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Attenuation of Cardiovascular Responses to Laryngoscopy and Intubation: A Comparative Study between I.V. Esmolol Hydrochloride and Fentanyl Citrate

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Abstract

Context: Endotracheal intubation and laryngoscopy are basic and fundamental tools of anaesthesiologists to take care of the airway. It is important to find an effective means of attenuating sympathetic response to laryngoscopy and intubation. *Aims:* Our aim was to compare and assess the efficacy of i.v esmolol and fentanyl before laryngoscopy and tracheal intubation and to observe the variations in sympathetic response to laryngoscopy and intubation. *Methods and Materials:* This study was a prospective randomized double-blind study on patients undergoing ENT, orthopaedics, gynaecological, general surgical, neurological and laparoscopic procedures. A clinical comparative study of attenuation of the sympathetic response to laryngoscopy and intubation was done in 60 patients of American Society of Anesthesiologist (ASA) grade I or II, age between 20 to 50 years of both the sexes and Mallampati airway assessment of grade I, posted for elective surgeries selected randomly. In study group I (n=30) patients receive 2 mg/kg esmolol IV, 3 minutes before laryngoscopy and intubation. In study group II (n=30) patients in this group receive 2 μg/kg of fentanyl IV, 5 minutes before laryngoscopy and intubation. *Statistical analysis used:* The statistical analysis was done by STATA 11.2 (College Station TX USA). Students independent sample t-test and Chi-square test were used. $p < 0.05$ considered as statistically significance. *Results:* Maximum rise in systolic blood pressure was observed at the post-intubation first minute, i.e., 133.73 ± 10.36 and 144.43 ± 10.92 in the Group I and II from the baseline, respectively but maximum rise of heart rate (103.43 ± 7.50) was during the first minute in group I but maximum rise of heart rate (87.83 ± 5.45) was in group I. The diastolic blood pressure and mean arterial pressure changes was significant between fentanyl and esmolol groups at 1 and 3 minute and post-induction, 1 and 5 minute respectively. Group I showed better control of heart rate during laryngoscopy and intubation at the first, 3 and 10 min after intubation compared to other groups ($p < 0.05$). *Conclusions:* Esmolol is more effective than fentanyl in attenuation of the sympathetic response to laryngoscopy and intubation.

Keywords: Attenuation; Esmolol; Fentanyl; Cardiovascular response; Intubation; Laryngoscopy.

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Introduction

Endotracheal + intubation and laryngoscopy are basicand fundamental tools of anaesthesiologists totake care of the airway. In view of anaesthetic management and critical care endotracheal intubationhas become ancrucial part and has been practised following its description by Rowbotham and Magill in 1921. circulatory response following laryngeal and tracheal stimulation following laryngoscopy and tracheal intubation as reflex sympathoadrenal stimulation [1,2] described by Reid and Brace (1940) and King and Harris (1951). In high-risk patients especially those with cardiovascular diseases, increased intracranial pressure or anomalies of cerebral vessels, increases in heart rate and blood pressure because of sympathoadrenal responsemay have detrimental effects although short lived. Pressor responses induced bylaryngoscopy and tracheal intubation have been associated with an increase in catecholamine levels [3]. Elevation of blood pressure and heart rateis related with the rise of these catecholamines.

Few authors additionally consider that the intubation period is one of the great risk factor in surgical patients with coronary artery diseases, hypertension, cardiac dysfunction or cerebrovascular disease, although the response is transient, invariable, significant, often persistent, and of great concern. Laryngoscopy and tracheal intubation techniques are notsolely confined to the operating room but are also used for resuscitative procedures. Some instances are diagnostic laryngoscopy, fiberoptic bronchoscopy; to prevent aspiration, protection of airway and for mechanical ventilation. Besides minimizing the cardiovascular response, anaesthesia for patients at risk should additionally satisfy the following requirements; it must be applied regardless of patient collaboration, prevent impairment of cerebral blood flow and avoid arousal of the patient. Among the suggested procedures IV lignocaine, fentanyl and esmolol appear to fulfil the above-mentioned criteria. In attenuation of pressor response, intravenous (IV) lignocaine has shown variable results. Large doses of fentanyl may result in unwanted side effects like nausea, vomiting, and respiratory depression. Esmolol has been consistently associated with control of pressor response to laryngoscopy and intubation.

The present study is designed to know the efficacy of esmolol 2 mg/kg IV bolus in comparison to IV fentanyl 2 μg/kg [4,6] in attenuating the sympathetic responses to laryngoscopy and tracheal intubation.

Materials and Methods

This study was a prospective randomized double-blind study on patients undergoing ENT, orthopaedics, gynaecological, general surgical, neurological and laparoscopic procedures. The study conformed to the Helsinki declaration (World Medical Association, 1995) and the applicable guidelines for good clinical practices were looked into consideration. After approval from the institutional ethical committee, written informed consent was obtained from all the patients before enrolment in the study. A clinical comparative study of attenuation of the sympathetic response to laryngoscopy and intubation was done in 60 patients of American Society of Anesthesiologist (ASA) grade I or II, agebetween 20 to 50 years of both the sexes and Mallampati airway assessment of grade I, posted for elective surgeries selected randomly. The exclusion criteria were unwilling patients, emergency surgeries, anticipated difficult intubation, ASA grade III or higher, patients with cardiovascular diseases, on beta blockers or calcium channel blockers, patients in whom laryngoscopy and intubation proved to be prolonged or difficult.

A prospective sample size calculation indicated that 30 patients were required in each group to have 80% power to detect a 25% difference at Type I (α) error of 0.05. 60 cases are divided into two with 30 cases in each group. In study group I (n=30) patients receive 2 mg/kg esmolol IV, 3 minutes before laryngoscopy and intubation. In study group II (n=30) patients in this group receive 2 μg/kg of fentanyl IV, 5 minutes before laryngoscopy and intubation.

On entering the Operation Theater, baseline vital parameters such as pulse oximeter (SpO_2), non-invasive blood pressure (NIBP) andelectrocardiogram (ECG) monitors were connected and preinduction heart rate (HR), systolic blood pressures (SBP) and diastolic blood pressure (DBP) were recorded. After securing the intravenous (i.v.) line, 10 ml/kg/h of Ringer's lactate (RL) infusion was started before infusing any medication. All the patients were preoxygenated with 100% oxygen for 3 minutes before induction. Induction was achieved with inj. Propofol 2 mg/kg IV. After induction of anaesthesia (loss of eyelash reflex) HR, SBP and DBP were recorded. In group I, esmolol i.v. was administered 3 minutes before laryngoscopy and intubation. In group II, fentanyl i.v. was administered 5 minutes before laryngoscopy and intubation.

Endotracheal intubation was facilitated by vecuronium bromide at a dose of 0.1 mg/kg IV. Laryngoscopy was done using rigid laryngoscope with a standard Macintosh blade. Intubation was done with appropriate sized, disposable, high volume low pressure cuffed endotracheal tube. Oral intubation was done for all surgical procedures. Laryngoscopy and intubation were done within 15 to 20 seconds. HR, SBP and DBP, were recorded at 1, 3, 5, and 10-minute intervals from the onset of laryngoscopy. Patients were connected to closed circuit and anaesthesia was maintained with oxygen (50%), N_2O (50%), Isoflurane 1%-2% and non-depolarizing muscle relaxant vecuronium bromide at a dose of 0.1 mg/kg IV and IPPV. Adequacy of ventilation was monitored clinically and SpO_2 was maintained at 99-100%. Positioning, epinephrine infiltration throat packing and surgery were withheld until the completion of recording. At the end of the surgery, residual neuromuscular blockade was reversed by an appropriate dose of neostigmine and glycopyrrolate followed by tracheal extubation. An observation was made related to adverse effects of drugs and anaesthesia related problems and was attended to appropriately.

Statistical Methods

The statistical analysis was done by STATA 11.2 (College Station TX USA). Shapiro Wilk test has been used to check the normality, Students independent sample t-test were used to find the significant difference between the age, heart rate, blood pressure with the treatment groups, the heart rate and blood pressure measured and analysed different time points of pre-induction, post induction, 1 minutes, 3 minutes, 5 minutes and 10 minutes and its expressed as mean and standard deviation. Chi-square test has been used to measure the association between the genders with treatments. $p < 0.05$ considered as statistically significance.

Results

Mean age of Group-I was 36.07 ± 10.92 years and that of Group-II was 35.23 ± 10.28 years, this difference was statistically not significant (p-0.762). Similarly, the mean weight of Group-I was 59.83 ± 6.64 kg and that of Group-II was 60.73 ± 4.51 kg. This difference was statistically not significant (p=0.688). The sex ratio between to two groups is also similar and statistically not significant (p-value 0.795). There was no significant difference in the demographic profile amongst both groups regarding age, sex, weight and ASA grade of the patients [Table 1].

Table 2 shows the mean basal heart rate i. e. heart rate before induction in Group I was 78.50 ± 6.03 and in Group II was 80.10 ± 7.26. This difference was statistically not significant (p=0.357). At 1 min, 3 min and 10 min post-intubation HR was significantly lower in the esmolol group (group I) compared to the fentanyl group (group II) (p<0.001) whereas at 5 min difference was statistically not significant (p=0.868).

Table 1: Demographic profile of the cases in the both groups

Particulars	Group I	Group II	p value
Age (years) (mean ± S.D)	36.07 ± 10.92	35.23 ± 10.28	0.762
Sex (male: female)	14/16	13/17	0.795
Weight (kg.) (mean ± S.D)	59.83 ± 6.64	60.73 ± 4.51	0.688
ASA (I: II)	19:11	22:8	0.598

Table 2: Comparison of heart rate among two groups

	Group I (Esmolol) Mean ± SD	Group II (Fentanyl) Mean ± SD	Mean difference	p-value
Pre induction	78.50 ± 6.03	80.10 ± 7.26	1.60	0.357
Post induction	83.0 ± 5.58	83.73 ± 7.68	0.73	0.674
1 Minute	87.7 ± 6.11	103.43 ± 7.50	15.73	<0.001
3 Minutes	87.83 ± 5.45	101.47 ± 9.98	13.63	<0.001
5 minutes	87.07 ± 5.17	87.27 ± 5.67	0.20	0.868
10 Minutes	77.30 ± 4.23	82.73 ± 5.67	5.43	<0.001

Table 3: Comparison of systolic blood pressure among study groups

	Group I (Esmolol) Mean ± SD	Group II (Fentanyl) Mean ± SD	Mean difference	p-value
Pre induction	128.87 ± 11.49	131.0 ± 11.64	2.13	0.478
Post induction	124.73 ± 11.12	129.83 ± 11.35	5.10	0.084
1 Minute	133.73 ± 10.36	144.43 ± 10.92	10.70	<0.001
3 Minutes	133.60 ± 9.60	142.20 ± 10.28	8.60	0.001
5 minutes	132.07 ± 9.23	137.37 ± 10.44	5.30	0.042
10 Minutes	127.57 ± 9.16	129.07 ± 11.74	1.50	0.583

Table 4: Comparison of diastolic blood pressure among study groups

	Group I (Esmolol) Mean ± SD	Group II (Fentanyl) Mean ± SD	Mean difference	p-value
Pre induction	76.63 ± 5.52	77.10 ± 5.79	0.47	0.751
Post induction	83.03 ± 21.12	75.90 ± 5.64	7.13	0.079
1 Minute	81.60 ± 4.68	86.10 ± 3.99	4.50	<0.001
3 Minutes	81.87 ± 4.09	84.43 ± 4.32	2.57	0.022
5 minutes	80.43 ± 4.43	80.43 ± 3.39	-	1.000
10 Minutes	77.50 ± 4.19	76.40 ± 4.85	1.10	0.351

Table 5: Comparison of mean arterial blood pressure among study groups

	Group I (Esmolol) Mean ± SD	Group II (Fentanyl) Mean ± SD	Mean difference	p-value
Pre induction	93.92 ± 5.79	95.07 ± 6.43	1.14	0.473
Post induction	90.83 ± 5.16	93.88 ± 6.15	3.04	0.042
1 Minute	98.95 ± 5.40	105.52 ± 5.41	6.57	<0.001
3 Minutes	99.08 ± 4.74	103.71 ± 5.34	4.63	0.001
5 minutes	97.61 ± 4.72	99.47 ± 4.44	1.86	0.121
10 Minutes	94.63 ± 4.71	93.95 ± 6.02	0.68	0.629

Table 3 shows mean preinduction systolic blood pressure in Group I was 128.87 ± 11.49 and in Group II was 131.0 ± 11.64. This difference was statistically not significant (p=0.478). At 1 min, 3 min and 5 min post-intubation SBP was significantly lower in the esmolol group (group I) compared to the fentanyl group (group II) whereas at 10 min difference was statistically not significant (p=0.583).

Table 4 shows mean preinduction diastolic blood pressure in Group I was 76.63 ± 5.52 and in Group II was 77.10 ± 5.79. This difference was statistically not significant (p=0.751). At 1 min and 3 min, post-intubation DBP was significantly lower in the esmolol group (group I) compared to the fentanyl group (group II) whereas at 5 and 10 min difference were statistically not significant.

Table 5 shows mean arterial blood pressure i. e. before induction in Group I was 93.92 ± 5.79 and in Group II was 95.07 ± 6.43. This difference was statistically not significant (p=0.473). At 1 min and 3 min, post-intubation MAP was significantly lower in the esmolol group (group I) compared to the fentanyl group (group II) whereas at 5 min and 10 min difference was statistically not significant.

Discussion

To provide general anaesthesia in patients undergoing various types of surgery, laryngoscopy and intubation is an integral procedure. Duration of laryngoscopyis found tobe the foremost vital laryngoscopic factor influencing the cardiovascular response [4]. Though these above-mentioned effects is also transient, these may have adverse effects in high-risk patients like those with cardiovascular diseases, increased intracranial pressure or anomalies of cerebral vessels [5]. Many pharmacological agents have been used to obtund this pressor response. To obtund the pressor response and to maintain hemodynamic stability during laryngoscopy and intubation, both esmolol and fentanyl have been demonstrated to be efficient.

The drugs used previously were either partially effective or had other undesirable effects on the patients. In various studies conducted, esmolol and opioids like fentanyl were found to be the most preferred drug to attenuate the pressor response. Both the drugs fulfil the criteria to be an effective agent to suppress the haemodynamic changes to laryngoscopy and intubation.

Patients intubated in the first attempt were enrolled in this study. Various methods and technique have been used to attenuate the response to laryngoscopy and endotracheal intubation which range from topical application of local anaesthetics, infiltration of nerve blocks, different drugs and techniques, [6,7] but no single anaesthetic technique is perfect in preventing or attenuating these responses. It was believed that by increasing the depth of anaesthesia and decreasing sympathetic discharge,fentanyl suppresses the hemodynamic response [8]. In our study we used a low dose of fentanyl because a large dose of fentanyl may leads to muscular rigidity, bradycardia, respiratory depression, nausea, and vomiting [9]. Optimal time of inj.fentanyl tominimize the hemodynamic responseto both laryngoscopy and endotracheal intubationwas 5 min before induction in other study [10]. In our study, we injected fentanyl 3 minutes before induction. Liu PL et al. [11] found that among the β-blockers, ultra-short-acting-like esmolol because of its distinctive pharmacokinetic behaviour, well-suited to control the cardiovascular response to tracheal intubation when used as continuous infusion.

Ghaus SM et al. [12] concluded thaton infusion of esmolol 0.3/kg/min for 4 min before induction and 0.2/kg/min for the next 6 min for maintenance during intubation causes minimal changes in hemodynamics. Previous studies [13,14] stated thata high bolus dose of esmolol ranging from 0.5 mg/kg to 5 mg/kg may be used as an alternative to infusion.To attenuate the hemodynamic response to laryngoscopy and intubation,Singhal SK et al. [15] found that intravenous bolus dose of esmolol 1.5 mg/kg, 3 min before induction was very effective when compared to 1.5 min and 6 min before induction. In our study, group fentanyl showed better control of heart rate during laryngoscopy and intubation, minimum 80.10 ± 7.26 to 83.73 ± 7.68 at preinduction and after intubation (postinduction) as compared to esmolol group.

From the present study, we can conclude that in patients with no measures/drugs to attenuate hemodynamic response to laryngoscopy and intubation, there will be a maximum rise in heart rate, SBP, DBP, and MAP when compared with the preinduction value. After giving bolus dose of fentanyl 2 µg/kg or esmolol 2 mg/kg before induction at 5 minutes & 3 minutes respectively significantly attenuates the hemodynamic response to laryngoscopy and intubation. In IHD patients, α-adrenoceptor blockademinimizes increases in the heart rate, contractility of myocardium (primary determinants of O_2 consumption) [16,17].

More attention was given on the use of selective β-adrenergic antagonists (esmolol) to prevent the reflex sympathoadrenal discharge-mediated tachycardia and hypertension during procedures of laryngoscopy and endotracheal intubation [18]. After laryngoscopy and endotracheal intubation increase in heart rate and blood pressure was significantly lower in comparison to the control group whenesmolol 1-2 mg/kg was used [19]. Neitherany rhythm abnormality nor ST segment change was found in any patients when esmolol was used. In our study we used low doses of fentanyl (2 µg/kg) and the efficacy was compared with esmolol group. We found that the supplementation of anaesthetic induction with low dose of fentanyl significantly attenuated the increase in heart rate and arterial pressure after laryngoscopy and intubation Pressor responsescompletely abolished by fentanyl 6µg/kg in previous study [20]. Postoperative respiratory depression is prevented markedly by low dose fentanylwhich significantly blunt post-intubation hypertension when thiopental used as an adjunct. This effect was similar in a study conducted by Martin DE et al. who used fentanyl, 8 µg/kg in patients underwent major vascular surgery [21]. Low doses of fentanyl were employed because a large dose was lead to muscular rigidity, bradycardia, nausea and vomiting. Large doses may also cause postoperative respiratory depression; especially in surgery of shorter duration of less than 1 hour. In geriatric patients, marked fluctuation of haemodynamic changes seen as heart rate variability decrease with increasing age and younger patients show more extreme changes. In our study age between 20 to 50 years were selected. Tone of the sympathetic nervous system may be increased bynitrous oxide. The direct action of N_2O is negative inotropism which is offset by increased sympathetic tone [22]. Nasotracheal intubation comprises three distinct stages: (a) nasopharyngeal intubation (b) direct laryngoscopy to identify the vocal cords and (c) passage of the tracheal tube into the trachea. The nasopharyngeal intubation causes a significant pressor response. This response is increased with the passage of the tracheal tube into the larynx and trachea [23]. Our study included only laryngoscopy and orotracheal intubation. During the first 45 seconds linear increases in heart rate and mean arterial pressure have been observed and further prolongation has little effect. During laryngoscopy, the force applied has only a minor effect. In the present study, the duration of laryngoscopy and intubation was limited to 15 seconds.

Beside hypoxia and hypercarbia, other factor of

hypertension and tachycardia may be continued manifestation of anxiety concerning anaesthesia and operation, atropine premedication; thiopentone inducedreflex baroreceptor effect and the possible effect of suxamethonium. These factorsis less important than laryngotracheal stimulation during laryngoscopy and intubation [24]. Variety of results exist about protective measures against haemodynamic response and catecholamine responses to laryngoscopy and intubation, but no single anaesthetic technique is being effective in preventing or attenuating these responses. Many techniques have been recommended. The medication used were either part effective or had different undesirable effects on the patients. [25] Topical application of local anaesthetics, [26] infiltration or nerve blocks, [26] ß-blockers, [19] calcium channel blockers, [19,27] droperidol, [28] clonidine, [25] sodium nitroprusside, [29] lignocaine, fentanyl etc. measure getting used but no single drug or technique is satisfactory.

Selection of an appropriate drug in the study criteria to prevent sympathetic response, the drug must be applicable regardless of patient collaboration, to prevent impairment of cerebral blood flow, and to avoid arousal of the patient. It should not be time-consuming and also the duration or modality of the ensuing anaesthesia should not be affected [30]. These criteria may be fulfil by Intravenous esmolol and fentanyl [31,32]. Previous studies have shown that unique pharmacokinetic behaviour of esmolol when used as a continuous infusion technique and makes it well suited for controlling the cardiovascular response to tracheal intubation and laryngoscopy [33]. Previous studies [19,31,34] showed that the 2 mg/kg IV bolus esmolol injected prior to induction has been effective in attenuating cardiovascular response to laryngoscopy and intubation. Optimal time to administer esmolol is 3 minutes before laryngoscopy and intubation and it also prevent the bispectral index during induction of anaesthesia and orotracheal intubation [35]. Fentanyl is suggested for attenuation of the sympathetic response to laryngoscopy and intubation in different literatures.[14,21,25,30,34] Blunting of sympathetic response is dose-dependent however, at high doses, fentanyl produces tissue accumulation and thus longer lasting plasma and brain concentration of the drug. These patients may require mechanical respiratory support. Fentanyl 2 µg/kg significantly attenuates arterial pressure and heart rate increase during laryngoscopy and intubation however, fentanyl 6 µg/kg completely abolishes [25]. Dose requirement may be reduced when administration of fentanyl is at an optimal time and the optimal injection time of fentanyl is 5 minutes before intubation at a dose of 2 µg/kg [34]. In our study heart rate was increased by 41.1% when compared with the preinduction value. Similar increase found with esmolol was 15.4% and fentanyl was 25.8%. Both esmolol and fentanyl attenuated the heart rate highly significantly ($p<0.001$). Esmolol suppresses maximum rise in heart rate which is statistically highly significant when compared with fentanyl ($p<0.001$). It remains significant to 5 minutes. SBP with the administration of fentanyl maximum increase compared to preinduction value was 11.7% and with esmolol, it was only 6.0%. Therefore among the two drugs, esmolol showed a better result ($p<.001$). The maximum increase in diastolic blood pressure was 17.2% when compared with the preinduction value. It was 10.0% and 4.8% in fentanyl and esmolol groups respectively. A 'P' value of <.001 with fentanyl and <.001 with esmolol was obtained. Both were significant. Attenuation by esmolol is highly significant than fentanyl ($p<.001$). Similarly, mean arterial pressure increased by 18.1% from the preinduction value and gradually reached a basal level over 10 minutes. Fentanyl limited the maximum rise to 10.7% ($p<.01$) while esmolol to only 4.9% ($p<.001$). It reached a preinduction level over 7 minutes in the fentanyl group and 5 minutes in the esmolol group. The attenuation of mean arterial pressure by esmolol is highly significant when compared with fentanyl ($p<.001$). The efficacy of esmolol over fentanyl has been verified in many other studies [31,32,34]. Both esmolol and fentanyl together are also recommended to suppress the pressor response [34].

However, the present study has the following limitations: Adequate depth of anaesthesia and neuromuscular relaxation was monitored clinically; various drugs used in the present studywere not evaluated which may influence the haemodynamic changes, haemodynamic changes during direct laryngoscopy and passage of the endotracheal intubation into the trachea were not studied separately.

Conclusion

Based on the present clinical comparative study to attenuate the sympathetic response to laryngoscopy and intubation, Esmolol is more effective than fentanyl in attenuation of sympathetic response to laryngoscopy and intubation. IV bolus dose of esmolol 2 mg/kg administered

3 minutes before laryngoscopy and intubation can be recommended to attenuate the sympathetic response to laryngoscopy and intubation without any side effects of the drug.

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