with p<0.01

At the end of 3 minutes after intubation, there was a significant fall from maximum values in both F2 (6.6213.56%) and 4 (-7.00 1.86%) groups as compared to Control group (14.7711.50%), however the difference between F2 and F4 was also highly significant, p<0.01

The end of the study period showed mean arterial pressure to be below baseline in both F2 (-6.3746.00%) and F4 (16:13:376%) groups as compared to Control group (1.8212.41%) with p<0.01 The difference between 2 pod F4 was again highly significant, p<0.01

Thus it is concluded that both F2 and F4 decreased mean arterial pressure rise in response to laryngoscopy and intubation with F4 much more effective than F2 The mean arterial pressure came down to near baseline value after 2 minutes of intubation in F4 group, however, it took about 5 minutes in 12 group.

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Rate pressure product (RPP):

After the administration of study drug and thiopentone sodium and just before laryngoscopy, there was an increase in rate pressure product from baseline in Control and F2 groups (8.3418.35% and 5.00:7.26% respectively). but a fall in F4 group (-12.303 35%) The difference between Control and F groups and that between F2 and F4 groups was highly significant, p<0.01

Immediately after intubation, rate pressure product increased in all groups The maximum percentage change from baseline rate pressure product in both F2 (71.805.85%) and F4 (46.4917.25%) was significantly less than the Control group (105.6347.58%), p<0.01 The difference between F2 and F4 groups was also highly significant with p <0.01

At the end of 3 minutes of intubation, there was a significant fall from maximum values in both F2 (31.1728.57%) and 4 (-27522.67%) groups as compared to Control group (52.654.02%). In F4 group, it is evident that rate pressure product tell even below baseline. The difference between 2 and 14 groups was also highly significant, p<0.01

At the end of study period, rate pressure product still remained significantly below baseline in Ft group (-22:46:6.56%) but not in F2 group (2.00:11.09%) as compared to Control group (3.705.61%).

Thus both F2 and F4 significantly attenuated the rate pressure product changes during intubation sequence, however F4 had significantly lower rate pressure product values compared to F2 because of the greater reduction in both systolic blood pressure and heart rate in F4 group.

We compared our study with the following previous studies

1) N. Dahlgren and K. Messeter (1981)[5]

They studied the efficacy of fentanyl 5ug/kg i.v. to attenuate stress response Systolic blood pressure

In their study, following administration of fentanyl 5pg/kg and thiopentone, there was an initial decrease in mean systolic blood pressure from baseline value of 151mmHg to 123mmHg Le, a decrease of 18.55% from baseline, which did not differ significantly from Control group (14.38% decrease).

In our study: In Control group-decrease by 2.01%

In F2 group-decrease by 6.10%

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In F4 group-decrease by 19.54%

Highest mean systolic blood pressure values post-induction showed a minimal rise from baseline value of 151mmHg to 153mmHg Le, an increase by 1.32% from baseline.

In our study : In F2 group-29.12% increase

In F4 group-20.64% increase

One minute after intubation, mean systolic blood pressure decreased from baseline value by 7.95%

In our study: In F2 group-increase by 20.33% from baseline

In F4 group-increase by 8.77% from baseline

Lowest mean systolic blood pressure value after intubation (10-15 minutes) was 25 16% less from baseline value of 151mmHg.

In our study, at 10 minutes after intubation,

In F2 group-decrease by 5.66% from baseline

In F4 group-decrease by 18.84% from baseline

Diastolic blood pressure

In the study by N. Dahlgren and K. Messeter, following administration of fentanyl Sug/kg and thiopentone, there was an initial decrease in mean diastolic blood pressure from baseline value of 77mmHg to 73mmHg i.e. a decreased by 5.2% from baseline.

In our study: In F2 group-decrease by 3.04%

In F4 group-decrease by 6.30%

Highest mean diastolic blood pressure values post intubation showed a rise from baseline value of 77mmHg to 95mmHg ie, an increase by 23.37% from baseline

In our study : In F2 group-Increase by 23.45% from baseline

In F4 group-Increase by 20.17% from baseline

One minute after intubation, mean diastolic blood pressure was 3mm g above baseline value of 77mmHg ie. 3.89% above baseline.

In our study: In F2 group - an increase by 15.28%

In F4 group-an increase by 10.21%

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Lowest mean diastolic blood pressure values after intubation (10-15 minutes) was 12.98% less from baseline.

In our study: In F2 group-6.91% less from baseline

In F4 group - 14.05% less from baseline

Heart rate (HR)

Changes in heart rate in the study done by N Dahlgren and K. Messeter followed the same pattern as blood pressure.Following administration of fentanyl Sug/kg and thiopentone, there was an increase in heart rate from a baseline value of 73/min to 81/min Le an increase by 10.95% from baseline.

In our study: In F2 group- an increase by 11 83%

In F4 group-an increase by 8.98%

Highest mean heart rate values after intubation showed a rise from baseline value of 73/min to 85/min i.e. an increase by 16.43% from baseline.

In our study: In F2 group-increase by 33.06% from baseline

In F4 group - increase by 21.36% from baseline

One minute after intubation, mean heart rate was 10.95% above baseline.

In our study: In F2 group-29.44% above baseline

In F4 group-12.37% above baseline

Lowest mean heart rate value after intubation (10-15 minutes) was 4.10% below baseline.

In our study: In F2 group-7.91% above baseline.

In F4 group - 4.49% below baseline.

Mean Arterial Pressure (MAP)

In the study by N. Dahlgren and K. Messeter, following administration of fentanyl Sug/kg and thiopentone and before laryngoscopy, there was a decrease in mean mean arterial pressure from baseline value of 101mmHg to 89mmHg Le, a decrease by 11.88% from baseline.

In our study: In F2 group-decrease by 4.36% from baseline

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In F4 group-decrease by 12.05% from baseline

Highest mean MAP value after intubation showed a rise from baseline value of 101mmHg to 114mmHg Le an increase by 12.87% from baseline

In our study : In F2 group-an increase by 25.94% from baseline

In F4 group- an increase by 20.37% from baseline

One minute after intubation, mean MAP was 100mmHg te 0.99% less than baseline value.

In our study, one minute after intubation: In F2 group-17.49% above baseline
In F4 group-9.56% above baseline

In our study, 2 minutes after intubation: In F2 group-11.92% above baseline

In F4 group-1.16% above baseline

Thus in our study, mean MAP in F4 group took a little more time to approach baseline value

Lowest mean MAP value after intubation (10.15 minutes) was 18.81% less

from baseline.

In our study, at 10 minutes after intubation,

In F2 group-6.37% less from baseline

In F4 group-16.13% less from baseline

Thus results in our study were comparable with that in the study conducted by N. Dahlgren and K. Messeter.

Regarding adverse effects in the study conducted by N. Dahlgren and K. Messeter, two patients in the Control group and one patient in the fentanyl 5ug/kg group developed transitory supraventricular extrasystoles as response to laryngoscopy and intubation.

2) Steven M. Helfmann et al (1991)[3]

This study compared lidocaine, fentanyl (25µg/kg) and esmolol to prevent tachycardia and hypertension associated with tracheal intubation. After laryngoscopy and intubation, anaesthesia was maintained with 1 MAC isoflurane in 60% nitrous oxide and oxygen at a 5 litre/min flow for 10 minutes.

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Heart rate (HR)

Following administration of thiopentone, fentanyl (2.5µg/kg) and succinylcholine, just before laryngoscopy, there was an increase in mean heart rate by 24% from baseline

In our study:

In F2 group-an increase by 11.83% from baseline

In F4 group-an increase by 8.98% from baseline The more increase by mean heart rate just before laryngoscopy in this study might be because laryngoscopy was done at 2 minutes after giving fentanyl whereas in our study laryngoscopy was done after about 35-4 minutes after giving fentanyl.

In this study by Steven M. Helfmann et al, highest mean heart rate value was

observed at about 1 minute after induction and was 37% above baseline.

In our study: In F2 group-29.44% above baseline

In F4 group-12.37% above baseline

At 5 minutes after intubation, mean heart rate value was 20% above baseline.

In our study: In F2 group-14.94% above baseline

In F4 group-0.53% above baseline

At 10 minutes after intubation, mean heart rate value was 7% above baseline

In our study: In F2 group-7.91% above baseline

In F4 group-4.49% below baseline

Thus the higher post-induction mean heart rate values in this study which used fentanyl 2.5µg/kg as compared to fentanyl 2µg/kg used in our study might be because of isofluorane used for maintenance in this study as it causes reflex baroreceptor mediated tachycardia.

Systolic blood pressure (SBP):

Following administration of thiopentone, fentanyl (2.5µg/kg) and succinylcholine and just before laryngoscopy, there was a fall in systolic blood pressure by 8% from baseline.

In our study:

In F2 group - fall by 6.10% from baseline In F4 group-fall by 19.54% from baseline

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Highest mean systolic blood pressure value after laryngoscopy and intubation was found at about 1 minute after intubation and was about 12%. above baseline.

In our study, at 1 minute after intubation,

In F2 group-20.33% above baseline

In F4 above baseline

At 5 minutes after intubation, mean systolic blood pressure value was 10% below baseline.

In our study:

In F2 group -0.08% below baseline

In F4 group - 14% below baseline

At 10 minutes after intubation, mean systolic blood pressure value was 21% below baseline.

In our study:

In F2 group-5% below baseline

In F4 group - 18% below baseline

Thus in this study, the trend was in the direction of lower systolic blood pressure levels with fentanyl 2.5µg/kg as compared to fentanyl 2µg/kg used in our study; even at 10 minutes after intubation, mean systolic blood

pressure with fentanyl 2.5µg/kg used in this study was lower as compared to mean systolic blood pressure with fentanyl 4µg/kg used in our study.

This trend towards lower mean systolic blood pressure might be due to the synergistic effect of fentanyl and isofluorane, used for maintenance in this stuy.

Adverse effects such as severe bradycardia, hypotension, rigidity or seizures did not occur in this study.

3) Randall C. Cork et al (1984)[6]

This study examined the use of low-dose fentanyl (5ug/kg) during rapid- sequence induction to attenuate the stress response. Fentanyl was given as lug/kg/min during 3 minutes of pre-oxygenation and final fentanyl dose of lug/kg was given during induction (total fentanyl dose 5µg/kg).

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Heart rate:

The mean heart rate value at 1 minute after intubation increased from

81/min (baseline) to 92/min i.e. increased by 13.58% from baseline.

In our study

In F2 group-increased by 29.44% from baseline In F4 group increased by 12.37% from baseline

In mean heart rate at 4 minutes after intubation was same as baseline value.

In our study, at 3 minutes after intubation: In F2 group-14.94% above baseline In F4 group-0.53% above baseline

Systolic blood pressure (SBP):

The mean systolic blood pressure 1 minute after intubation increased from 150mmHg (baseline) to 159mmHg ie. increased by 6%.

In our study:

In F2 group-increased by 20.33% from baseline In F4 group increased by 8.77% from baseline

The mean systolic blood pressure at 4 minutes after intubation was 6.66% below baseline.

In our study, at 3 minutes after intubation:

In F2 group-6.92% above baseline

"In F4 group-8.17% below baseline

Diastolic blood pressure:

The mean diastolic blood pressure at 1 minute after intubation increased from 82mmHg (baseline) to 92mmHg i.e. increased by 12.19% from baseline.

In our study:

In F2 group - increased by 15.28% from baseline In F4 group - increased by 10.21% from baseline

Thus the slightly lower systolic blood pressure and diastolic blood pressure seen fentanyl 4ug in our study as compared to systolic blood pressure and diastolic blood

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pressure seen with fentanyl 5ug/kg used in this study might be because in our study we gave fentanyl an intravenous bolus dose our 90 seconds, whereas in this study fentanyl was given over a period of 4-5 minutes.

Mean arterial pressure (MAP):

The mean MAP at 1 minute after intubation increased from 105mg (baseline) to 114mmHg i.e. increased by 8.57% from baseline.

In our study:

In F2 group - increased by 17.49% from baseline In F4 group - increased by 9.56% from baseline

The mean MAP at 4 minutes after intubation was 5.71% below baseline.

In our study, at 3 minutes after intubation:

In F2 group-6.62% above baseline In F4 group -7.00% below baseline

Rate pressure product (RPP):

The mean rate pressure product at 1 minute after intubation increased from 121 torr/min (baseline) to 14.9 torr/min i.e. increased by 23.14% from baseline.

In our study:

In F2 group - increased by 55.80% from baseline In F4 group - increased by 22.28% from baseline.

The mean rate pressure product at 4 minutes after intubation was 11.6 torr/min i.e. a decrease by 4.13% from baseline.

In our study:

In F2 group - an increase by 31.17% from baseline In F4 group - an increase by 2.75% from baseline

In this study, none of the patients in the fentanyl group lost consciousness during fentanyl preloading and none developed chest wall rigidity.

4) K. Sam Chung et al (1992)[7]

This study compared the ability of a combination of fentanyl and esmolol to blunt pressor response with that of either agent alone ie. a comparison among:

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Fentanyl 2µg/kg

ii) Esmolol 2mg/ kg

Combination of fentanyl 2ug/kg and esmolol 2mg/kg and

iv) Fentanyl 5µg/kg

Heart rate:

Following intubation, the maximum percentage change from baseline heart rate was 16% in fentanyl 5ug/kg group and 22% in fentanyl 2ug/kg group.

In our study, maximum percentage change from baseline was

In F2 group-33.06% In F4 group-21.36%

Blood pressure (systolic blood pressure and diastolic blood pressure):

Following intubation, maximum percentage change from baseline, systolic blood pressure was 6% in fentanyl 5ug/kg group and 24% in fentanyl 2µg/kg group.

In our study, maximum percentage change from baseline systolic blood pressure was:

In F2 group-29.12%

In F4 group-20.64%

In general, diastolic blood pressure paralleled changes in systolic blood pressure throughout the study period which was also seen with our study for both F2 and F4 group.

Thus in this study, the maximum percentage change in heart rate, systolic blood pressure and diastolic blood pressure with both fentanyl 2µg/kg and fentanyl 5µg/kg was less than that found in our study with fentanyl 2µg/kg and fentanyl 4µg/kg.

This might be because in this study, 1 minute after intubation, 1% isofluorane and 70% nitrous oxide were used and moreover this study used fentanyl 5µg/kg whereas we used fentanyl 4µg/kg.

In this study, except for one case of apnoea requiring assisted ventilation before induction in the fentanyl 5ug/kg group, there were no other adverse events i.e. severe bradycardia, hypotension, chest wall rigidity or post surgical respiratory depression.

Adverse effects:

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McClain[8] reported apnoeic episodes in 4/7 patients who received 3.2- 6.5ug/kg fentanyl. K Sam Chung et al (1992)[7] found one case of apnoea requiring assisted ventilation before induction in the fentanyl 5µg/kg group (out of total 26 patients).

In our 3/50 patients in F4 group had chest wall rigidity with apnoea following fentanyl-thiopental administration and required assisted ventilation.

In a study of fentanyl at increasing doses of 0, 2, 5, 10 and 15µg/kg (lyer V, Russell W)[9], it was found that doses >5µg/kg were associated with an 11- 45% incidence of hypotension (MAP 70mmHg). In the study done by Donald E Martin et al (1982)[10], 7/18 patients given fentanyl-thiopental (Sug/kg and 3mg/kg); and 4/18 patients given thiopentone (6mg/kg) alone required ephedrine to treat hypotension before intubation. In our study, hypotension following fentanyl-thiopentone administration was seen in 12%, 4% and 2% patients in F4, F2 and Control group respectively.

In the same study done by Donald E Martin et al (1982)[10], 1/18 patients given fentanyl-thiopentone and 3/18 patient given thiopentone alone thiopentone alone had arrythmias related to intubation. In the study conducted by N Dahlgren and K Messenter (1981)[5], 2/7 patients in the control group and 1/8 patient in fentanyl 5ug/kg group developed transitory supraventricular extrasystoles as response to laryngoscopy and intubation. In our study, 18%, 6% and 4% patients had dysrythmias during induction sequence in Control, F4 and F2 groups respectively and all were self-limited.

Steven M Helfmann et al (1991)[3] did not find any adverse effects in his study. Similarly in the study conducted by Randall C Cork et al (1984)[6] none of the patients in fentanyl group lost consciousness during fentanyl preloading and none developed chest wall rigidity. Again, except for one case of apnoea in the fentanyl 5ug/kg group, there were no adverse events in the study conducted by K Sam Chung et al[7].

CONCLUSION

We conclude that fentanyl 4µg/kg i.v. provides more effective suppression of heart rate and blood pressure responses to laryngoscopy and intubation than fentanyl 2ug/kg as follows:

1) The maximum percentage change following laryngoscopy and intubation from baseline pulse, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product with F2 group was 33.06+4.27%, 29.12+1.77%, 23.45+3.22%, 25.94 +1.99% and 71.8015.85% respectively whereas with F4 group it

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was 21.33±2.95% p<0.05), 20.6413.81% (p<0.01), 20.1744.81% ('p' N.S.), 20.37+3.90% (p<0.01) and 46.49+7.25% (p<0.01) respectively.

2) Similarly with F4, the heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product approached baseline values after 5 minutes, 2 minutes, 3 minutes, 2 minutes and 3 minutes of intubation respectively. However with F2, all these variables took longer time to reach baseline values after intubation, the heart rate and rate pressure product were above baseline even after 10 minutes of intubation while systolic blood pressure, diastolicblood pressure and mean arterial pressure each approached baseline values after 5 minutes of intubation.As an index of myocardial oxygen consumption, changes in rate pressure product occurring in our patients in the Control group imply increased myocardial oxygen consumption which has an association with myocardial ischaemia. Our study reveals that fentanyl 4µg/kg provides bettr: protection than fentanyl 2µg/kg in this regard too.

Although fentanyl 4ug/kg was more effective than fentanyl 2µg/kg, it too was only partially effective in blunting haemodynamic response to laryngoscopy and intubation and did not consistently provide haemodynamic stability, and was also associated with a few adverse effects in some of the patients like chest wall rigidity, hypotension, postoperative respiration depression though not significant statistically ('p'>0.05).

Further increasing the dose of fentanyl hold the theoretical possibility of increased incidence of some potentially disturbing side effects such as chest wall rigidity with apnoea, bradycardia (central vagomimetic effect) and 60

: hypotension and the well documented post anaesthetic prolonged and recurrent respiratory depression especially after relatively short surgical procedures lasting less than 2 hours.

Follow-up studies evaluating the safety and efficacy of fentanyl 4µg/kg and higher doses in higher risk patients are warranted.

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