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"Attenuation of hemodynamic response to laryngoscopy and endotracheal intubation - comparison of fentanyl, esmolol and metoprolol" in normotensive individuals

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Abstract

Introduction: Direct laryngoscopy and endotracheal intubation is an intrinsic component of general anaesthetic technique. It is a powerful stimulus which may evoke a plethora of sympathoadrenal stress responses. Various methods have been tried to attenuate the hemodynamic response. The objective of this study is to compare the effects of fentanyl, metoprolol, esmolol on the hemodynamic response during laryngoscopy and endotracheal intubation in normotensive individuals

Methods: These 120 patients were randomly divided into 4 groups (F, M, E and S) to receive either the test drug or the control. GROUP F received fentanyl 1µg kg^{-1}, GROUP M received Metoprolol 25µg kg^{-1}, GROUP E received Esmolol 100µg kg^{-1} and GROUP S received saline to determine which drug best attenuated the pressor response to laryngoscopy and endotracheal intubation. Baseline heart rate and blood pressure were recorded during laryngoscopy, endotracheal intubation and up to 10 minutes prior to surgery.

Results: Esmolol effectively reduced the increase in heart rate when given half a minute prior to laryngoscopy and endotracheal intubation. Fentanyl effectively reduced the increase in mean arterial pressure only after 3 minutes of laryngoscopy and endotracheal intubation (LETI). Metoprolol 25µg kg^{-1} produced a gradual reduction in heart rate and mean arterial pressure only after minutes of laryngoscopy making it ineffective for the same purpose.

Conclusion: We conclude that esmolol and fentanyl can be safely used to attenuate the pressor response during laryngoscopy and intubation. Fentanyl may be used to attenuate pressor response in patient whom β-blockers are contraindicated like patients with second and third degree heart block, congestive heart failure, acute bronchospasm, and other hemodynamic instability.

Keywords: Hemodynamic response, Esmolol, Metoprolol, Fentanyl, Intubation, Laryngoscopy.

Introduction

Direct laryngoscopy and endotracheal intubation is an intrinsic component of general anaesthetic technique. It is a powerful stimulus which may evoke a plethora of sympathoadrenal stress responses. The effects of laryngoscopy and endotracheal intubation were noted as early as 1940 when Reid and Brace concluded that cardiac reflex could originate in the trachea, larynx, bronchi or lungs.[(1)] Brunstein and others concluded that these changes could be attributed to the stimulation of cardio-accelerator nerves, implying an increase in the cardiac sympathetic tone rather than increase in vagal tone.[(2)] In 1951, King et al demonstrated that direct laryngoscopy or tracheal intubation is characterized by increase in the blood pressure and heart rate.[(3)] This increase in blood pressure and heart rate are mostly transient and variable.[(3-6)]

The haemodynamic response to laryngoscopy and endotracheal intubation usually does not pose a problem for most patients but may be problematic to those with hypertension, cardiovascular or cerebrovascular diseases.[(7,8)] Various attempts have been made to attenuate the pressor response including anaesthesia, adrenergic blocking drugs, sodium nitroprusside and hydralazine among others.

Thiopental induction is often supplemented with small doses of fentanyl to minimize the intolerance towards the endotracheal tube. In addition, there is evidence from neurosurgical patients that fentanyl supplementation 5µg kg^{-1} provides some protection against increase in arterial pressure and heart rate following laryngoscopy and endotracheal intubation.[(9)] Further it is known that fentanyl in large doses in cardiac patients effectively blunts the intubation response in cardiac patients.[(10)]

Many authorities advocate the use of beta adrenergic antagonists to inhibit the sympatho adrenal response which follows tracheal intubation.[(11-16)] Coleman and Jordan reported only a small increase in systolic arterial pressure in patients who received metoprolol.[(17)] More attention is given to the use of selective beta adrenergic antagonists especially metoprolol and esmolol in preventing the reflex sympathoadrenal responses.[(18-20)]

The objective of this study was to compare the effects of fentanyl, metoprolol, esmolol on the hemodynamic response during laryngoscopy and endotracheal intubation.

This randomized prospective double blind clinical study was conducted over a period of two years in the department of Anaesthesiology of a tertiary hospital.

Materials and Methods

The approval for performing this study was obtained from the ethical committee. One hundred and

twenty patients admitted in our hospital for undergoing surgery under general anaesthesia in age group of fifteen to sixty-five years belonging to ASA grade I and ASA grade II were included in the study. The patients were randomly divided into four groups (F, M, S and E) of thirty each by the consultant in charge. Trial drugs and dosages of our study drugs were group F-fentanyl 1 µg kg^{-1}, group M- metoprolol 25 µg kg^{-1}, group S-saline 5ml saline and group E-esmolol 100 µg kg^{-1}.

Patients with hypertension, diabetes mellitus, ischemic heart disease, patients with second and third degree heart block, congestive heart failure, acute bronchospasm, low systolic blood pressure (less than 100 of Hg), slow heart rate(less than 60 beats per minute) and other hemodynamic instability and patients with anticipated difficulty in intubation, those who required more than one attempt for intubation and those patients in whom the duration of laryngoscopy exceeded 30 s were excluded from the study.

Written informed consent was obtained from all patients. All these patients were premedicated with oral diazepam 0.1 mg kg^{-1} the night prior to surgery. Randomization was based on computer generated number. The grouping of the patients as well as the coding of the trial drugs was known only to the anaesthesiologist 1, who allotted the drugs to each patient. The trial drugs including saline as control was prepared and diluted in equal volumes (5ml) by the same anaesthesiologist 1. The drugs were prepared in two syringes (one with the drug and other with saline labelled as A and B, since the duration of action of both the study drugs are different esmolol (Group E) was given 30 seconds before laryngoscopy here the first syringe A will be saline and second syringe B will be esmolol and metoprolol(Group M) and fentanyl(Group F) was given 3 minutes before laryngoscopy, here the syringe A will have either Fentanyl or Metoprolol according to coding and second syringe B will have saline, only the anaesthetist loading the drugs was aware about drugs used in study according to coding this was specifically done to blind the anaesthetist who is delivering the drug and to avoid bias, saline group(Group S) both the syringes will be loaded with saline) drugs was administered by anaesthesiologist 2 who also monitored the parameters was not aware about the drug in both the syringes.

The patients were premedicated with oral diazepam 0.1 mg kg^{-1} one hour prior to surgery. After shifting the patient to the operating room, standard non-invasive monitoring of electrocardiography (ECG), non-invasive blood pressure (NBP), oxygen saturation (SaO2), were instituted and baseline values of heart rate and blood pressure were recorded.

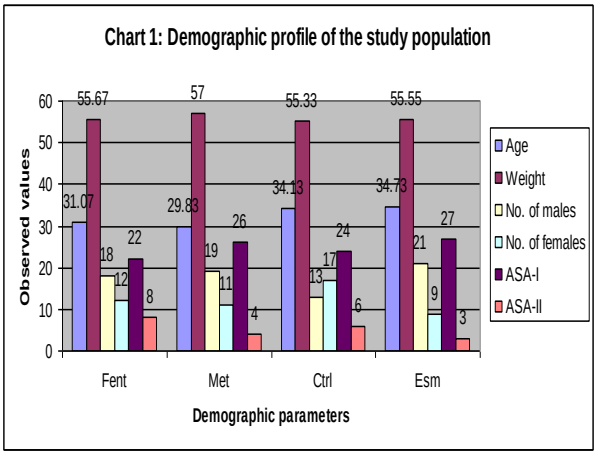
After preoxygenation with 100% oxygen for three minutes, anaesthesia was induced using intravenous thiopentone sodium 4-5 mg kg^{-1}, oxygen 40%, nitrous oxide 60% isoflurane 0.5% and injection vecuronium 0.1 mg kg^{-1} along with one of the prepared solution (A) was given intravenously. Two and a half minutes later the second syringe(B) loaded with the prepared study drug was given intravenously. Three minutes after vecuronium a gentle laryngoscopy was done by a consultant, the trachea was intubated with appropriate sized endotracheal tube in less than 30 seconds. Heart rate and blood pressure were noted at one, two, three, five and ten minutes' intervals Anaesthesia was maintained using nitrous oxide and oxygen (60%-40%), isoflurane 0.5 -0.8% and intermittent doses of vecuronium 0.02mg kg^{-1}. Positioning of the patient and commencement of the surgery was allowed only after the first ten minutes to avoid any haemodynamic response to the same.

Statistical Analysis: All data were recorded in Microsoft excel chart, and statistical analysis was done by Statistical Package for Social Sciences (SPSS Statistics for Windows, Version 17.0. SPSS Inc., Chicago) software version 17. Hemodynamic data (HR, SBP, DBP, and MAP) was expressed as mean±standard deviation. Haemodynamic data were analysed using repeated measures of ANOVA to find the statistical difference within the groups.

Results

The following observations were made after studying 120 patients belonging to 4 groups in whom the study drugs or the control drug was used to attenuate the hemodynamic response to laryngoscopy and endotracheal intubation. Group F Fentanyl, Group M: Metoprolol, Group S: Control, Group E: Esmolol.

The demographic profile in all the four groups was comparable in terms of age, sex, weight and ASA physical status. (Chart 1)



The baseline heart rate was comparable between the groups and there was no significant difference. However, Group E(esmolol) differed significantly in comparison to group F(fentanyl) and group S with (P <0.05) during laryngoscopy. The heart rate of group E (esmolol) at 2 minutes after laryngoscopy and endotracheal intubation was significantly low from

baseline heart rate in comparison to all the other groups ($P < 0.05$). The heart rate of group E (esmolol) at 3 minutes after laryngoscopy and endotracheal intubation remained significantly low ($P < 0.01$) in comparison to group F and group S. With fentanyl and metoprolol the mean heart rate increased significantly at the time of laryngoscopy (103.70 ± 15.905) and (98.90± 11.151) respectively, and remained so in the first to tenth minute after laryngoscopy and reached baseline only after ten minutes. With control there was rise in the mean heart rate during the time of intubation and remained elevated up to the tenth following intubation and did not reach the baseline values. (Table 1)

Table 1: Changes observed in heart rate in the study population

S No.	Time	Fentanyl (n = 30)	Metoprolol (n = 30)	Control (n = 30)	Esmolol (n = 30)
1	Before premedication	92.10 ± 6.930	84.83 ±10.168	91.87 ± 13.670	90.40 ± 16.446
2	After premedication	96.67 ± 10.327	85.57 ± 11.74	94.83 ± 12.365	93.87 ± 11.584
3	At induction	98.60 ± 11.346	88.27 ±14.895	92.37 ± 9.736	89.87 ± 8.809
4	After study drug	97.70 ± 12.991	93.80 ± 13.361	96.68 ± 8.531	90.13 ± 9.254
5	At intubation	103.70 ±15.905	98.90 ± 11.151	103.60 ±12.923	93.93 ± 12.966 *$
6	1 minute	96.87 ± 12.635	95.83 ± 10.346	97.00 ± 11.774	91.87 ± 11.343
7	2 minutes	96.33 ± 11.845	98.17 ± 9.385	96.20 ± 11.047	88.00 ± 12.401*†$
8	3 minutes	95.40 ± 12.878	90.87 ± 6.230	94.00 ± 10.505	85.07 ± 11.020*$
9	5 minutes	90.50 ± 15.441	87.20 ± 10.104	89.67 ± 12.677	83.40 ± 13.446
10	10 minutes	89.13 ± 11.991	84.07 ± 10.531	86.77 ± 10.747	82.87 ± 10.371

*****Significance between group M with group S and group E, † Significance between group F and other groups, **$** Significance between group S and group E

The baseline systolic blood pressures, diastolic blood pressures and mean arterial pressure in all the four were comparable. A significant difference ($P<0.001$) was found between group F (fentanyl) with Group M and group S. At one-minute following intubation a significant difference ($P<0.001$) was found in patients with fentanyl in comparison to patients on esmolol ($P < 0.01$) and control ($P < 0.05$). The systolic blood pressure of group F was significantly low in comparison to group M ($P < 0.005$) and group C ($P< 0.05$). (Tables 2, 3, 4)

Table 2: Changes observed in systolic blood pressure in the study population

S. No.	Time	Fentanyl (n = 30)	Metoprolol (n = 30)	Control (n = 30)	Esmolol (n = 30)
1	Before premedication	130.80 ± 18.06	133.47±18.73	135.97±19.50	139.60±16.74
2	After premedication	130.50 ±22.18	127.80±16.00	131.73±20.02	137.07±17.53
3	At induction	121.47 ± 16.97	124.93±14.32	128.93±16.05	120.93±18.84
4	After study drug	121.87 ±15.38	135.27±19.57	133.87±23.07	127.53±23.90
5	At intubation	137.60± 26.26	157.17±16.57*	159.20±24.68*	152.13±16.60
6	1 minute	130.47± 21.25	151.13±14.19*	145.70±22.28*	137.07±19.41†
7	2 minutes	127.10±15.99	144.20±15.15*	140.30±20.52*	135.27±19.62
8	3 minutes	122.60 ±16.51	131.43±12.63	129.93±16.25	126.07±17.63
9	5 minutes	121.03± 13.14	124.40±10.48	126.33±11.47	125.73±17.17
10	10 minutes	122.03 ±15.99	121.80±10.21	125.37 13.60	126.20±17.12

* Significance between group F and other groups † Significance between group M with group S and group E

Table 3: Changes obversed in diastolic blood pressure in the study population

Sl. No.	Time	Fentanyl (n = 30)	Metoprolol (n = 30)	Control (n = 30)	Esmolol (n = 30)
1	Before premedication	84.03±10.987	80.90± 9.915	83.63±7.313	85.20±6.228
2	After premedication	83.67±13.581	77.70±14.108	81.70 ± 12.546	88.80±6.197
3	At induction	79.47±15.081	80.73±15.552	81.03 ± 16.338	74.40±15.913
4	After study drug	76.17±12.641	86.17±16.511	80.63± 16.664	73.87±16.511
5	At intubation	88.23±18.277	97.60±13.903	97.57± 19.006	88.20±16.935†
6	1 minute	84.83±18050	92.53±14.503	88.67±19.148	82.33±12.691
7	2 minutes	84.73±13.365	88.50±13.521	86.33±15.955	83.93±11.026

8	3 minutes	79.23±12.508	85.43±9.706	82.63±11.980	76.67±11.028
9	5 minutes	77.63±9.099	79.6312.004	78.83 ±11.980	75.20±10.091
10	10 minutes	78.97±10.397	78.67±10.759	78.27±11.956	74.20±12.257

† Significance between group S and group E

Table 4: Changes observed in mean arterial pressure in the study population

Sl. No.	Time	Fentanyl (n = 30)	Metoprolol (n = 30)	Control (n = 30)	Esmolol (n = 30)
1	Before premed	99.62± 11.47	98.42± 11.42	101.07 ±8.84	103.33± 9.14
2	After premed	99.37± 14.29	94.49 ±13.12	98.37 ±13.20	100.22± 9.83
3	At induction	93.44 ±13.91	95.45 ±14.73	97.00 ±15.34	89.91± 15.56
4	After study drug	91.40 ±11.08	102.53± 16.70	98.37± 15.44	91.75 ±12.25
5	At intubation	104.68 ±19.72	117.455± 14.06*	118.11 ±19.90*	109.51 ±15.65
6	1 minute	100.04± 17.99	112.06 ±13.46*	107.67± 19.17	100.57± 13.02
7	2 minutes	98.86± 13.28	107.07 ±12.623	104.32± 15.84	101.04 ±11.23
8	3minutes	93.69± 12.59	100.77 ±9.85	98.40 ±13.25	93.13 ±11.29
9	5 minutes	92.10± 9.40	94.55± 9.72	94.63± 9.91	92.04 ±11.22
10	10 minutes	93.32 ±11.45	93.04± 9.47	93.04± 9.47	91.53± 10.61

* Group F is significant with Group M and Group S.

Discussion

Maintenance of airway by means of endotracheal intubation is the integral part of general anaesthesia which allows intermittent positive pressure ventilation and prevents pulmonary aspiration. However, laryngoscopy and endotracheal intubation produces haemodynamic stress response, which is manifested as increase in blood pressure and heart rate. This increase in heart rate and blood pressure is transient in normotensive individual, but in patients with cardiac or cerebrovascular diseases it can cause several complications like ischaemia, ventricular arrhythmias and pulmonary edema, thinning or rupture of cerebral or aortic aneurysms.[7] Therefore attempts have been made to minimise these reflex responses by different intravenous and inhalational agents.[8]

Changes in Heart Rate: In our study, we studied the haemodynamic response to laryngoscopy and endotracheal intubation up to 10 minutes. There were no significant heart rate differences at baseline. An increase in the mean heart rate was noted in all the groups in comparison to the baseline values during laryngoscopy. But Group E (esmolol) showed a significantly reduced mean heart rate of 93.93 ± 12.966 during laryngoscopy in comparison to other groups ($P < 0.05$) where the increase in heart rate was only 3.75% from the baseline in comparison to the other groups at laryngoscopy. The mean heart rate was found to be significantly reduced at the first to tenth minute following laryngoscopy and endotracheal intubation and thereafter remained below the baseline in group E when compared to the other group ($P < 0.01$).

Steven et al,[21] noted maximum increase in heart rate was seen with placebo and lidocaine and fentanyl group during intubation and a fall in heart rate was observed with esmolol (18%) with $P < 0.05$. Singh Het al[22] compared lidocaine, nitroglycerin and Esmolol, concluded that esmolol was more effective in attenuating the pressor response when compared to lidocaine and nitroglycerine and the response to esmolol was similar to our study. Hussain AM, Sultan ST[23] in their study compared the efficacy of single bolus dose of esmolol and fentanyl found that the rise in heart rate was minimal in esmolol group and was statistically significant. Javaid et al[24] compared the effects of bolus doses of metoprolol and esmolol in attenuating the pressor response. They observed significant fall in heart rate by 11.70% at the time of intubation and up to five minutes following intubation in patients who received esmolol ($P <0.001$). This study also correlated well with the changes in heart rate seen in our study.

Changes in Systolic Blood Pressure: The baseline values of systolic blood pressure with our study drugs were comparable in all the four groups. An increase in systolic blood pressure was noticed in all the groups during laryngoscopy in comparison to the baseline values. The systolic blood pressure increased by 5.1% in group F, 17.75% in group M, 17.08% in group S and 9.3% in group E during laryngoscopy. Group F (fentanyl) showed a significantly reduced systolic blood pressure during laryngoscopy in comparison to other groups ($P < 0.001$) where the increase in systolic blood pressure was only 5.1% from the baseline in comparison to the other groups at laryngoscopy. Group E also showed a decrease in systolic blood pressure (an increase of 9.3% from the baseline) in comparison to group M and group S, however this reduction was not statistically significant ($P <0.05$). The reduction in systolic blood pressure in the fentanyl group was consistently found to be present, at one minute, two minutes, three minutes, five minutes and ten minutes following intubation ($P < 0.001$). The systolic blood pressure changes seen in our study correlates well with

the study performed by Dahlgren et al[14] where subjects were randomly allocated to receive saline or fentanyl 5µg kg^{-1} at the time of induction of anaesthesia and intubation performed. It was found that there was an initial decrease in systolic blood pressure by 24.50% with P <0.05 in patients who received fentanyl when compared to placebo. This study showed that haemodynamic response can be significantly attenuated by intravenous administration of opioid analgesic. Kautto et al[15] performed a study on 45 normotensive surgical patients who received fentanyl and placebo three minutes before laryngoscopy and intubation and they found that fentanyl group showed a significant decrease in systolic blood pressure during laryngoscopy and endotracheal intubation by 13% (P < 0.001).

Changes in Diastolic Pressure: Similarly, the baseline diastolic blood pressure values were found to be comparable among the four groups. An increase in diastolic blood pressure was noticed in all the groups during laryngoscopy in comparison to the baseline values. The diastolic blood pressure increased by 5. 71% in group F (88.23 ± 18.277), 20.64% (97.60 ± 13.903) in group M, 15.97% (97.57 ± 19.006) in group S and 3.52% (88.20 ± 16.935) in group E (esmolol). Group E showed a significantly reduced diastolic blood pressure of 88.20 ± 16.935 during laryngoscopy in comparison to other groups (P< 0.001) where the increase in diastolic blood pressure was only 3.52% from the baseline in comparison to the other groups at laryngoscopy Group F also showed a decrease in diastolic blood pressure (an increase of 5.71% from the baseline) in comparison to group M and group S, however this reduction was not statistica1ly significant (P < 0.05). Esmolol was found to be most effective in reducing the diastolic blood pressure in comparison to all the other study drugs (P < 0.05). The diastolic blood pressure remained reduced from the first to the tenth minute following laryngoscopy and intubation. Javaid et al[24] compared the effects of bolus doses of metoprolol with esmolol in attenuating the pressor response. These patients randomly received the placebo or the trial drugs. They observed significant fall in diastolic blood pressure by 11.5% (P <0.05) at the time of intubation and up to five minutes following intubation. This study also correlated well with our study.

Changes in Mean Arterial Pressure: The baseline mean arterial pressures in all the four groups were comparable. The mean arterial pressure in all the four groups increased during laryngoscopy in comparison to the baseline values. The mean arterial pressure increased by 4.17% in group F (104.68 ± 11.08), 17% (102.53 ± 14.06) in group M, 16.87% (118.11 ± 19.90) in group S and 5.9% (109.51 ± 15.65) in group E during laryngoscopy. It was observed that there was a significant reduction in the mean arterial pressure in group F during laryngoscopy in comparison to other groups (P < 0.05) where the increase in mean arterial pressure at the time of laryngoscopy was only 4.17% in comparison to the other groups in comparison to the baseline values Group E also showed a decrease in mean arterial pressure (an increase of 5.9% from the baseline) in comparison to group M and group S, however this reduction was not statistically significant(P <0.05). This reduction in the mean arterial pressure was consistently present in the first, second, third fifth and the tenth minute in group F (P <0.05). In the study performed by Chung et al[25] on mean arterial pressure, systolic and diastolic blood pressure rise were significantly smaller in the group receiving fentanyl at one-minute post intubation in the control group, compared to the fentanyl group. There was an exaggerated rise in mean arterial pressure were in the control group compared to the fentanyl group. In the study by Ko et al[26] the group which received fentanyl there was a 15% increase in the heart rate and a 11% increase in the MAP from baseline during intubation. The rise was higher in the other groups (28-40%). This is consistent with our findings. In Iyer et al[27] studied the rise in MAP was 17% in controls and 7% in 2µg kg^{-1} group, being lower than the baseline with higher doses of fentanyl. Splinter et al[28] in a study on elderly patients receiving 1.5 or 3.0 µg kg^{-1} of fentanyl showed minimal fall in systolic, diastolic and mean arterial pressure, heart rate and rate pressure product (P < 0.05). Fentanyl decreased the incidence of marked fluctuations in hemodynamic variables often seen in geriatric patients in comparison to lidocaine (P <0.05). In fentanyl group, mean arterial pressure was below baseline throughout the study period.[27,28] In our study anaesthesia was induced using injection thiopentone sodium 4-5 mg kg^{-1} nitrous oxide and oxygen (60% - 40%) isoflurane 0.5 %. In case of group F and group M, the prepared solution was given along with injection vecuronium 0.1 mg kg^{-1}. Two and half minutes later the control solution (saline) was given intravenously. Endotracheal intubation was performed three minutes after administration of vecuronium with appropriate sized endotracheal tube. In case of group E, the control was given along with the induction agents and esmolol was given two and half minutes later and trachea intubated three minutes after administration of vecuronium. Above data suggests that fentanyl in the dose as low as 1µg kg^{-1} given intravenously along with the induction agents keeps the mean arterial pressure below the baseline values and esmolol 100 µg kg^{-1} given two and half minutes after the induction agents prevents increase in heart rate during intubation and therefore useful in attenuation of pressor response to laryngoscopy and endotracheal intubation.

We conclude that esmolol and fentanyl can be safely used to attenuate the hemodynamic response during laryngoscopy and intubation. Metoprolol may be used in patients who are already receiving beta blockers as it helps in controlling diastolic blood pressure for

longer period and is less expensive compared to esmolol. Saline group, the increased hemodynamic parameters did not touch baseline even after ten minutes after laryngoscopy and intubation, thus it is better to use one of the study drug to attenuate hemodynamic response. Fentanyl may be used to attenuate pressor response in patient whom β-blockers are contraindicated like patients with second and third degree heart block, congestive heart failure, acute bronchospasm, low systolic blood pressure (less than 100 of Hg), slow heart rate (less than 60 beats per minute) and other hemodynamic instability.

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