

“Effect of Esmolol, Fentanyl and Dexmedetomidine on attenuating the haemodynamic response to intubation: A randomized double blind clinical study”.

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Abstract:-

Aim: To compare the effect of intravenous Esmolol, Fentanyl and Dexmedetomidine on haemodynamic response to laryngoscopy & tracheal intubation in patients posted for elective surgical procedures and to study the safety and side effects of these drugs.

Settings and Design: Prospective, randomized & double blind study.

Methods and Material: 150 elective surgical patients of aged 18 to 65 years were included in study. All patients underwent elective surgical procedures under general anaesthesia. Patients were randomized into three groups. Group A: Received Esmolol 2mg/kg, Group B :Received Fentanyl 2µg/kg, Group C :Received Dexmedetomidine 1µg/kg.

The following parameter (HR, SAP, MAP, DAP, and SpO₂) levels were measured and recorded: - Average of three readings taken in operation theatre were considered as baseline and all other measurements were compared with the baseline.

Statistical analysis used: All data were calculated as mean, standard deviation, proportions and percentage. Chi-square test and Analysis of variance were also used

Results: When basal levels were compared with the measurements of the groups, it was found that 5 and 10 min after intubation heart rate in Group C and systolic, diastolic, mean arterial pressures in Group A were lower than other measurements.

Conclusions: Dexmedetomidine was superior than Esmolol and Fentanyl in the prevention of tachycardia. Esmolol

prevented systolic, diastolic, mean arterial pressure increases following intubation better than fentanyl.

Key-words: Esmolol, Fentanyl, Dexmedetomidine, haemodynamic, rate pressure product.

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I. Introduction:

Laryngoscopy and endotracheal intubation form the basic integral part of balanced anaesthesia wherein the airway is secured and controlled ventilation can be administered to the patient. However, undesired haemodynamic fluctuations are encountered with laryngoscopy and endotracheal intubation. These changes are especially in the form of an increase or decrease in heart rate, arterial blood pressure and myocardial oxygen demand along with cardiac rhythm disturbances¹, which were demonstrated as early as 1940s & 1950s².

Dexmedetomidine is an imidazole derivative and highly selective alpha (α)-2-adrenergic receptor agonist³ which decreases noradrenaline release resulting in attenuation of sympathoadrenal responses. Fentanyl is an opioid μ receptor agonist in high doses blunts the sympathetic response during intubation⁴. Esmolol is a cardio-selective β adrenergic blocker that has a rapid onset of action and short half life span also used for attenuating raised blood pressure during perioperative period. Studies in the west have also compared the three drugs for their efficacy, but a similar study in the Indian subpopulation is lacking.

II. Material and Methods:

This prospective, randomized & double blind study was conducted in the Department of Anaesthesia and Critical Care, Tata Main Hospital, Jamshedpur, India which is a 940 bedded multidisciplinary teaching hospital.

Study Design: Prospective randomized double blind clinical study

Study Location: Teaching hospital based study done in Department of Anaesthesia and Critical Care, Tata Main Hospital, Jamshedpur, India.

Study Duration: Time frame to address the study was from January 2015 to October 2016.

Sample size: Total study population taken was 150 patients.

Selection criteria: ASA I and II patients of aged between 18 to 65 years undergoing elective surgical procedure under general anaesthesia with tracheal intubation were included. Patients with difficult intubation, emergency cases pregnant patients and on medications like beta blockers, opioids and α agonists were excluded from the study.

Randomization and Grouping:

Sample size calculation: Patients fulfilling the inclusion criteria were randomly divided into three groups. The randomization list was generated into one of the three groups by a random number function using a computer generated table of random numbers, resulting in a list of 150 patients. The study drug was premixed to a volume of 10 ml and presented as coded syringes to the Anesthesiologist who was not an investigator in the study. All recordings were done by an Anesthesiologist blinded to the group allocation. The patients were randomly divided into three groups each (n=50) and study drug was administered over a period of 10 minutes:-

Group A (Esmolol Group):- received Esmolol 2mg/kg diluted to 10ml in 0.9% normal saline.

Group B (Fentanyl Group):- received Fentanyl 2 μ g/kg diluted to 10ml in 0.9% normal saline.

Group C (Dexmedetomidine Group):- received Dexmedetomidine 1 μ g/kg diluted to 10ml in 0.9% normal saline. The drug administrator and the person making the observation were blinded to the study. Intubation was done by an experienced anaesthesiologist not involved in the study.

III. Methods:

All patients were examined one day before and their lab results and consent were reviewed. At operation theatre fasting status confirmed, vascular access taken and patients were connected to pulse oximeter, electrocardiograph monitor and automated non-invasive blood pressure. Baseline (average of three readings) parameters of patients including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), rate pressure product (RPP) and peripheral oxygen saturation (SpO₂) were recorded in the operation theatre.

Patients were pre-oxygenated and study drug given in infusion over 10min as per protocol. Induction done using Inj. Propofol 2mg/kg and Inj. Succinylcholine 2 mg / kg intravenously followed by laryngoscopy and intubation at single attempt within 15 sec were included in the study.

Anaesthesia was maintained with oxygen/nitrous oxide (1:3), 0.8% to 1.5% isoflurane and Inj. vecuronium (initial intravenous bolus dose of 0.08 mg/kg followed by intermittent dose of 0.02 mg/kg) intravenously.

An average of three readings (T₀) taken in operation theatre were considered as baseline and all other measurements were compared with the baseline. Further readings are as: after study drug infusion (T₁), after induction agents given (T₂), immediately after intubation (T₃) and 1min (T₄), 3min (T₅), 5min (T₆), 7min (T₇) and 10 min (T₈) following intubation in all patients. The haemodynamic alterations like a decrease in MAP greater than 20% below the baseline value or SBP less than 90 mm of Hg were treated primarily by increasing the IV fluid infusion rate and then reducing isoflurane concentration. If hypotension (SBP < 90 mm of Hg) did not respond to fluid administration, then injection mephentermine 6mg IV was administered. Any incidence of bradycardia (HR < 50/min) was treated with injection atropine 0.6 mg IV. Surgical incision was done following the completion of the initial 10 mins of monitoring. The patients were ventilated & end tidal CO₂ level was maintained between 30 and 35 mm Hg. Intraoperative HR, SBP, DBP, MAP, RPP and SpO₂ levels were recorded at 5 min intervals. Additional doses of injection fentanyl 1 μ g/kg were administered according to hemodynamic variables to all the groups as rescue analgesia.

At the end of the surgery all patients were reversed using neostigmine 0.05 mg/kg and atropine 0.02mg/kg IV. Patients were extubated after adequate recovery and then shifted to anaesthesia recovery room and monitored for 60 min for any side effects like respiratory depression, hypotension, bradycardia, drowsiness, shivering, nausea or vomiting.

IV. Observations:

All groups were compared for demographic data (age, sex, weight, height, BMI), duration of surgery, MP scores, ASA grading and laryngoscopy time were measured. Haemodynamic parameters (HR, SBP, DBP, MAP, RPP and SpO₂) levels were measured and recorded along with any side effects.

V. Results:

Table 1- Comparison of Demographic parameters, Mallampatti scores, Laryngoscopy time and Duration of surgery among Group A(Esmolol), Group B(Fentanyl) and Group C(Dexmedetomidine).

	Group – A (N=50)	Group - B(N=50)	Group - C(N=50)
AGE	42.16 ± 10.98	43.08 ± 12.91	45.72 ± 13
GENDER(M/F)	21/29	16/34	17/33
ASA(I/II)	20/30	23/27	19/31
WEIGHT(KG)	67.15 ± 11.82	63.56 ± 12.65	67.24 ± 12.47
HEIGHT	163.52 ± 9.89	162.34 ± 10.33	162.22 ± 9.02
B.M.I	25.46 ± 4.05	24.08 ± 4.16	25.55 ± 4.41
MP(I/II/III)	16/24/10	19/21/10	12/26/12
LARYNGOSCOPY TIME	11.02 ± 0.89	10.82 ± 1.06	11.02 ± 0.96
DURATION OF SURGERY	59.38 ± 30.99	54.84 ± 28.61	56.62 25.97

There was no difference between three groups according to demographic parameters like age, sex, height, weight, body mass index ASA grading, Mallampatti scores, laryngoscopic time and duration of surgery as observed in table no- 1.

Table No-2 Comparison of mean heart rateamong Group A(Esmolol), Group B(Fentanyl) and Group C(Dexmedetomidine) at different time intervals:

Time interval	Group name			F _{cal} .	P – value
	Group -A	Group - B	Group - C		
T ₀ min	82.95 ± 8.99	85.97 ± 14.59	83.19 ± 7.26	1.22	p>0.05
T ₁ min	75.82 ± 8.67	82.6 ± 14.23	77.4 ± 7.27	5.71	P<0.05
T ₂ min	71.8 ± 8.31	78.9 ± 14.44	72.64 ± 6.70	7.00	P<0.05
T ₃ min	84.4 ± 6.63	94.12 ± 16.37	82.18 ± 5.69	17.57	P<0.05
T ₄ min	87.1 ± 6.52	96.02 ± 15.53	84.34 ± 4.37	18.46	P<0.05
T ₅ min	83.04 ± 6.26	93.74 ± 12.86	80.34 ± 4.14	32.25	P<0.05
T ₆ min	78.92 ± 5.81	89.08 ± 12.82	77.74 ± 3.97	27.26	P<0.05
T ₇ min	76.26 ± 5.42	85.3 ± 11.74	74.2 ± 3.81	28.79	P<0.05
T ₈ min	75.98 ± 4.40	80.38 ± 9.88	74.16 ± 3.15	12.08	P<0.05

Mean heart rate was significantly lower in Group- A and Group- C at most intervals with p < 0.05 as compared to Group- B when observed in table no-2. Group C had p < 0.05 at T₂ to T₈ time intervals as compared to Group-A and Group- B.

Table No-3 Comparison of mean SBP among Group A (Esmolol), GroupB (Fentanyl) and Group C (Dexmedetomidine) at different time intervals:-

Time Time interval	Group name			F _{cal} .	P – value
	Group -A	Group - B	Group - C		
T ₀ min	130.71 ± 9.53	132.15 ± 11.81	132.61 ± 11.61	0.40	p>0.05
T ₁ min	126.36 ± 8.82	126.04 ± 9.98	122.42 ± 4.61	3.61	P<0.05
T ₂ min	116.86 ± 7.60	116.98 ± 8.39	112.34 ± 4.48	7.08	P<0.05
T ₃ min	142 ± 7.08	144.36 ± 10.45	140.64 ± 5.32	2.83	P<0.05
T ₄ min	138.20 ± 6.07	142.82 ± 10.55	135.68 ± 4.83	11.47	P<0.05
T ₅ min	129.92 ± 4.32	131.98 ± 9.49	126.6 ± 3.83	8.96	P<0.05
T ₆ min	122.82 ± 4.59	121.96 ± 7.65	119.62 ± 3.19	4.59	P<0.05
T ₇ min	116.56 ± 3.18	117.3 ± 5.63	115.22 ± 2.82	3.35	P<0.05
T ₈ min	113.12 ± 2.82	113.96 ± 4.67	110.38 ± 6.33	7.52	P<0.05

Mean systolic blood pressure was significantly lower in Group- A and Group- C at T₁, T₂, T₄, T₅,T₆,T₇ and T₈ intervals with p < 0.05 as compared to Group- B when observed in table no-3.Group C had better attenuation of mean SBP as compared to Group A at all-time intervals except at T₀ and T₃ intervals.

Table No-4 Comparison of mean DBP among Group A (Esmolol), Group B (Fentanyl) and Group C (Dexmedetomidine) at different time intervals

Time interval	Group name			F _{cal} .	P – value
	Group -A	Group - B	Group - C		
T ₀ min	79.97 ± 4.23	80.71 ± 7.50	81.82 ± 6.05	1.17	p>0.05
T ₁ min	78.4 ± 5.11	77.06 ± 5.44	75.96 ± 3.66	3.24	P<0.05
T ₂ min	71.18 ± 3.01	72.56 ± 5.37	73.22 ± 2.57	3.66	P<0.05
T ₃ min	88.74 ± 2.28	89.72 ± 4.33	88.38 ± 2.78	2.27	P>0.05

T₄ min	88.44 ± 2.35	89.88 ± 3.92	88.92 ± 2.69	2.87	P>0.05
T₅ min	80.98 ± 2.63	83.88 ± 3.15	79.34 ± 3.43	27.68	P<0.05
T₆ min	74.2 ± 2.59	76.9 ± 3.22	73.26 ± 2.93	20.89	P<0.05
T₇ min	70.3 ± 3.11	71.8 ± 3.40	69.76 ± 2.98	5.56	P<0.05
T₈ min	69.24 ± 3.15	70.26 ± 2.45	68.14 ± 3.33	6.25	P<0.05

Mean diastolic blood pressure was significantly lower in Group- A and Group- C at some time intervals with p < 0.05 as compared to Group-B when observed in table no-4. Group A had p < 0.05 at T₄, T₅, T₆ and T₇ intervals when compared to Group-B.

Table No-05 Comparison of mean MAP among Group A (Esmolol), Group B (Fentanyl) and Group C (Dexmedetomidine) at different time intervals.:

Time interval	Group name			F _{cat}	P – value
	Group -A	Group - B	Group - C		
T₀ min	96.89 ± 4.87	97.86 ± 7.73	98.75 ± 6.65	1.02	p>0.05
T₁ min	94.38 ± 4.66	93.22 ± 6.01	91.54 ± 3.31	4.44	P>0.05
T₂ min	86.4 ± 3.16	87.38 ± 5.42	86.22 ± 2.32	1.31	P>0.05
T₃ min	106.48 ± 2.60	107.16 ± 5.08	105.76 ± 2.40	1.91	P>0.05
T₄ min	105.10 ± 2.98	107.48 ± 4.17	104.46 ± 2.87	11.02	P<0.05
T₅ min	97.24 ± 2.34	99.84 ± 3.89	95.08 ± 2.45	32.02	P<0.05
T₆ min	90.38 ± 2.39	91.84 ± 3.47	88.64 ± 2.18	17.09	P<0.05
T₇ min	85.72 ± 2.19	86.98 ± 3.21	84.86 ± 2.07	8.80	P<0.05
T₈ min	83.9 ± 2.26	84.88 ± 2.32	82.18 ± 2.80	15.25	P<0.05

Mean arterial blood pressure was significantly lower in Group- A and Group- C at some time intervals with p < 0.05 as compared to Group- B when observed in table no-5. Group A had p < 0.05 at T₄, T₅, T₆, T₇ and T₈ intervals in controlling mean MAP than Group B. Group C had p < 0.05 at T₅, T₆, T₇ and T₈ intervals than Group A. Group C found to have strongly significant at T₂ to T₈ intervals than Group B.

Table No 6- Comparison of mean RPP among three groups namely Group A (Esmolol), Group B (Fentanyl) and Group C (Dexmedetomidine) at different time intervals.

Time interval	Group name			F _{cat}	P – value
	Group -A	Group - B	Group - C		
T₀ min	10855 ± 1512.41	11400 ± 2477.40	11036 ± 1431.08	1.104	p>0.05
T₁ min	9591 ± 1364.67	10444.96 ± 2244.78	9474.8 ± 974.98	5.359	P<0.05
T₂ min	8406 ± 1244.05	9258 ± 2039.72	8166.46 ± 896.03	7.583	P<0.05
T₃ min	12001 ± 1296.47	13645.08 ± 2964.13	11555.4 ± 871.07	16.18	P<0.05
T₄ min	12047 ± 1153.52	13749.8 ± 2706.10	11444.6 ± 740.87	23.30	P<0.05
T₅ min	10793 ± 947.97	12375.82 ± 1950.27	10233.9 ± 598.54	36.58	P<0.05
T₆ min	9701 ± 885.89	10874.18 ± 1783.82	9298.46 ± 520.36	23.73	P<0.05
T₇ min	8890 ± 690.46	10006.88 ± 1462.49	8546.58 ± 433.87	31.19	P<0.05
T₈ min	8595 ± 537.79	9159.68 ± 1181.27	8189.06 ± 612.84	17.30	P<0.05

Mean rate pressure product was significantly lower in Group- A and Group- C at most time intervals with p < 0.05 as compared to Group- B when observed in table no-6. Group C had lesser increase in myocardial oxygen demand at all-time intervals as compared to Group A.

Side effects were not observed in any of the study groups.

Henceforth, among the three groups, Group C (Dexmedetomidine) causes minimal increase in myocardial oxygen demand following laryngoscopy and intubation and was found to be superior than both Group A (Esmolol) and Group B (Fentanyl). Group A (Esmolol) was more effective than Group B (Fentanyl).

VI. Discussion:

Haemodynamic responses to laryngoscopy and endotracheal intubation have been a topic of discussion since first observed by Reid et al² in 1940. These responses are transitory but in patients with ischemic heart disease, systemic hypertension and cerebrovascular diseases can result in deleterious effects like left ventricular failure, pulmonary oedema and myocardial ischemia. Therefore, there is a need to blunt this response.

Louizos et al⁵ concluded that Esmolol 2 mg/kg provides better hemodynamic stability than Esmolol 1.5 mg/kg which do not completely prevent the pressor and tachycardic response to laryngoscopy and intubation as studied by Shrestha et al.⁶ So, in present study, we had taken Esmolol 2 mg/kg as infusion dose as shown in previous studies⁷. In our study, Fentanyl was given at the dose of 2 µg/kg diluted in 10 ml normal saline over 10 min prior to induction given as infusion similar to study by Kharwar et al.⁸

Dexmedetomidine infusion of 1µg/kg done over 10 minutes in our study correlates with the studies conducted by Gogus et al,¹³ and this dose was found to be associated with lesser complications like severe bradycardia, hypotension and rhythm changes.

Comparison of Mean Heart rate:

It was observed that Esmolol leads to maximum increase in mean HR by 5% as compared to 11% by Fentanyl post intubation; moreover Esmolol had prolonged control over mean HR at T₅,T₆,T₇ andT₈ intervals which correlates with Feng et al⁹.

In our study Dexmedetomidine had maximum increase in mean HR by 1% whereas Esmolol by 1.5% when compared to their baseline. However, our study results are similar with Uysal HY et al¹¹. In our study Fentanyl leads to rise in mean HR by 11% whereas it was only 1% for Dexmedetomidine which correlates with study by Patel et al.¹⁴ Dexmedetomidine is better than Fentanyl in controlling heart rate correlates with studies done by Gunalan et al.¹⁵Hence, Esmolol is better than Fentanyl in attenuating the tachycardic response to laryngoscopy and intubation. However, Dexmedetomidine is superior to both Esmolol and Fentanyl in controlling the same.

Comparison of Mean Systolic blood pressure:

In our study Esmolol and Fentanyl had comparable effect in attenuating the mean SBP at almost all time intervals except at T₄ with p<0.0085. Our study not strongly correlates with post-intubation results of Feng et al⁹.

In our study increase in mean SBP was by 9% in Esmolol whereas it was only 6% for Dexmedetomidine which is contrary to Gogus N et al¹³ but it is similar with Vinit KS et al¹² which signifies Dexmedetomidine is better than Esmolol.

In the study conducted by Patel et al¹⁴ it was observed that Dexmedetomidine significantly attenuates stress response at intubation with lower increase in SBP (6%) compared with Fentanyl (23%), which is similar to our study, in which SBP decreased in the Dexmedetomidine group. However, Dexmedetomidine was found to exhibit superior effect compared to Esmolol and Fentanyl in controlling mean SBP following laryngoscopy and intubation.

Comparison of Mean Diastolic blood pressure:

Esmolol and Fentanyl had comparable effects at T₀, T₁, T₂, T₃ and T₈ but Esmolol had statistically significant control over mean DBP at T₄ (p= 0.0282), T₅, T₆ (p<0.0001) & T₇ (p= 0.0235) which correlate with Feng et al⁹.

Maximum rise in mean DBP was around 11% for Esmolol but only 8% for Dexmedetomidine group, our study result is contrary to Gogus N et al¹³ but it is similar with Vinit KS et al¹² and Uysal HY et al¹¹.Dexmedetomidine had statistically significant value at T₅, T₆ (p<0.0001), T₇ (p=0.0019)& T₈ (p= 0.0005) when compared with Fentanyl which is in concordance with that of Jain V¹⁶. Esmolol exhibits better response than Fentanyl in later periods. Dexmedetomidine exhibits a superior response compared to Esmolol and Fentanyl in controlling mean DBP.

Comparison of Mean MAP:

Esmolol was significantly better than Fentanyl in prevention of MAP at T₄, T₅, T₆, T₇ and T₈ post-intubation periods which correlate with Feng et al⁹.

Dexmedetomidine was found to have significantly superior effect than Esmolol at T₅ with P<0.0001 and T₆, T₇ and T₈ with p-value < 0.05 the results were similar with Uysal HY et al¹¹. Hence, the above observation signifies that overall Dexmedetomidine was found to have a superior effect than both Esmolol and Fentanyl in attenuating MAP. Comparing Esmolol and Fentanyl, Esmolol has better preservation of mean MAP than Fentanyl.

Comparison of Mean rate pressure product:

Rate pressure product is a measure of the stress put on the cardiac muscle based on the number of times it needs to beat per minute (HR) and the arterial blood pressure that it is pumping against (SBP). Levels of RPP in excess of 20,000 are more commonly associated with angina pectoris and myocardial ischemia.

Calculated as:

$$\text{Rate Pressure Product (RPP)} = \text{Heart Rate (HR)} \times \text{Systolic Blood Pressure (SBP)}$$

In our study, all three groups had comparable RPP at baseline (T₀) and there was no statistical difference. None of our observation shows an increased myocardial oxygen demand as all the values lies in low region (10000-14999) only.

Esmolol effect in preventing an abnormal rise in RPP was more pronounced at T₅, T₆ and T₇ post-intubation periods with p-value < 0.0001 which correlates with Ugur et al¹⁰. Dexmedetomidine group had lesser myocardial oxygen demand as compared to Esmolol and this difference was statistically significant. Dexmedetomidine had statistically significant control over mean RPP as compared to Fentanyl with p < 0.0001 at post-intubation periods of upto 10min.

VII. Conclusion

Hence, we concluded that Dexmedetomidine is superior to both Esmolol and Fentanyl. Between Esmolol & Fentanyl, Esmolol was found to have better myocardial oxygen demand profile as compared to Fentanyl during the post-intubation periods. No side effects observed in our study. As we did not evaluate whether the hemodynamic responses measured for “several minutes” after intubation could affect perioperative outcomes¹⁷ was limitation to our study. The sample size of the study (150) also disabled us to demonstrate other factors that might enroll to the changes for hemodynamic parameters. Hence, larger studies are still required to validate the findings.

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