Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1): 122-134
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.18

Comparative Study between Intravenous Clonidine and Intravenous Fentanyl to Attenuate Hemodynamic Response to Laryngoscopy and Tracheal Intubation

Smita Joshi[1], Harshi S. Shah[2], Rakesh. D[3]

[1]Professor [2]Senior Resident [3]Junior Resident, Department of Anaesthesiology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune, Maharashtra 411018, India.

Abstract

Background: Laryngoscopy and intubation are associated with acute hemodynamic responses. In susceptible patients even this short period (2-7 minutes) of hypertension and tachycardia can result in myocardial ischemia or increased intracranial pressure. *Aims and objectives:* To evaluate and compare the effect of intravenous (I.V.) Fentanyl and intravenous (I.V.) Clonidine in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation. *Settings and design:* This study was designed to compare the effect of I.V. Fentanyl and I.V. Clonidine in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation in adult patients undergoing elective surgeries under general anaesthesia. *Methods and material:* A prospective, randomized, double-blind, comparative study was conducted on 60 patients, randomly allocated into two groups of 30 each i.e. group C and group F receiving 2mcg/kg Clonidine and 2mcg/kg Fentanyl, respectively, 5 minutes prior to induction. Hemodynamic parameters and postoperative sedation scores were recorded. *Statistical analysis:* Mean ± standard deviation for quantitative continuous data and compared by unpaired t-test. *Result:* The hemodynamic variables in Fentanyl group were significantly lower than Clonidine group for the first five minutes after laryngoscopy and intubation. *Conclusion:* Both fentanyl and clonidine were able to attenuate the hemodynamic response to laryngoscopy and intubation, however, fentanyl 2 mcg/kg I.V. given 5 min prior to intubation kept the hemodynamic variables significantly lower than those seen in clonidine 2 mcg/kg I.V. given 5 min prior to intubation. However, after 5 min of intubation the effects of both the drugs were comparable.

Keywords: Clonidine; Endotracheal Intubation; Fentanyl; Hemodynamic Response; Laryngoscopy.

How to cite this article:

Smita Joshi, Harshi S. Shah, Rakesh. D. Comparative Study between Intravenous Clonidine and Intravenous Fentanyl to Attenuate Hemodynamic Response to Laryngoscopy and Tracheal Intubation. Indian J Anesth Analg. 2019;6(1):122-134.

Introduction

Direct laryngoscopy and endotracheal intubation are known to cause sympathoadrenal stimulation which manifests as hypertension and tachycardia [1]. This response occurs 30 seconds (sec) after starting laryngoscopy and intubation and lasts for less than 10 minutes (min) [2]. If no specific measures are taken to attenuate these hemodynamic responses, the pulse rate can increase from 26% to 66% depending on the method of induction, and arterial systolic blood pressure can increase from 36% to 45% [3,4]. Also, it is previously reported that 10%–18% of the patients develop ischemic ST-segment changes during the procedure, making it important to blunt this response [5].

Corresponding Author: Harshi S. Shah, Senior Resident, Department of Anaesthesiology, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune, Maharashtra 411018, India.

E-mail: shahharshi91@gmail.com

Received on 26.09.2018, **Accepted on** 16.10.2018

Complications resulting from these hemodynamic events include left ventricular dysfunction, [6,7] hypertensive crisis, [8] pulmonary oedema,[8] cardiac dysrhythmias, [3,9] myocardial ischemia, [10,11] and myocardial necrosis [11].

Over the years, various pharmacological and non – pharmacological methods have been used to attenuate this hemodynamic response [12]. These include shorter duration of laryngoscopy, smooth and gentle intubation, McCoy laryngoscope, use of intravenous opioids, [13] vasodilators, [14] calcium channel blockers, [15] intravenous and topical lignocaine and adrenoceptor blocking drugs alone or in combination with other drugs. However, none of the above approaches or agents have proved to be ideal. Hence, the search for an ideal agent to attenuate the hemodynamic responses is still continuing.

Clonidine, an imidazoline derivative, is a centrally acting selective partial alpha-2 adrenergic receptor agonist (220:1 - alpha-2 to alpha1 receptor preference) [16]. It has sedative, analgesic and antihypertensive actions [17]. It binds to the alpha 2A receptors and mediates these effects. It stimulates alpha 2A inhibitory neurons in the medullary vasomotor centre. As a result, there is decrease in sympathetic nervous system outflow from central nervous system (CNS) to peripheral tissues. This is manifested as peripheral vasodilatation and decreases in systemic blood pressure, heart rate and cardiac output. The alpha-2 receptors are present in high density in the pontine locus coeruleus, inhibition of which is responsible for the sedative effects of clonidine. It blunts reflex tachycardia associated with direct laryngoscopy, decreases intraoperative lability of blood pressure and heart rate, decreases plasma catecholamine concentrations, and dramatically decreases anaesthetic requirements for inhaled (Minimum Alveolar Concentration, MAC) and injected drugs [16]. Therefore, clonidine seems well suited as premedication for attenuating hemodynamic response associated with laryngoscopy and intubation.

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist structurally related to meperidine. As an analgesic, it is 75-125 times more potent than morphine. It produces analgesia by binding to specific G protein-coupled receptors located in the brain and spinal cord regions involved in transmission and modulation of pain and also acts on opioid receptors on peripheral sensory nerve endings [18]. High concentrations of opioid receptors are present in the solitary nuclei and the nuclei of the 9th and 10th cranial nerves, associated with the visceral afferent fibres of these nerves which originate in the pharynx and larynx. These receptors provide a possible mechanism for blunting of the response to laryngeal stimulation [19,20]. Fentanyl reduces heart rate and decreases blood pressure and cardiac output. It reduces the dosing requirement for the volatile agents. Peak analgesic effect is achieved after 5 min of I.V. administration.

This randomized prospective study has been designed to compare the effects of I.V. fentanyl with I.V. clonidine on the changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) observed during laryngoscopy and tracheal intubation.

Materials and Methods

This prospective, randomized, double-blind, comparative study was conducted on 60 adult patients undergoing elective surgeries under general anaesthesia with endotracheal intubation.

Patients belonging to ASA (American Society of Anaesthesiologists) physical status I and II, aged between 20 to 50 years of either sex and hemodynamically stable patients with all routine investigations within normal limits were included in the study. Patients belonging to ASA physical status III or more, posted for emergency surgery, those who refused to participate, patients with anticipated difficult intubation, patients on antihypertensive medication, patients on any opioid or any sedative medication in the week prior to the surgery, patients who were known to be allergic to any of the test drugs, pregnant patients, patients with cardiovascular, respiratory, renal, hepatic or endocrine diseases were excluded from the study.

Data Collection

Sample Size

Sample size was calculated using Winpepi statistical package at significance level of 5% with power of 80% using the inputs given below –

According to study "Comparison of Fentanyl and Clonidine for Attenuation of the Haemodynamic Response to Laryngoscopy and Endotracheal Intubation", conducted by Sameenakousar et al. [21] we took the following inputs –

Heart Rate (beats per minute)	Fentanyl (Mean±SD)	Clonidine (Mean±SD)
Immediately after laryngoscopy and intubation	101.14±15.01	86.88±10.00

Standard Deviation (SD) of heart rate immediately after laryngoscopy for fentanyl was 15.01, Standard Deviation of heart rate immediately after laryngoscopy for clonidine was 10.0, and difference in mean heart rate between two groups immediately after laryngoscopy was 14.26, hence we arrived at a minimal sample size of 26 patients.

Hence, we enrolled a total of 60 patients (30 in each group) to account for potential dropouts or protocol violation.

Selection Method

Randomization was done. Patients were divided into two groups using computer generated random number table, where -

Group C received I.V. Clonidine 2 mcg/kg and Group F received I.V. Fentanyl 2 mcg/kg.

Method of Blinding

The patients were unaware of which study drug group they belonged to. The study drug syringes were prepared by a separate anaesthesiologist who was not involved in the study procedures. Therefore, the anaesthesiologist who administered the drugs and assessed the parameters was blinded to the study drugs. Also, the syringes were identical and the colours of the drugs were the same.

Methods

Institute Ethical Committee approval was obtained. After obtaining written informed consent from every case selected for the study, pre-anaesthetic evaluation of the patient was done and necessary investigations were sent and reviewed, a day prior to surgery. The patients were enrolled for the study according to the inclusion and exclusion criteria. These were then randomly allocated to one of the two study groups according to the drug to be used:-

Group C - received intravenous clonidine 2 mcg/kg diluted in 10 ml normal saline, given slowly I.V., 5 minutes prior to induction of anaesthesia.

Group F - received intravenous fentanyl 2 mcg/kg diluted in 10 ml normal saline, given slowly I.V., 5 minutes prior to induction of anaesthesia.

Patients were kept fasting as per standard NPO (nil per oral) guidelines. On arrival in the operative room, Ringer lactate infusion was started through 20 G I.V. cannula. Electrocardiograph (ECG), peripheral oxygen saturation and non-invasive blood pressure monitors were attached to the patient and the patient's heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were noted (baseline values).

All patients were premedicated with injection (inj.) glycopyrrolate 0.004 mg/kg I.V. and inj. ondansetron 0.1 mg/kg I.V. Thirty patients were given inj. fentanyl 2 mcg/kg slowly I.V. diluted in 10 ml normal saline. Thirty patients were given inj. clonidine 2 mcg/kg slowly I.V. diluted in 10 ml normal saline, both 5 min prior to induction. After 3 minutes of preoxygenation with 100% oxygen, anaesthesia was induced with inj. propofol 2 mg/kg I.V. and inj. succinylcholine 2 mg/kg I.V. The duration of laryngoscopy and intubation was limited to 30 seconds in all the patients. After confirmation of proper placement of endotracheal tube, inj. vecuronium 0.1 mg/kg I.V. was given as a long acting muscle relaxant. Thereafter mechanical ventilation was continued throughout the procedure and anaesthesia maintained with 33% oxygen, 66% nitrous oxide, 0.5-1% isoflurane and intermittent boluses of vecuronium as a relaxant. No other procedure was performed or medication was administered during the first 15 minutes of data collection period after tracheal intubation. Intraoperative analgesia was provided with inj. paracetamol 15 mg/kg I.V. At the end of the surgery, neuromuscular blockade was reversed with inj. neostigmine 0.05 mg/kg I.V. and inj. glycopyrrolate 0.008 mg/kg I.V. followed by extubation.

In case of severe hemodynamic fluctuations, medical intervention other than adjustment of isoflurane was done. Hypotension was defined as a decrease in systolic BP (blood pressure) of more than 30 mmHg from baseline or a mean arterial pressure of less than 60 mmHg and was corrected with I.V. fluids and if required, with small doses of inj. mephentermine 3 mg I.V. Bradycardia was defined as a HR of less than 60/minute and was corrected, if associated with hemodynamic instability, with inj. atropine 0.6 mg I.V. Replacement of fluid loss was done with crystalloids or colloids and if blood loss was more than 20% of the blood volume it was replaced with appropriate quantity of cross matched blood.

Following parameters i.e. heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded at baseline, 5 min after administration of study drugs, after induction, at laryngoscopy and intubation (T0), 1 min after

intubation (T1), 3 min after intubation (T3), 5 min after intubation (T5), 10 min after intubation (T10), 15 min after intubation (T15). ECG was continuously monitored.

Ramsay Sedation Score was used to assess postoperative sedation:

1 = agitated, restless

2 = cooperative, tranquil

3 = responds to verbal commands while sleeping

4 = brisk response to glabellar tap or loud noise while sleeping

5 = sluggish response to glabellar tap or loud noise while sleeping

6 = no response to glabellar tap or loud noise while sleeping

Patients were monitored for side effects of both the drugs preoperatively, intraoperatively and postoperatively.

Statistical Analysis

Data were tabulated using Microsoft Excel 2010 software. Results were statistically analysed.

Categorical variables of gender, ASA physical status were analysed using Chi Square test. Continuous variables like age, weight, heart rate, blood pressure were analysed using unpaired t – test. p value < 0.05 was considered significant.

Results

The patients in both the groups did not show any statistically significant differences in their age, gender and weight distribution [Tables 1,2,3]. Also they were similar in terms of ASA grading [Table 4].

Baseline values (before administering any drug) of HR, SBP, DBP, MAP were comparable (p=0.30, p=0.29, p=0.74, p=0.36 respectively) in both the groups C and F [Table 5].

Demographic Profile of the two Groups:

Table 1: Comparison of Age Between the two Groups (Mean±SD)

Demographic Profile	Group C	Group F	p Value	Significance
Age (Years)	29.5±7.56	28.96±9.16	0.806	Not Significant

Table 2: Comparison of Gender Distribution Between the two Groups

Demographic Profile	Group C (%)	Group F (%)	p Value	Significance
Male	16 (53.33)	12 (40)	0.300	Not Significant
Female	14 (46.66)	18 (60)		

Table 3: Comparison of Mean Weight Between the two Groups (Mean±SD)

Demographic Profile	Group C	Group F	p Value	Significance
Weight (Kg)	52.23±6.15	51.86±5.91	0.814	Not Significant

Table 4: ASA Physical Status Distribution Between the two Groups

ASA Grade	Group C (%)	Group F (%)	p Value	Significance
I	19 (63.33)	16 (53.33)	0.432	Not Significant
II	11 (36.66)	14 (46.66)		

Hemodynamic Parameters

Table 5: Baseline Vital Parameters (Mean±SD)

Vital Parameters	Group C	Group F	p Value	Significance
Heart Rate (beats per minute)	91.67±4.26	92.9±4.90	0.30	Not Significant
SBP (mmHg)	123.53±7.83	121.4±7.72	0.29	Not Significant
DBP (mmHg)	75.26±6.31	74.73±6.57	0.74	Not Significant
MAP (mmHg)	91.35±4.17	90.28±4.82	0.36	Not Significant

Heart Rate [Table 6, Figure 1]

There was significant difference in heart rate values 5 min after administration of study drugs and after induction when the values were lower in group C and the difference was statistically significant ($p < 0.05$). However, at intubation (T0), 1 min and 3 min after intubation, the heart rate values were lower in group F and the difference was found to be statistically significant ($p < 0.05$). At 5 min, 10 min and 15 min after intubation, there was no statistically significant difference between the heart rate values of both the groups ($p > 0.05$).

Systolic Blood Pressure [Table 7, Figure 2]

There was significant difference in systolic blood pressure at intubation, 1 min and 3 min after intubation between the two groups. Values were relatively higher in group C and the difference was found to be statistically significant ($p < 0.05$). However, there was no statistically significant difference between group C and group F with respect to systolic blood pressure values at baseline, 5 min after administration of study drug and after induction and 5 min, 10 min and 15 min after intubation ($p > 0.05$).

Table 6: Changes in Heart Rates in two Groups (Mean ± SD)

Heart Rate	Group C	Group F	p Value	Significance
Baseline	91.67 ± 4.26	92.9 ± 4.90	0.30	Not Significant
5 min After Study Drug Administration	76.16 ± 4.23	84.23 ± 12.9	0.0025	Significant
After Induction	77.16 ± 4.57	81.63 ±10.58	0.04	Significant
At Intubation (T0)	86.26 ± 5.9	81.3 ± 10.07	0.02	Significant
1 min After Intubation (T1)	86 ± 3.98	81.16 ± 9.08	0.01	Significant
3 min After Intubation (T3)	84.73 ± 3.75	80.63 ± 7.81	0.01	Significant
5 min After Intubation (T5)	80.96 ± 6.03	78.33 ± 7.68	0.14	Not Significant
10 min After Intubation (T10)	79.8 ± 5.49	77.86 ± 7.27	0.25	Not Significant
15 min After Intubation (T15)	78.86 ± 5.33	77.93 ± 6.89	0.56	Not Significant

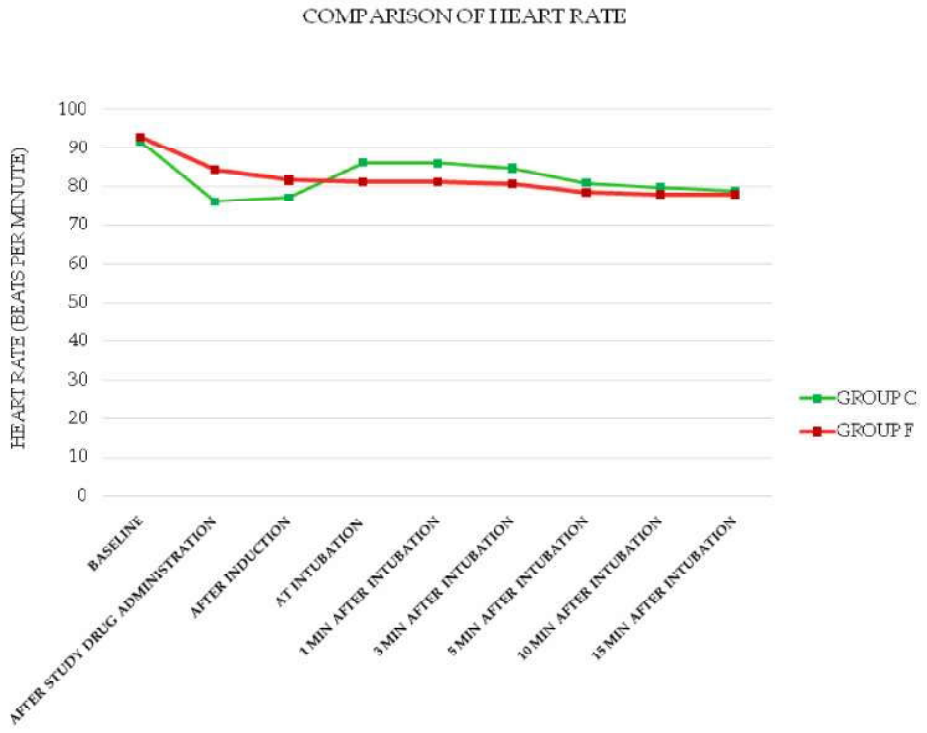

Fig. 1: Line diagram showing comparison of Heart rate between two groups

Diastolic Blood Pressure [Table 8, Figure 3]

Diastolic blood pressure values were relatively higher in group C at intubation, 1 min and 3 min after intubation and the difference was statistically significant ($p < 0.05$). All the other diastolic blood pressure readings did not show statistically significant difference ($p > 0.05$).

Table 7: Changes in Systolic Blood Pressure in two Groups (Mean±SD)

Systolic Blood Pressure	Group C	Group F	p Value	Significance
Baseline	123.53±7.83	121.4±7.72	0.29	Not Significant
5 min After Study Drug Administration	115.4±6.89	112.93±6.86	0.17	Not Significant
After Induction	107.06±5.57	104.8±5.13	0.10	Not Significant
At Intubation (T0)	113.66±5.46	109.53±6.98	0.01	Significant
1 min After Intubation (T1)	114.6±6.26	111.13±3.84	0.01	Significant
3 min After Intubation (T3)	114.66±4.40	111.46±5.96	0.02	Significant
5 min After Intubation (T5)	110.46±3.66	109.66±5.99	0.53	Not Significant
10 min After Intubation (T10)	108.06±4.77	106.26±3.99	0.11	Not Significant
15 min After Intubation (T15)	107.13±3.88	105.46±3.67	0.09	Not Significant

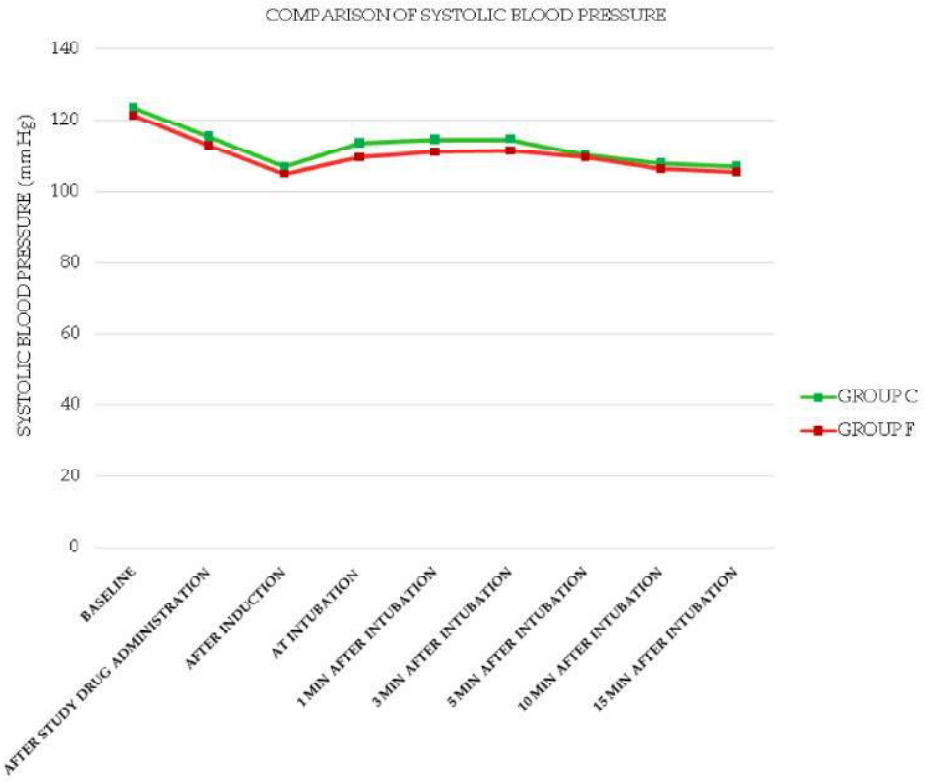

Fig. 2: Line diagram showing comparison of SBP between two groups

Table 8: Changes in Diastolic Blood Pressure in two Groups (Mean±SD)

Diastolic Blood Pressure	Group C	Group F	p Value	Significance
Baseline	75.26±6.31	74.73±6.57	0.74	Not Significant
5 min After Study Drug Administration	73.93± 3.76	72.66±6.06	0.33	Not Significant
After Induction	68.2±5.76	69.26±3.38	0.38	Not Significant
At Intubation (T0)	75±6.59	71±5.08	0.01	Significant
1 min After Intubation (T1)	73.2±6.29	69.73±3.88	0.01	Significant
3 min After Intubation (T3)	73.13±5.88	69.8±3.87	0.01	Significant
5 min After Intubation (T5)	73.13±5.42	71.4±3.86	0.15	Not Significant
10 min After Intubation (T10)	71.2±4.22	71.13±3.81	0.94	Not Significant
15 min After Intubation (T15)	69.73±3.81	70.33±3.24	0.51	Not Significant

Mean Arterial Pressure [Table 9, Figure 4]

A significant difference was noticed in the mean arterial pressure values between both the groups at intubation, 1 min and 3 min after intubation ($p < 0.05$). Values were relatively higher in group C. At all other times, both groups were not significantly different in terms of mean arterial

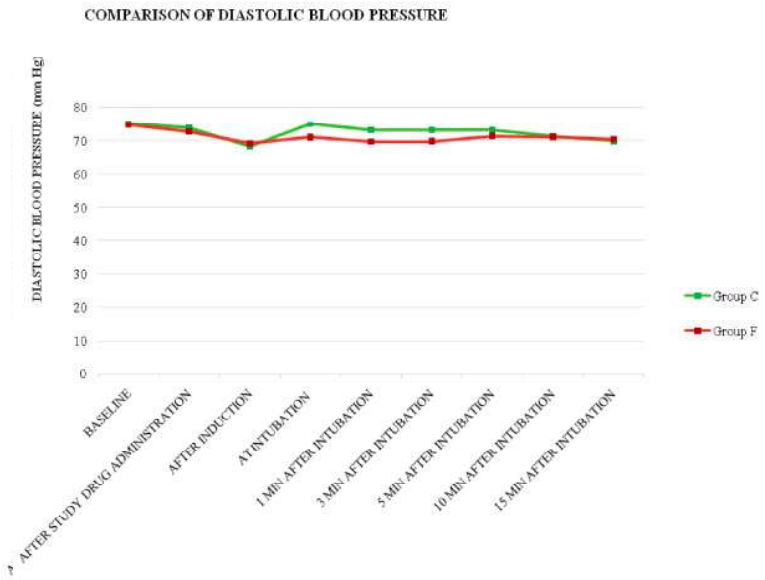

Fig. 3: Line diagram showing comparison of DBP between two groups

Table 9: Changes in Mean Arterial Pressure in two Groups (Mean ± SD)

Mean Arterial Blood Pressure	Group C	Group F	P Value	Significance
Baseline	91.35±4.17	90.28±4.82	0.36	Not Significant
5 min After Study Drug Administration	87.7±3.35	86.08±3.94	0.08	Not Significant
After Induction	81.15±3.70	81.11±2.52	0.95	Not Significant
At Intubation (T0)	87.88±4.48	83.84±4.37	0.00	Significant
1 min After Intubation (T1)	87±4.30	83.53±2.77	0.00	Significant
3 min After Intubation (T3)	86.97±4.28	83.68±3.55	0.00	Significant
5 min After Intubation (T5)	85.57±3.80	84.15±2.93	0.11	Not Significant
10 min After Intubation (T10)	83.48±3.04	82.84±2.87	0.40	Not Significant
15 min After Intubation (T15)	82.2±2.74	82.04±2.50	0.81	Not Significant

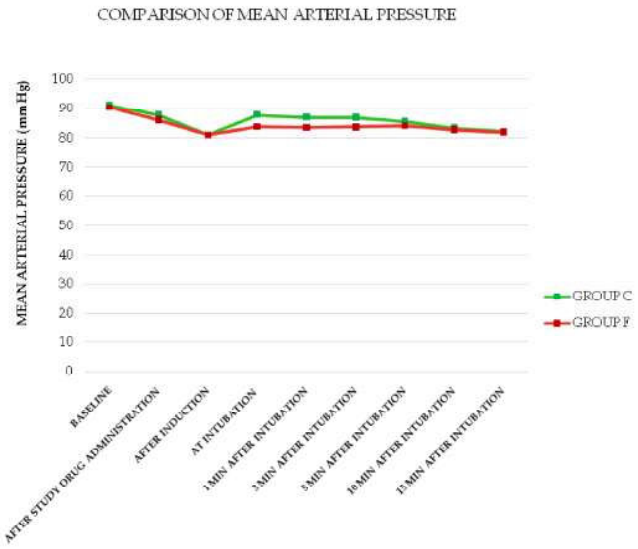

Fig. 4: Line diagram showing comparison of MAP between two groups

pressures (p >0.05).

Oxygen Saturation

There was no statistically significant difference between group C and group F with respect to SpO_2 values.

ECG

ECG was monitored continuously in all cases for both the groups. ECG was within normal limits throughout the procedures in all the patients.

Ramsay Sedation Scores [Table 10, Figure 5]

The values of Ramsay sedation score were recorded at fixed intervals in both the groups as shown in the table. There was significant difference

Table 10: Comparison of Ramsay Sedation Score Values of Patients in Both Groups (Mean ± SD)

Ramsay Sedation Score	Group C	Group F	p Value	Significance
Immediately After Surgery	3.06 ± 0.52	2.5 ± 0.57	0.00	Significant
15 Min After Surgery	2.9 ± 0.54	2.36 ± 0.61	0.00	Significant
30 Min After Surgery	2.7 ± 0.46	2.23 ± 0.50	0.00	Significant
45 Min After Surgery	2.6 ± 0.49	2.13 ± 0.57	0.00	Significant
60 Min After Surgery	1.86 ± 0.50	1.76 ± 0.43	0.41	Not Significant

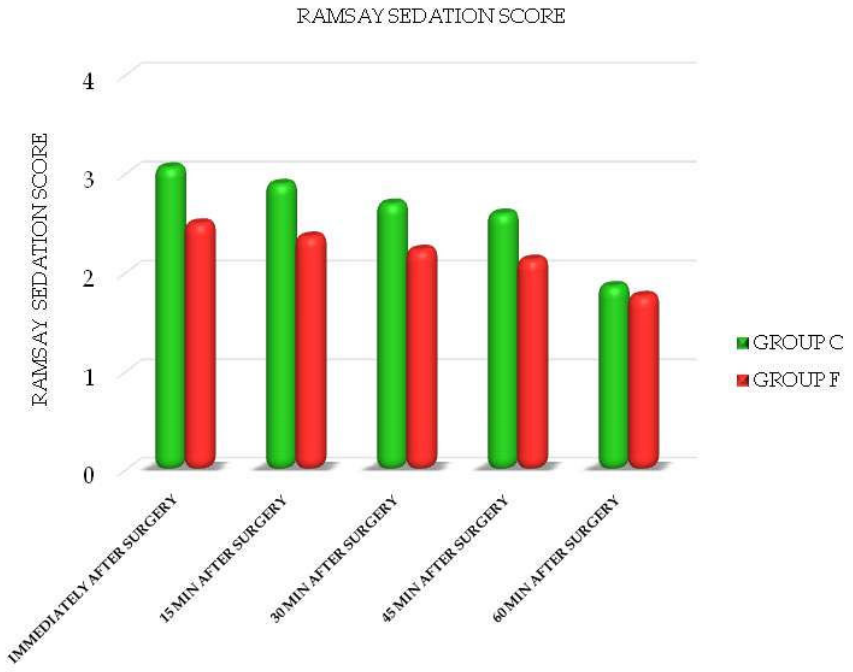

Fig. 5: Bar diagram showing comparison of Ramsay sedation score between two groups

Table 11: Side Effects in Group C

Side Effects	Group C (n=30)
Hypotension	2
Bradycardia	3
Sedation	2

Table 12: Side Effects in Group F

Side Effects	Group F (n=30)
Postoperative Nausea and Vomiting	2
Hypotension	1
Chest Rigidity	1

between the two groups with respect to sedation score values immediately after surgery, 15 minutes, 30 minutes and 45 minutes postoperatively. Values were higher in group C and the difference was found to be statistically significant ($p < 0.05$). 60 minutes post operatively, there was no statistically significant difference between the sedation scores of the two groups ($p > 0.05$).

Incidence of side effects as illustrated in tables 11,12 was minimum in both the groups.

Discussion

Laryngoscopy and tracheal intubation are potent stimuli that increase heart rate and blood pressure as has been recognised since 1951 by King and Harris [22]. These are produced due to sympathetic reflex provoked by stimulation of epipharynx and laryngopharynx. Reid and Brace in 1940 first described the effect of endotracheal intubation on electrocardiograph which were in the form of premature ventricular beat, nodal rhythm and sinus bradycardia [23]. The sensitive receptor area of epiglottis when mechanically stimulated by instrumentation evokes reflex response [22,23]. Measurements of the plasma catecholamines have demonstrated an increase in noradrenaline following laryngoscopy and thus confirmed sympathetic mediation to this response.

These above mentioned effects may have serious repercussions on the high risk patients like those with cardiovascular disease, increased intracranial pressure or anomalies of the cerebral vessels. Attenuation of such responses is of great importance in the prevention of the perioperative morbidity and mortality [24].

A diversity of results exists about the protective measures against the hemodynamic and the catecholamine responses to laryngoscopy and intubation, but no single anaesthetic technique has become generally accepted as being effective in preventing or attenuating these responses.

Selection of Drugs and Doses

In any study which is conducted, the criteria for the selection of the appropriate drug to prevent a sympathetic response must include the following:

1. The drug must prevent impairment of the cerebral blood flow.
2. It must avoid arousal of the patient.
3. The administration of the drug should neither be time consuming nor should the drug affect the duration or the modality of the ensuing anaesthesia.

Intravenous fentanyl and clonidine appear to best fulfil the above criteria [25].

Laryngoscopy and intubation are among the most painful processes carried out on the human body which are associated with acute hemodynamic responses.

Fentanyl is advocated for the attenuation of the sympathetic response to laryngoscopy and intubation. Narcotics may block afferent nerve impulses resulting from stimulation of the pharynx and larynx during intubation. Atweh and Kuhar used autoradiographic techniques in the rat, and found high concentrations of opiate receptors in the solitary nuclei and the nuclei of the 9th and 10th cranial nerves, associated with the visceral afferent fibers of these nerves which originate in the pharynx and larynx. Also, 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 blunting of the response to laryngeal stimulation [19,20]. The blunting of the sympathetic response is dose dependent. Fentanyl at 6 mcg/kg, completely abolishes, while at 2 mcg/kg, it significantly attenuates the arterial pressure and the heart rate increase during laryngoscopy and intubation. The administration of fentanyl at the optimal time reduces the dose which is required. The optimal injection time of fentanyl is 5 minutes before an intubation, at a dose of 2 mcg/kg [26].

Clonidine is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased systemic vascular resistance and cardiac output. It has many properties of an ideal premedicant and it also has beneficial effects on the hemodynamics during stressful conditions like laryngoscopy and endotracheal intubation. It was shown by Zalunardo MP et al. [27] in 1997, that intravenous clonidine was better than oral clonidine in attenuating the pressor response. Hence, in our study, intravenous clonidine was used. The effects of clonidine on the hemodynamic variables are dose related but when the dose is increased to more than 4 mcg/kg, no further enhancement of the efficacy was seen. Hence, in our study, we used 2 mcg/kg.

This study was undertaken to compare the effects of I.V. fentanyl and I.V. clonidine on the attenuation of the hemodynamic response to laryngoscopy and

endotracheal intubation.

We enrolled 60 patients of ASA physical status I and II, of either sex, in the age group of 20-50 years undergoing elective surgeries under general anaesthesia. Patients were randomly divided into two groups of 30 each.

Group C- received intravenous clonidine 2 mcg/kg diluted in 10 ml normal saline, given slowly I.V., 5 minutes prior to induction of anaesthesia.

Group F- received intravenous fentanyl 2 mcg/kg diluted in 10 ml normal saline, given slowly I.V., 5 minutes prior to induction of anaesthesia.

We selected the optimal age range of 20 to 50 years. This is because, the variability of the heart rate changes decreases with increasing age and younger patients show more extreme changes. The anaesthetic technique was chosen such that the drugs which were administered did not have any significant effects on the heart rate or the blood pressure.

In our study, baseline values (before administering any drug) of HR, SBP, DBP, MAP were comparable (p=0.30, p=0.29, p=0.74, p=0.36 respectively) in both the groups C and F.

All the groups were similarly premedicated regarding anxiolysis.

There was clinically and statistically significant difference in heart rate values 5 min after administration of study drugs and after induction (p=0.002, p=0.04, respectively). The heart rate was lower in group C compared to group F at both these times. Clonidine stimulates the central alpha 2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result, there is a decrease in sympathetic nervous system outflow from central nervous system to peripheral tissues. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and decrease in systemic blood pressure, HR, and cardiac output [16,28].

At intubation, 1 min and 3 min after intubation (p=0.02, p=0.01, p=0.01, respectively), the heart rate was maintained lower than baseline in both the groups, however, the values were lower in group F as compared to group C and this was statistically significant (p <0.05). Malde AD et al. [29] in a 2007 study, compared lignocaine and fentanyl efficacy on hemodynamic stability and revealed that lignocaine and fentanyl both attenuated the rise in heart rate, however, fentanyl produced better results. A single I.V. dose of fentanyl has a rapid onset of action because of greater lipid solubility which facilitates its passage across the blood brain barrier. The effect-site equilibration time between blood and the brain for fentanyl is 6.4 minutes [30].

In our study, the maximum rise in heart rate values was seen at 0 min after intubation (group C - 86.26±6, group F - 81.3±10.07). However, in the study by Sameenakousar et al [21] the first heart rate values were recorded only after 5 min of intubation where they found lower values in clonidine group.

Laryngoscopy and endotracheal intubation is often associated with hypertension and tachycardia because of sympathoadrenal stimulation which is usually transient and lasts for up to 5-10 minutes [31]. The above contradictory finding could be because clonidine was administered 5 min prior to induction in our study as per the study by Sameenakousar et al. [21] in contrast to all other studies done for observing the hemodynamic response to intubation after clonidine administration, where it was administered atleast 15 min prior to induction.

From the pharmacokinetic profile, it is seen that the distribution half-life of intravenous clonidine is approximately 11 minutes [31,32]. It has also been found that the maximum effect of intravenous clonidine occurs approximately 15 minutes after its administration [33-35]. In view of this, patients in the study by Harshavardhana HS et al. [31] in 2013, received injection clonidine 3 mcg/kg, diluted to 10 ml normal saline intravenously over 120 seconds, 15 minutes prior to laryngoscopy and intubation. Whereas, in case of fentanyl, 80% of the injected dose of fentanyl leaves the plasma to enter the highly vascular tissues (brain, lungs, heart) in less than 5 minutes (distribution half-life is about 5 minutes) [30].

At 5 min, 10 min and 15 min after intubation, the heart rate values continued to be lower than baseline in both the groups but after 5 min following intubation, there was no statistically significant difference between the two groups (p >0.05).

The maximum rise in systolic blood pressure values was seen at 1 min after intubation in our study (group C - 114.6±6.2, group F - 111.13±3.8). However, this value was lower in fentanyl group and was statistically significant (p <0.05). Malde AD et al. [29] in 2007, studied the efficacy of fentanyl and fentanyl plus lignocaine in attenuating the hemodynamic responses to laryngoscopy and endotracheal intubation in 37 hypertensive patients. The fentanyl group received 2 mcg/kg and the fentanyl plus lignocaine group received 1.5 mg/kg lignocaine and 2 mcg/kg fentanyl. They observed that lignocaine attenuated the rise

in blood pressure with intubation while fentanyl inhibited it totally.

Hoda A et al. [36] in 2011, concluded that addition of 2 mcg/kg fentanyl bolus to 1 MAC sevoflurane anaesthesia at induction attenuated the hemodynamic response to a maximum of 15% above baseline values.

The maximum rise in diastolic blood pressure values was seen at 0 min after intubation in our study (group C - 73.2±6.2, group F – 70± 3.8). However, this value was lower in fentanyl group and was statistically significant ($p < 0.05$). Splinter WM et al. [37] in 1989, conducted a study comparing hemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients after administration of fentanyl, lignocaine and thiopentone and observed that fentanyl 1.5 or 3 mcg/kg reduced the rise in systolic, diastolic and mean arterial pressures and also decreased the incidence of marked fluctuations in hemodynamic variables, often seen in geriatric patients.

The maximum rise in mean arterial pressure values was seen at 0 min after intubation in our study (group C - 87.88±4.4, group F - 83.84±4.3). However, this value was lower in fentanyl group and was statistically significant ($p < 0.05$).

In our study, at 5 min, 10 min and 15 min after intubation, the mean arterial pressure values continued to be lower than baseline in both the groups but after 5 min following intubation there was no statistically significant difference between the two groups ($p > 0.05$).

Both clonidine and fentanyl were able to blunt the rise in mean arterial pressure occurring during laryngoscopy and intubation. However, fentanyl had a better efficacy in blunting the response which was statistically significant.

Thus, we see that fentanyl did not allow marked fluctuations in the systolic, diastolic and mean arterial pressures and these were well maintained near the baseline values. This property can have a positive significance in high risk patients.

Further, after 5 min of intubation, clonidine group also showed stable hemodynamics. This indicates that at the time of intubation, there was incomplete sympathetic blockade. Therefore, one can speculate that a higher dose or an earlier administration of clonidine before laryngoscopy would result in complete sympathetic outflow blockade which would keep the hemodynamic variables closer to the baseline.

The SpO_2 was maintained between 99 to 100% in both the groups. No fall in saturation was observed in any patient ($p > 0.05$).

The patients who received clonidine were sedated but arousable (i.e. showed a brisk response to glabellar tap or loud noise while sleeping) for 45-60 min postoperatively. However, in the fentanyl group, the patients responded to verbal commands and they were calm and co-operative.

Study done to evaluate the effect of clonidine as pre-anaesthetic medication by Wright et al [38] found that clonidine produced a significant reduction in anxiety ($p < 0.05$) and caused sedation.

In the clonidine group, three patients had bradycardia and responded to atropine, two patients had hypotension which was treated by reducing concentration of inhalational agents and giving bolus I.V. fluids. Two patients were sedated postoperatively for more than an hour. Side effects were found to be statistically insignificant ($p > 0.05$).

In the fentanyl group, chest rigidity was observed in one patient during bag and mask ventilation during induction. One patient had hypotension intraoperatively, which was managed by bolus of I.V. fluids. Two patients complained of nausea in the immediate postoperative period. None of them had an episode of vomiting. Side effects were found to be statistically insignificant ($p > 0.05$). Postoperative respiratory depression was not seen in any of the patients.

Limitations

Our study was conducted on patients with ASA physical status I and II. So, further studies on elderly patients and those with compromised cardiac function are required to recommend its use in such high risk patients. Also we did not measure the plasma catecholamine levels.

Conclusion

1. Both I.V. fentanyl and I.V. clonidine were able to attenuate the hemodynamic response to laryngoscopy and intubation, however, I.V. fentanyl 2 mcg/kg given 5 min prior to intubation was better than I.V. clonidine 2 mcg/kg given 5 min prior to intubation as fentanyl did not allow marked fluctuations in SBP, DBP and MAP and they were well maintained near baseline.
2. After 5 min of intubation both the drugs

were comparable in terms of hemodynamic stability.

3. Ramsay sedation score was higher with clonidine as compared to fentanyl for 45 min after extubation.
4. Incidences of side effects were less in both groups and those present, were not statistically significant.

References

1. Prys-Roberts C, Greene LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension II: Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth. 1971;43:531-47.
2. Stoelting RK. Circulatory Changes during Laryngoscopy and Tracheal Intubation: Influence of Duration of Laryngoscopy With or Without Lidocaine. Anaesthesiology. 1977;47:381-3.
3. Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effect of lidocaine, esmolol and NTG in modifying the hemodynamic response to laryngoscopy and intubation. Clin Anaesth. 1995;7:1155-8.
4. Chung KS, Sinatra RS, Halevy JD, Paige D, Silverman DG. Comparison of fentanyl, esmolol and their combination for blunting the hemodynamic responses during rapid sequence induction. Can J Anaesth. 1992;39:774-9.
5. Matot I, Sichel JY, Yofe V, Gozal Y. The effect of clonidine premedication on hemodynamic responses to microlaryngoscopy and rigid bronchoscopy. Anesth Analg. 2000;91(4):828-33.
6. Stoelting RK. Blood pressure and heart rate changes during short-duration laryngoscopy for tracheal intubation: Influence of viscous or intravenous lidocaine. Anesth Analg. 1978;57:197-9.
7. Sharma S, Mitra S, Grover VK, Kalra R. Esmolol blunts the haemodynamic responses to tracheal intubation in treated hypertensive patients. Can J Anaesth. 1996;43:778-82.
8. Braunwald E. Control of myocardial oxygen consumption: physiological and clinical considerations. Am J Cardiol. 1971;27(4):416-32.
9. Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effect of lidocaine, esmolol and NTG in modifying the hemodynamic response to laryngoscopy and intubation. Clin Anaesth. 1995;7:1155-8.
10. Vanden Berg AA, Savva D, Honjol NM. Attenuation of the haemodynamic responses to noxious stimuli in patients undergoing cataract surgery. A comparison of magnesium sulphate, esmolol, lignocaine, nitroglycerin and placebo given I.V. with induction of anaesthesia. European Journal of Anaesthesiology. 1997;14(2):134-47.
11. Masson AHB. Pulmonary edema during or after surgery. Anesth Analg. 1964;43(5):446-51.
12. Sharma A, Shankaranarayana PP. Premedication with I.V. dexmedetomidine vs I.V. clonidine in attenuating the pressor response during laryngoscopy and endotracheal intubation. International Journal of Biomedical Research. 2014;5(7):465-7.
13. Maguire A, Thompson JP, Guest C, Sadler PJ, Strupish JW, West KJ, et al. Comparison of the effects of intravenous alfentanil and esmolol on the cardiovascular response to double-lumen endotracheal intubation. Anaesthesia. 2001;56(4)319-25.
14. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg. 1979;58:116-9.
15. Milkawa K, Nishina K, Maekawa N, Obara H. Comparison of nicardipine, diltiazem and verapamil for controlling cardiovascular responses to tracheal intubation. Br J Anaesth. 1996;76(2):221-6.
16. Stoelting RK, Hillier SC. Antihypertensive Drugs. In: Pharmacology and Physiology in Anesthetic Practice. 4th edition. Brown B, editor. Lippincott Williams and Wilkins; Philadelphia. 2006;340-4.
17. Zalunardo MP, Serafino D, Szelloe P, Weisser F, Zollinger A, Seifert B, et al. Preoperative clonidine blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet pressure during general anaesthesia. Anesth Analg. 2002;94(3):615-8.
18. Stoelting RK, Hillier SC. Opioid Agonists and Antagonists. In: Pharmacology and Physiology in Anesthetic Practice. 4th edition. Brown B, editor. Lippincott Williams and Wilkins; Philadelphia: 2006;87-90.
19. Atweh SF, Kuhar MJ. Autoradiographic localization of opiate receptors in rat brain. I. Spinal cord and lower medulla. Brain Res. 1977;124:53-67.
20. Martin DE, Rosenberg H, Aukburg SJ, Bartkowski RR, Edwards MW, Greenhow E, et al. Low-Dose Fentanyl Blunts Circulatory Responses to Tracheal Intubation Anesth Analg. 1982;61:680-4.
21. Sameenakousar, Mahesh, Srinivasan KV. Comparison of Fentanyl and Clonidine for Attenuation of the Haemodynamic Response to Laryngocopy and Endotracheal Intubation. Journal of Clinical and Diagnostic Research. 2013;7(1):106-11.
22. King BD, Harrison LC, Greifenstein FE, Edder JD, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anaesthesia. Anaesthesiology. 1951;12:556-66.
23. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart. Surg Gynaec & Obst. 1940;70:157-62.

24. Chremmer-Jorgensen B, Hertel S, Strom J, Hoilund-Carlsen PF, Bjerre-Jepsen K. Catecholamine response to laryngoscopy and intubation. Anaesthesia. 1992;47:750-6.
25. Bachofen M. Suppression of blood pressure increases during intubation: lidocaine or fentanyl? Anaesthesist. 1988;37(3):156-61.
26. Ko SH, Kim DC, Han YJ, Song HS. Small-dose fentanyl: optimal time of injection for blunting the circulatory responses to tracheal intubation. Anesth Analg. 1998;86(3):658-61.
27. Zalunardo MP, Zollinger A, Spahn DR, Seifert B. Effects of intravenous and oral clonidine on haemodynamic and plasma – catecholamine response due to endotracheal intubation. Journal of Clinical Anaesthesia. 1997;9(2):143-7.
28. Arora S, Kulkarni A, Bhargava AK. Attenuation of hemodynamic response to laryngoscopy and orotracheal intubation using intravenous clonidine. Journal of Anaesthesiology Clinical Pharmacology. 2015;31(1):110-4.
29. Malde AD, Sarode V. Attenuation of the hemodynamic response to endotracheal intubation: fentanyl versus lignocaine. The Internet Journal of Anesthesiology. 2007;12(1).
30. Stoelting RK, Hillier SC. Opioid Agonists and Antagonists. In: Pharmacology and Physiology in Anesthetic Practice. 4th edition. Brown B, editor. Lippincott Williams and Wilkins; Philadelphia. 2006;104-9.
31. Harshavardhana HS. Attenuation of haemodynamic response to laryngoscopy and tracheal intubation in adult patients with a single intravenous bolus dose of 3 µg/kg clonidine: A prospective, randomized, double blind study. Journal of Evolution of Medical and Dental Sciences. 2013;2(51):9975-86.
32. Dollery CT, Davis DS, Draffan GH, Dargie HJ, Dean CR, Reild JL, et al. Clinical Pharmacology and Pharmacokinetics of Clonidine. Clinical Pharmacology and Therapeutics. 1976;19(1):11-7.
33. Altan A, Turgut N, Yildiz F, Turkmen A, Ustiin H. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery. Br J Anaesth. 2005:93(4):438-41.
34. Kock MD, Laterre PF, Obbergh LV, Carlier M, Lerut J. The effects of intra-operative intravenous clonidine on fluid requirements, haemodynamic variables, and support during liver transplantation: A prospective, randomized study. Anesth Analg. 1998;86:468-76.
35. Ray M, Bhattacharjee DP, Hajra B, Pal R. Effect of clonidine and magnesium sulphate on anaesthetic consumption, haemodynamics and postoperative recovery: A comparative study. Indian Journal of Anaesthesia. 2010;54(2):137-41.
36. Hoda A, Khan FA. Effect of one minimum alveolar concentration sevoflurane with and without fentanyl on hemodynamic response to laryngoscopy and tracheal intubation. Journal of Anaesthesiology Clinical Pharmacology. 2011;27:522-6.
37. Splinter WM, Cervenko F. Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: effects of fentanyl, lidocaine and thiopentone. Can J Anaesth. 1989;36(4):370-6.
38. Wright PM, Carabine UA, McClune S, Orr DA, Moore J. Pre anaesthetic medication with clonidine. Br J Anaesth. 1990;65:628-32.