INTRAVENOUS 2 µG/KG CLONIDINE IN COMPARISON TO INTRAVENOUS 2 µG/KG FENTANYL FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND OROTRACHEAL INTUBATION

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ABSTRACT

BACKGROUND

Laryngoscopy and intubation cause discernible haemodynamic changes following sympathetic stimulation. These responses are endured by healthy individuals, however, can produce calamitous changes in compromised individuals. Hence, attenuation is prudent and favourable.

AIM

To compare the effectiveness and safety of Clonidine and Fentanyl in attenuation of pressor response to direct laryngoscopy and endotracheal intubation.

SETTING

Tertiary care hospital.

DESIGN

Randomized, prospective, double blind study.

METHODS

100 patients, aged 18-60 years who presented for elective, non-cardiovascular surgeries were divided into 2 groups; group-C to receive IV Clonidine; and group-F IV Fentanyl respectively, administered 5 min. prior to intubation. Each group had 50 patients of ASA-1 or II. We monitored the heart rate, systolic, diastolic and mean arterial blood pressure.

STATISTICAL ANALYSIS

ANOVA (Analysis of Variance) method for intragroup comparison. The ANOVA method calculated Greenhouse-Geisser value, degree of freedom and p value. A p value <0.05 was considered significant.

RESULTS

At 10 min. of intubation, decrease in heart rate was maximum with Clonidine than Fentanyl with mean values 61.84/min and 84.64/min respectively, statistically significant (p<0.001). The systolic and diastolic blood pressure also showed a significant suppression (P<.001) with Clonidine showing better results.

CONCLUSION

Sympathetic response is better attenuated with Clonidine, which is statistically highly significant. Administration of intravenous Clonidine 2 µg/kg, 5 minutes before the laryngoscopy can be recommended to attenuate the sympathetic response to laryngoscopy and intubation.

KEYWORDS

Haemodynamic Response, Laryngoscopy, Intubation.

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INTRODUCTION

Reid and Brace pioneered studies involving haemodynamic response to laryngoscopy and intubation in 1940.[1] The circulatory response commonly observed are tachycardia and systolic hypertension, which may be dependent on various factors such as depth of anaesthesia, expertise of the anaesthesiologist, duration of laryngoscopy and intubation, measures taken prior to airway manipulation and the anaesthetic agent used.

The attenuation of haemodynamic response to laryngoscopy and intubation is a laudable objective with benefits that extend to entire intraoperative period.

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MATERIALS AND METHODS

This study was carried out in 100 patients undergoing elective, non-cardiac, surgical procedures under general anaesthesia with tracheal intubation, in our hospital. The design of the study was prospective, randomized, double blind study. Permission from the Institutional Ethical Committee was obtained. Patients were selected amongst those individuals undergoing elective surgeries in the fields of Orthopaedic,

Otorhinology and General Surgery. A written informed consent was obtained from each patient. These patients were then randomly allocated into 2 groups namely:

Group C-(n=50) who received a bolus of intravenous Clonidine in the dose of 2 µg/kg.

Group F-(n=50) who received a bolus of intravenous Fentanyl in the dose of 2 µg/kg.

These drugs were administered 5 min. prior to intubation.

Sample size was determined by power analysis performed after a pilot study and a sample size of 50 patients per group was selected to detect a change in heart rate and blood pressure between the time at which drug administered and intubation time. Data are expressed as the mean±standard deviation.

Inclusion Criteria

Age 18-60 years, both male and female, weight 40-70 kg normotensive, ASA I and II, elective surgery.

Exclusion Criteria

Patients on antihypertensive drugs, past history of myocardial infarction, hypertension, cerebrovascular, hepatic, renal dysfunction and psychiatric illness, history of allergy to either Clonidine or Fentanyl, anticipated difficult intubation and emergency surgery.

In the Operation Theatre

Monitors were attached which included pulse oximetry, Non-Invasive Blood Pressure (NIBP), ECG and capnography. Baseline Heart Rate (HR), Systolic Blood pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Oxygen saturation and end tidal CO_2 were recorded. The haemodynamic parameters were recorded by an observer who was blinded to the study drug. Patients were premedicated with only IV Ondansetron 0.1 mg/kg and the study drug was administered 5 min. prior to intubation. HR, SBP, DBP, MAP were recorded as 0 min. All patients were pre-oxygenated with 100% Oxygen for 3 min. using Bain circuit with appropriate sized mask. Induction of anaesthesia was standardized for all patients who received IV 2.5% Thiopentone Sodium until the loss of eyelash reflex. After confirming ventilation, intravenous vecuronium 0.1 mg/kg was given.

After 5 minutes of administration of the study drug, laryngoscopy and intubation were performed using appropriate sized Macintosh blade and endotracheal tube. In patients where the duration of laryngoscopy and intubation exceeded 30 seconds or those who required a second attempt at intubation were excluded from the study. Readings were taken at 0, 1, 3, 5, 7 and 10 min. of drug administration.

Hypertension was defined as an MAP more than 30% of the patient's baseline value or 130 mmHg, whichever was greater.[2] Hypotension was defined as a MAP less than 30% of the patient's baseline value or 65 mmHg, whichever was less.

Tachycardia and bradycardia were defined as an HR greater than 120 bpm and <60 bpm, respectively. The incidence of hypertension, hypotension, tachycardia and bradycardia was recorded during the study period and compared among the two groups. The incidence of dysrhythmia after intubation was also compared among the two groups.[2] A dysrhythmia was defined as any ventricular or supraventricular premature beat or any sustained rhythm other than sinus rhythm.[2]

The patients in both the groups were ventilated on Oxygen and Nitrous oxide in the ratio 33% and 66% respectively. No additional agents or any surgical stimulus was given to these patients for first 5 min. post-intubation. Sevoflurane was then started in the concentration of 2% using Bain's circuit. Intravenous Glycopyrrolate 0.01 mg/kg was given to both groups after 10 min. Analgesia was maintained with 1 µg/kg Fentanyl top ups in both groups. Muscle relaxation was maintained with IV vecuronium 1 mg bolus top ups as needed.

The heart rate and blood pressure were also monitored throughout the surgery.

In both groups, Rate Pressure Product (RPP) was calculated using the following formula:

(RPP=Systolic blood pressure x pulse rate)

At the end of surgery, patients were reversed with IV Neostigmine 0.05 mg/kg, Glycopyrrolate 0.01 mg/kg; IV paracetamol was given 15 mg/kg.

Patients were extubated and shifted to recovery and monitored for an hour for adverse effects such as bradycardia, hypotension, dysrhythmias, respiratory depression (arterial oxygen saturation less than 95) and sedation.

Ethics

The permission of Institutional Ethical Committee was sought and approved.

Statistical Analysis

In both the groups, Statistical Package for Social Sciences version 14 was used to calculate mean, standard deviation and p value. To find out statistical difference, we used unpaired 't' test and Chi-square test was used for comparison between the two groups.

ANOVA (Analysis of Variance) method for intragroup comparison. The ANOVA method calculated Greenhouse-Geisser value, degree of freedom (df) and p value. A p value <0.05 was considered significant.

OBSERVATION AND RESULTS

Heart Rate (HR)	Mean (Beats/Minute)		Standard Deviation		
	Group C	Group F	Group C	Group F	p-value
H0 (at 0 min.)	87.16	80.86	9.528	13.343	
H1 (at 1 min.)	82.76	81.86	8.989	13.132	0.016
H3 (at 3 min.)	77.20	90.26	7.897	12.314	0.0461
H5 (at 5 min.)	73.08	99.52	7.897	14.780	0.048
H7 (at 7 min.)	68.40	90.60	6.615	13.509	0.001
H10 (at 10 min.)	61.84	84.64	6.4855	12.232	0.000

Table 1: Group-wise Comparison of Heart Rate

Using the one-way Anova test, the F value as per Greenhouse-Geisser is 2.628. The degree of freedom df is 79.9. The p value is 0.000. Thus, there is statistical significance between the two groups.

Systolic BP	Mean (mmHg)		Standard Deviation		
	Group C	Group F	Group C	Group F	p-value
S0 (at 0 min.)	125.96	125.40	7.028	11.706	
S1 (at 1 min.)	122.20	122.40	6.184	11.766	0.533
S3 (at 3 min.)	117.64	111.64	6.398	18.873	0.273
S5 (at 5 min.)	112.20	126.12	7.454	12.437	0.000
S7 (at 7 min.)	106.76	118.28	7.708	13.357	0.000
S10 (at 10 min.)	99.68	113.92	9.083	11.697	0.000

Table 2: Group-wise Comparison of Systolic Blood Pressure

Using the one-way Anova test, the F value as per Greenhouse-Geisser is 26.881. The degree of freedom df is 4.014. The p value is 0.000. Thus, there is statistical significance between the two groups.

Diastolic BP mmHg	Mean (mmHg)		Standard Deviation		
	Group C	Group F	Group C	Group F	p-value
D0 (0 min.)	77.72	81.32	5.540	5.579	
D1 (1 min.)	74.84	80.00	5.016	7.730	0.265
D3 (3 min.)	71.52	75.36	4.652	6.369	0.859
D5 (5 min.)	69.60	82.44	4.815	7.508	0.000
D7 (7 min.)	65.48	77.92	5.027	7.384	0.000
D10 (10 min.)	61.48	75.60	4.743	7.918	0.000

Table 3: Group-wise Comparison of Diastolic Blood Pressure

Using the one-way Anova test, the F value as per Greenhouse-Geisser is 24.362. The degree of freedom df is 4.566. The p value is 0.000. Thus, there is statistical significance between the two groups.

Mean Arterial BP mmHg	Mean (mmHg)		Standard Deviation		
	Group C	Group F	Group C	Group F	p-value
M0 (0 min.)	93.06	96.32	6.588	6.953	
M1 (1 min.)	89.92	93.22	6.262	7.571	0.976
M3 (3 min.)	86.14	88.40	5.925	7.546	0.481
M5 (5 min.)	83.20	97.08	6.734	8.790	0.000
M7 (7 min.)	78.52	91.46	5.936	8.452	0.000
M10 (10 min.)	73.70	88.40	6.122	8.480	0.000

Table 4: Group-wise Comparison of Mean Arterial Pressure

Using the one-way Anova test, the F value as per Greenhouse-Geisser is 34.901. The degree of freedom df is 3.477. The p value is 0.000. Thus, there is statistical significance between the two groups.

Rate Pressure Product	Mean		Standard Deviation		
	Group C	Group F	Group C	Group F	p-value
R0 (0 min.)	10987.12	10126.64	1412.639	1862.300	
R1 (1 min.)	10125.36	10007.28	1326.970	1793.496	0.001
R3 (3 min.)	9086.72	10066.36	1103.745	2200.094	0.000
R5 (5 min.)	8225.92	12606.68	1245.502	2532.941	0.000
R7 (7 min.)	7324.08	10780.88	1056.026	1832.488	0.000
R10 (10 min.)	6190.72	9662.52	1066.804	1902.328	0.000

Table 5: Group-wise Comparison of Rate Pressure Product

	Group C (No. of Patients)	Group F (No. of Patients)
Bradycardia	12	1
Hypotension	1	-
Dysrhythmias	-	-
Respiratory depression	-	-

Table 6: Adverse Effects

The comparison between groups showed statistical significance ($p<0.05$). Using the one-way ANOVA test, the F value as per Greenhouse-Geisser is 73.798. The degree of freedom df is 3.364. The p value is 0.000. Thus, there is statistical significance between the two groups.

DISCUSSION

Laryngoscopy and intubation engendered momentary hypertension and tachycardia are probably of no consequences in healthy individuals, but either one or both maybe hazardous to those with myocardial insufficiency, hypertension or cerebrovascular disease.[3]

A diversity of protective measures exists against the haemodynamic responses to laryngoscopy and intubation, but

no sole drug has been accepted in preventing or attenuating these responses. The drugs which were used were either not totally effective or they were associated with undesirable effects on patients.[3][4]

The study drug should fulfil the following criteria; prevent a sympathetic response, applicable, prevent impairment of the cerebral blood flow and avoid arousing the patient. Administering the drug should neither cause a time delay nor should the duration or mode of anaesthesia be altered.[5] IV Fentanyl and Clonidine appear to fulfil the above criteria.[5]

Fentanyl is a pure agonist acting on β opioid receptors on pituitary adrenal axis, having high potency, rapid onset, short duration and preventing sympathetic response. We chose Fentanyl at 2 μg/kg, as it was feasible and proved by the study.[6] to attenuate the pressor response, while higher doses 25-75 μg/kg can even obtund the response, nevertheless with postoperative complications like respiratory depression, bradycardia, nausea, vomiting and muscle rigidity.[7] Administration of Fentanyl at the appropriate time decreases the dose which is required. The optimal injection time of 2 μg/kg Fentanyl is 5 minutes before intubation.[6],[8],[9]

Clonidine, α_2 adrenoceptor agonists has been utilized as premedicant due to its beneficial effects on the haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation. Clonidine is also an antihypertensive agent with effects lasting throughout perioperative period and lesser side effects.[10],[11] we chose intravenous Clonidine as unlike oral Clonidine has precise bioavailability.[12]

We compared 2 μg/kg of intravenous Clonidine with Fentanyl, as there are very few studies reported using this comparison.[5],[10]

Sameenakousar.[5] used a sample-size of 50 patients per group, which provided a power of 95% at a level of 0.05 for identifying 30% attenuation in the post-intubation increase in heart rate. Similarly, in our study a sample size was determined by power analysis performed after a pilot study and a sample size of 50 patients per group was selected to detect a change in heart rate and blood pressure between the time of administration of the study drug and intubation time. Data are expressed as the mean±standard deviation.

The patients in both the groups did not show any statistical significance in their age, weight or sex distributions. We selected the optimal age range of 20 to 60 years. This is because the variability of the heart rate changes decreases with increasing age and younger patients show more extreme changes.

Patients on antihypertensives were excluded as antihypertensives may exhibit a decrease in pressor response.

Both the groups were premedicated with Ondansetron and no anxiolytic was used so as to prevent confounding factor.

Atropine and Glycopyrrolate were not given as premedication, as these drugs cause marked tachycardia. However, after 5 minutes of intubation, Glycopyrrolate was given for its anti-sialagogue action. Although, Clonidine has anti-sialagogue action, patients did not complain of excessive dryness of mouth.

Standard induction was used for both groups with Thiopentone sodium as intravenous inducing agent and Vecuronium as these agents are relatively more cardiostable and cause lesser haemodynamic changes. Unlike other non-depolarizing skeletal muscle relaxants, Vecuronium has lesser clinical effects on haemodynamic parameters. Vecuronium will not counteract those haemodynamic changes of other drugs.

Fentanyl was used as top up for analgesia, as Clonidine has parsimonious analgesic effects and its prolonged elimination half-life of 8.5 hours makes its use for continuous IV sedation and analgesia arduous, also appropriate dosage is not accorded.[9] Nevertheless, the adverse effect of Clonidine and its inadequacy as analgesic limits its use as routine postoperative analgesic. Sevoflurane was added after intubation in both the groups to avoid effects of confounding factors. Arterial baroreflex action is known to be notably reduced during sevoflurane and nitrous oxide anaesthesia.

The decrease in heart rate in Clonidine group may be attributed to its central sympatholytic properties and also stimulates parasympathetic outflow with increased vagal tone.[13] Premedication with Clonidine thus effectively blunts reflex tachycardia affiliated with laryngoscopy and intubation.[12] In addition, some of the antihypertensive effects of Clonidine may be mediated by activation of presynaptic alpha$_2$ receptors that suppress the release of Noradrenaline, ATP and neuropeptide Y from postganglionic sympathetic nerves.[13] The rise in pulse rate after induction with Thiopentone is a compensatory response to fall in blood pressure.

Patients who received Fentanyl showed rise of 99.52/min. in heart rate. This was also reported in a study carried out by Hussain AM.[14] who concluded that bolus injection of Fentanyl 2 μg/kg prior to laryngoscopy and intubation failed to protect against elevation of both the heart rate and systolic blood pressure.[14]

Dipak and Malini, reported the effectiveness of oral Clonidine to the haemodynamic response to laryngoscopy and endotracheal intubation.[15] They found that the heart rate in the Clonidine group returned to the basal value, 1 min. after the intubation and this persisted till 5 minutes of the intubation. Its values were also statistically highly significant.[15]

Sharma et al. in their study also showed that tachycardia in response to intubation was attenuated by Clonidine.[16]

In 2013, Gupta K et al.[9] premedicated the patients with IV Clonidine and Fentanyl for laparoscopic cholecystectomy for attenuation of haemodynamic response. Clonidine or Fentanyl premedication has attenuated the haemodynamic responses of laryngoscopy as well as laparoscopy. Clonidine has surpassing effects than Fentanyl for intraoperative haemodynamic stability.

The antihypertensive effects of Clonidine favours decrease in systolic blood pressure more than decrease in diastolic blood pressure. In patients treated chronically, systemic vascular resistance is little affected and cardiac output which is initially decreased, returns towards pre-drug levels. Homeostatic cardiovascular reflexes are maintained, thus avoiding the problems of orthostatic hypotension or hypotension during exercise.[13] The administration of Clonidine acutely decreases blood pressure, heart rate, cardiac output and stroke volume without consistent changes in calculated total peripheral resistance.[17],[18],[19],[20]

Clonidine has better attenuation of pressor response than Fentanyl. Sameenakousar advised Intravenous Clonidine 2 μg/kg, 5 min. prior to laryngoscopy to attenuate the sympathetic response to the laryngoscopy and the

intubation.[5] This was in concordance with Nand Kishore Kalra.[17] which showed that the preoperative administration of Clonidine reduced the sympathoadrenal response to painful stimuli and that it improved the intraoperative haemodynamic stability. Nand Kishore Kalra in 2011, concluded that intravenous Clonidine had the desirable effects and no consequential hypotension.[17]

Fentanyl, as an adjunct to barbiturate induction, effectively reduced the doses of thiopentone and lessened the pressor response to laryngoscopy and intubation.[6]

Rate pressure product is defined as the product of pulse rate and peak systolic blood pressure. There is a correlation between rate pressure product and myocardial blood flow, myocardial oxygen consumption which may correlate with signs of ischaemia especially during exercise. Identical RPPs can be produced from multiple combinations of heart rate and blood pressure and hence is not a definite indicator of perioperative ischaemia.[21]

Our study shows that Clonidine effectively attenuates increase in rate pressure product following laryngoscopy and intubation.

Overall, the patients in our study showed increase in the heart rate and the blood pressure in response to laryngoscopy and intubation. The Clonidine premedicated patients showed little or no rise in the heart rate and the blood pressure. The magnitude of the rise and the decline between the 2 groups was statistically significant. Both the blood pressure response and the heart rate were attenuated more effectively in the Clonidine group. This finding was in accordance with the study conducted by H. Talebi in 2010.[22]

In our study amongst the 50 patients who received intravenous Clonidine, 12 patients had bradycardia which responded to intravenous Glycopyrrolate 0.01 mg/kg and 1 had hypotension which responded to intravenous Ephedrine 6 mg. Similar hypotension was seen in study.[23] In the Fentanyl group, 1 patient developed bradycardia which was transient and subsided without any pharmacological intervention. Decrease in sympathetic tone by central action, norepinephrine inhibition pre-synaptically mediated and vagomimetic action at nucleus tractus solitarius by Clonidine is accountable for bradycardia. No patient experienced dysrhythmia or respiratory depression after premedication.

The limitations of our study were that we did not use control group as our patients were not given anxiolytics and we did not want our patients to undergo the stress of laryngoscopy without attenuation.

Our study shows fall in haemodynamic parameters following administration of intravenous Clonidine, while other studies had minimal rise in heart rate and blood pressure prior to intubation and at intubation.[5] This may be attributable to the fact that Clonidine a centrally acting α_2 agonist decreases the central sympathetic outflow and also stimulates parasympathetic outflow. Also in our study, we have not measured catecholamine values to infer the physiological effects of laryngoscopy as facilities to measure the same were not available at our institution. This provides an avenue for further research of pressor response.

Nevertheless, the results of the present study should encourage the use of IV Clonidine as a premedication for laryngoscopy and intubation. By providing improved haemodynamics, Clonidine proved to be more beneficial as compared to Fentanyl as seen in Sameenakousar et al.[5] study, which compared the attenuation of pressor response to Clonidine and Fentanyl to find the drug which was best suited for this purpose and the most favourable time for its administration. Intravenous Clonidine 2 µg/kg, which is administered 5 minutes before the laryngoscopy can be advocated to attenuate the sympathetic response to the laryngoscopy and the intubation.

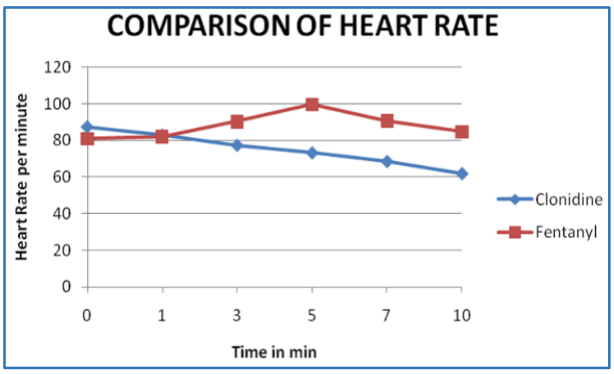

Fig. 1: Group-wise Comparison of Heart Rate

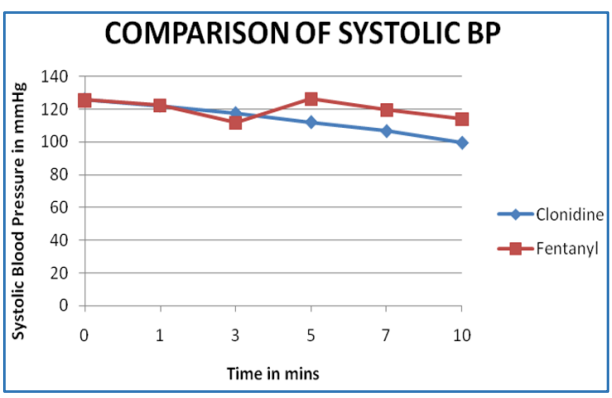

Fig. 2: Group-wise Comparison of Systolic Blood Pressure

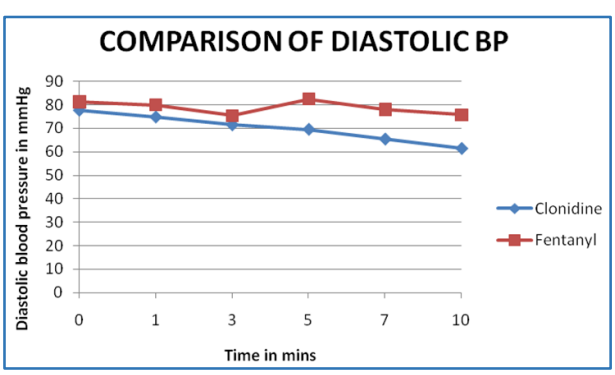

Fig. 3: Group-wise Comparison of Diastolic Blood Pressure

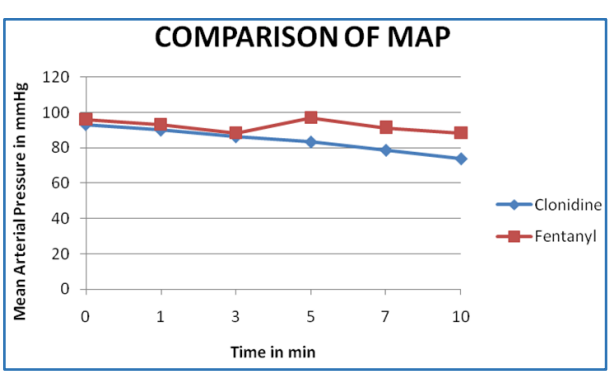

Fig. 4: Group-wise Comparison of Mean Arterial Pressure

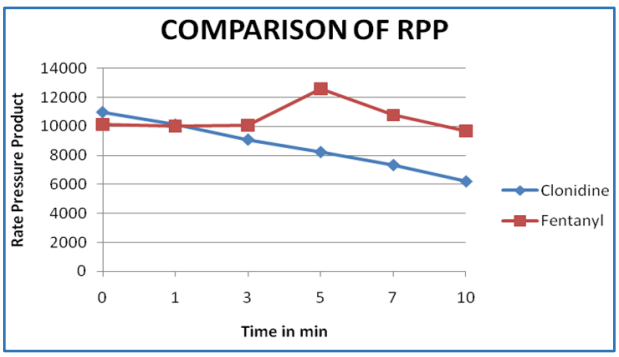

Fig. 5: Group-wise Comparison of Rate Pressure Product

CONCLUSION

Intravenous Clonidine 2 µg/kg and Fentanyl 2 µg/kg attenuates pressor response to laryngoscopy and intubation. Although, Clonidine attenuates more effectively than Fentanyl.

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