

## A Comparative Study of Effect of Propofol, Etomidate and Propofol Plus Etomidate Induction on Hemodynamic Response to Endotracheal Intubation: A RCT

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### Abstract

**Objective:** The primary objective of this study was to compare the efficacy of 3 different anesthesia induction approach (Inj. Propofol, Inj. Etomidate and Inj. propofol plus Inj Etomidate) in maintaining hemodynamic stability during induction and following endotracheal intubation in elective surgery.

**Material and method:** Ethical committee clearance taken, 90 patients aged 15 to 60 years of either sex and ASA physical status I or II scheduled for elective surgery under general anesthesia were taken for study. Written and informed consent was taken. The patients were randomly placed into three groups. Group I induced with Inj. Propofol (2.5 mg/kg) intravenous, Group II with Inj. Etomidate (0.3 mg/kg) intravenous and Group III with Inj. Propofol (1 mg/kg) plus Inj. Etomidate (0.2 mg/kg) intravenous. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SPO<sub>2</sub>) were noted at different time interval.

**Results:** Heart rate in all study groups decreases after induction and it was more in group I compared to group II and III ( $p < 0.000$ ) and after intubation HR increases in all three groups but this increase is greater in group II than other two groups. MAP among all three groups decreases after induction and it was more in group I than group II and III. Significant increase in MAP was seen at 1 min after intubation in all three groups but this increase was not sustained and returned to baseline in group II and III.

**Conclusion:** The combination of etomidate plus propofol has better hemodynamic stability than etomidate alone at 1 min after intubation, though etomidate was equally stable at other points of time. The combination proved to be significantly better than either propofol or etomidate alone.

**Keywords:** Propofol; Etomidate; Mean arterial pressure; Heart rate; Laryngoscopy

### Introduction

In general anesthesia airway management and patient safety is the most important aspect of patient management. Endotracheal intubation is the gold standard and safest method for protecting the airway, delivering anesthetic gases and ensuring protection against aspiration [1,2]. Stress response during laryngoscopy and intubation leads to hemodynamic changes especially for patients who are under cardiac risk factors like hypertension and ischemic heart disease [3]. The unavoidable effects of laryngoscopy and tracheal intubation includes dysrhythmia, hypertension, myocardial ischemia, infarction, hypoxia, hypercapnea, laryngospasm, and bronchospasm, and some rare side effects such as increased intracranial pressure and increased intraocular pressure.

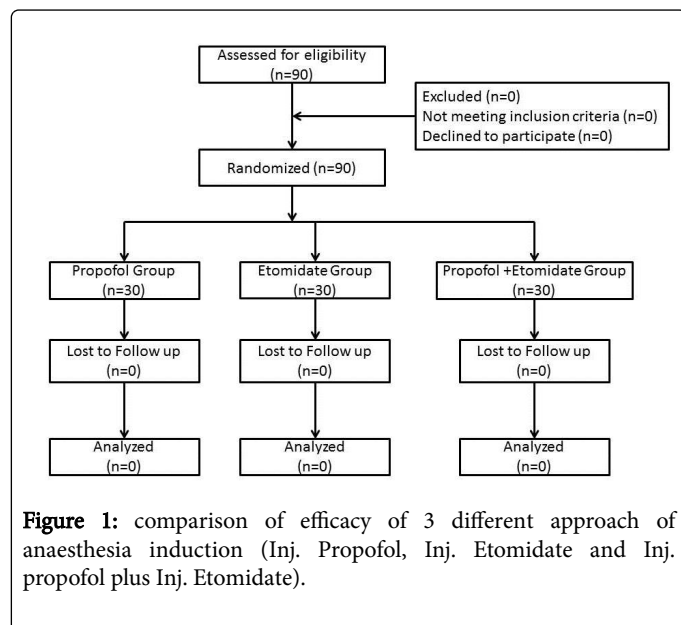
Since the introduction of general anesthesia, no ideal induction agent has yet been discovered in term of providing a stable hemodynamics during endotracheal intubation. Also there are very few published studies in the literature that have compared the

physiological effect of various induction agents during laryngoscopy and intubation.

Propofol is one the commonly used drug for induction of general anesthesia. This is a short acting intravenous anesthetic agent. Recommended dose of propofol for induction is 1-2.5 mg/kg. Unwanted complication associated with this drug is hemodynamic instability and cardiovascular complications. Propofol can lead to bradycardia by increasing the production and release of nitrous oxide [4-6]. Also causes pain at injection site. Etomidate is a hypnotic agent which is cardiostable with no release of histamine. It is short acting drug, used for induction and maintenance of anesthesia [7]. The most important side effects of Etomidate are nausea and vomiting that may lead to aspiration in patients [8-10]. Intravenous Injection of Etomidate would cause a burning sensation. One of the most important, but rare side effects of this drug is the suppression of steroids production by reversible inhibition of 11beta-hydroxylase enzyme [10,11]. Induction of anesthesia by Etomidate would lead to a stable hemodynamic condition for performing laryngoscopy and endotracheal intubation [9,10,12].

In past many studies have been comparing different anesthetic induction agents, but studies regarding combination of propofol and etomidate are only few. These studies are focused on hemodynamic

changes only during anesthesia induction and LMA insertion. The primary objective of this study was to compare the efficacy of 3 different approach of anesthesia induction (Inj. Propofol, Inj. Etomidate and Inj. propofol plus Inj. Etomidate) in maintaining hemodynamic stability during induction and following endotracheal intubation in elective surgery (Figure 1).



**Figure 1:** comparison of efficacy of 3 different approach of anaesthesia induction (Inj. Propofol, Inj. Etomidate and Inj. propofol plus Inj. Etomidate).

## Material and Methods

This randomized double blind clinical trial was conducted at Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Study period was from 2015-2016. After approval from institutional ethical committee, 90 patients aged between 15 to 60 years of either sex and ASA physical status I and II scheduled for elective surgery under general anesthesia were taken for study [13,14]. Written informed consent was taken from all patients. The patients were randomly divided into three groups. Randomization was done by computer generated random number tables.

- Group I Induction with Inj. Propofol (2.5 mg/kg) iv.
- Group II Induction with Inj. Etomidate (0.3 mg/kg) iv.
- Group III Induction with Inj. Propofol (1 mg/kg) plus Inj. Etomidate (0.2 mg/kg) iv. [15]

### Patient having following criteria were excluded from the study

- Patient refusal.
- ASA physical status III and IV.
- Emergency surgery.
- Patient with history of hypersensitivity to Propofol /Etomidate.
- Mouth opening <2.5 cm.
- Patients with cardiovascular diseases like ischemic heart disease or hypertension.
- Bronchial asthma.
- Mallampati grade 3 and 4
- Existence of considerable pathology in pharynx / larynx.
- Patient with GERD.

Airway assessment like mouth opening, mallampati grading, dentition, neck flexion and extension of all patients was done. Baseline (preoperative) heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SPO<sub>2</sub>) were noted.

The patients were kept nil per orally for 8 hours prior to surgery. All patients were premedicated with tab. Alprozolam 0.25 mg, tab. Ranitidine 150 mg and tab. Metoclopramide 10 mg, at the night before surgery and in the morning. All patients received inj. glycopyrolate 0.2 mg IM 45 minutes before induction in the preoperative ward. On arrival at Operation Theater standard anesthesia monitors including electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oxymetry were attached and hemodynamic parameters were recorded. A 18 G intravenous (IV) canula was secured in left hand and ringer lactate infusion was started. Inj. midazolam 0.025 mg/kg IV and Inj. fentanyl 2 µg/kg IV was given 2 minutes before induction. For induction group I received inj. Propofol 2.5 mg/kg IV, group II received inj. Etomidate 0.3 mg/kg IV and group III received inj. Propofol 1 mg/kg plus inj. Etomidate 0.2 mg/kg IV. All study drugs were prepared by an anesthesiologist who was blinded to the details of the study. Volume of medication and speed of injection (10 seconds) were equal in all three groups. After induction of anesthesia, hemodynamic variables were recorded. Later 60 seconds after of loss of consciousness, which was confirmed by inability to respond to verbal commands and loss of eyelash reflex. Inj. vecuronium (0.1 mg/kg) was given, Laryngoscopy and endotracheal intubation was done by experienced anesthesiologist. Duration of laryngoscopy was kept less than 10 seconds. Trachea was intubated with adequate size endotracheal tube. Proper placement of endotracheal tube was confirmed by capnography and bilateral auscultation of chest. Following successful placement of ET tube anesthesia was maintained by isoflurane 1-1.5% and equal mixtures of oxygen-nitrous oxide (4 L/min) along with intermittent bolus of vecuronium as required throughout the surgery.

At the end of the surgery residual neuromuscular block was antagonized with inj. neostigmine (0.05 mg/kg) IV and inj. glycopyrolate (0.01 mg/kg) IV and extubation was performed when respiration was adequate and patient was able to obey verbal commands.

Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure and oxygen saturation were continuously monitored and recorded before induction, after induction and at 1 minute, 2 minute, 3 minute, 5 minute after intubation.

### Power analysis

It is calculated according to previous studies, when MAP at the first minute of intubation is taken, as the main result in the event of at least 30 patients in each group, it was calculated that in respect of hemodynamic parameters, a 10% difference could be determined between the group at 80% power and 5% significance ( $\alpha=0.05$ ,  $\beta=0.80$ ).

### Statistical analysis

The obtained data were analyzed using SPSS 16; descriptive data was compared and presented as Mean  $\pm$  SD for continuous variables and as no and percentage for nominal variable. The various categorical variables studied during observation period were compared using Chi-square test. The various hemodynamic variable parameters studied during observation period were compared using ANOVA test and inter

group comparison of hemodynamic variable were made by post hoc test. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

## Results

Data of 90 patients were evaluated. There was no statistically significance difference was observed between the groups regarding patient characteristic and ASA score (Tables 1, 2A and 2B).

	Group I	Group II	Group III	p-value
Age (Y)	34.47 ± 6.72	33.90 ± 6.28	37.30 ± 9.39	0.178
BMI (kg/m)	22.46 ± 2.59	21.99 ± 1.95	22.77 ± 2.73	0.704
Gender ( M/F)	14/16	15/15	20/10	0.241
Height (feet and inches)	5.41 ± 0.45	5.38 ± 0.41	5.42 ± 0.38	0.742
BMI: Body Mass Index; M/F: Male/Female; ASA: American Society of Anesthesiologist; Data presented as Mean ± SD or frequencies				

**Table 1:** Patient's characteristics.

Baseline and pre-induction HR were comparable among all three groups with no statistical significant differences (p>0.05) Inter group comparison showed that there are significant differences (p<0.05) in heart rate among all three groups at time interval (after induction and 1, 2, 3 min after intubation). At 5min after intubation there are significant differences among groups except between group II and group III (Tables 3A and 3B).

Baseline and pre-induction SBP were comparable among all the three groups with no statistical significant differences (p>0.05). But SBP of three groups after induction and at 1, 2, 3, 5 minute after intubation were different both clinically and statistically, with p value <0.05.

Inter group comparison of SBP (mean ± SD) revealed significant differences among various groups at different points of time except that among group II and group III. Between group II and group III there was significant difference only at 1 min after intubation (Tables 4A and 4B).

Time Interval	Group I	Group II	Group III	f-value	p-value
Baseline SBP	129.87 ± 6.146	127.83 ± 5.376	127.80 ± 7.208	0.876	0.456
SBP pre induction	125.50 ± 6.067	123.67 ± 5.839	124.97 ± 7.117	0.730	0.536
SBP after induction	100.53 ± 8.905	117.73 ± 5.705	118.40 ± 6.750	43.148	0.000
SBP 1min after intubation	111.77 ± 6.474	133.87 ± 5.758	130.57 ± 4.826	169.731	0.000
SBP 2mins after intubation	115.33 ± 7.906	129.10 ± 3.836	126.97 ± 3.891	79.327	0.000
SBP 3mins after intubation	121.73 ± 4.586	125.30 ± 4.473	125.20 ± 3.995	30.153	0.000
SBP 5mins after intubation	126.83 ± 3.270	122.47 ± 5.457	123.50 ± 4.431	20.563	0.000

**Table 3A:** SBP (systolic blood pressure) in (mmHg).

Time Interval	Group I	Group II	Group III	f-value	p-value
Baseline HR	78.33 ± 6.572	76.40 ± 6.667	77.30 ± 5.466	0.686	0.562
HR pre induction	89.60 ± 5.975	88.03 ± 6.775	88.33 ± 5.785	0.355	0.786
HR after induction	69.43 ± 5.151	88.27 ± 7.249	82.63 ± 6.780	123.808	0.000
HR 1min after intubation	76.57 ± 4.539	99.30 ± 5.926	93.50 ± 6.648	274.713	0.000
HR 2mins after intubation	80.13 ± 4.747	96.37 ± 6.031	91.17 ± 6.747	112.567	0.000
HR 3mins after intubation	83.27 ± 4.863	94.40 ± 5.852	90.17 ± 6.018	43.931	0.000
HR 5mins after intubation	85.43 ± 4.337	92.50 ± 6.096	89.83 ± 5.670	15.984	0.000

**Table 2A:** Mean HR (Heart Rate) in (beats per minute).

Time Interval	Group I vs. II	Group I vs. III	Group II vs. III
Baseline HR	0.253	0.540	0.594
HR pre induction	0.355	0.455	0.859
HR after induction	0.000	0.000	0.001
HR 1min after intubation	0.000	0.000	0.000
HR 2mins after intubation	0.000	0.000	0.002
HR 3mins after intubation	0.000	0.000	0.016
HR 5mins after intubation	0.000	0.008	0.102

**Table 2B:** Group comparisons mean HR.

Baseline and pre-induction DBP were comparable among all the three groups with no statistical significant differences ( $p > 0.05$ ). But DBP of three groups after induction and at 1,2,3,5 minute after intubation were different both clinically and statistically, with  $p$  value  $< 0.05$ .

Time Interval	Group I vs. II	Group I vs. III	Group II vs. III
Baseline SBP	0.198	0.191	0.983
SBP pre induction	0.251	0.738	0.415
SBP after induction	0.000	0.000	0.710
SBP 1min after intubation	0.000	0.000	0.035
SBP 2mins after intubation	0.000	0.000	0.120
SBP 3mins after intubation	0.002	0.002	0.929
SBP 5mins after intubation	0.000	0.006	0.384

**Table 3B:** Group comparison SBP.

Time Interval	Group I	Group II	Group III	f-value	p-value
Baseline DBP	75.80 ± 6.228	74.70 ± 4.757	75.23 ± 5.184	.336	.799
DBP pre induction	73.23 ± 6.447	72.17 ± 4.340	71.90 ± 5.498	0.377	0.770
DBP after induction	60.30 ± 4.236	68.00 ± 4.307	68.30 ± 5.338	22.357	0.000
DBP 1min after intubation	65.63 ± 3.728	77.00 ± 4.299	73.13 ± 4.183	76.835	0.000
DBP 2mins after intubation	67.37 ± 3.285	73.00 ± 3.833	72.27 ± 3.805	47.669	0.000
DBP 3mins after intubation	68.43 ± 3.191	72.37 ± 3.023	71.43 ± 3.598	35.550	0.000
DBP 5mins after intubation	72.40 ± 2.943	71.43 ± 2.269	70.27 ± 4.093	16.330	0.000

**Table 4A:** DBP (Diastolic Blood Pressure) in (mmHg).

Time Interval	Group I vs. II	Group I vs. III	Group II vs. III
Baseline DBP	0.427	0.682	0.700
DBP pre induction	0.428	0.322	0.843
DBP after induction	0.000	0.000	0.787
DBP 1min after intubation	0.000	0.000	0.005
DBP 2mins after intubation	0.000	0.000	0.580
DBP 3mins after intubation	0.000	0.004	0.357
DBP 5mins after intubation	0.305	0.025	0.216

**Table 4B:** Group comparison DBP (mmHg).

There were significant differences ( $p < 0.05$ ) in inter group comparison of DBP (mean ± SD) among the groups except group II and III. But there was significant difference between group II and III only at 1 min after intubation. At 5 min after intubation there were no significant differences between group I vs. II and group II vs. III (Tables 5A and 5B).

Baseline and pre-induction MAP were comparable among all the three groups with no statistical significant differences ( $p > 0.05$ ). But MAP of three groups after induction and at 1,2,3,5 minute after intubation were different both clinically and statistically, with  $p$  value  $< 0.05$ . Inter group comparison of MAP (mean ± SD) revealed significant differences among various groups at different points of time except that among group II vs. group III. Between groups II vs. group III there was significant difference only at 1 min after intubation.

## Discussion

Combinations of various anesthetic agents have been used; these combinations have created separate beneficial sedative, amnestic and hypnotic effect in anesthesia induction. With this method there has been evident reduction in anesthetic medication, significant reduction in side effect and cost [13,14].

Etomidate is one of the intravenous anesthetics used in anesthesia induction, either alone or in combination with other anesthetic drugs [16]. In a study by Hosseinzadeh et al. [15], comparing hemodynamic changes during placement of laryngeal mask airway (LMA) using propofol, etomidate and etomidate-propofol combination, after the administration of inj. fentanyl 2 mg/kg, group one was given inj. propofol 2.5 mg/kg, group two received inj etomidate 0.3 mg/kg and group three 1 mg/kg propofol+0.2 mg/kg etomidate. LMA placement was done after loss of eyelash reflex and no response to verbal command. The main finding of the study was that more stable hemodynamics was provided by combination of propofol and etomidate compared to propofol and etomidate and alone. Although the dose of both drugs are reduced in the combination of propofol and etomidate, it was reported that more stable hemodynamic state and better condition for LMA placement was provided.

Time Interval	Group I	Group II	Group III	f-value	p-value
Baseline Mean BP	93.70 ± 5.383	92.17 ± 4.379	91.73 ± 5.638	1.119	0.344
Mean BP pre induction	89.57 ± 4.783	88.57 ± 4.321	89.53 ± 5.686	.300	0.826
Mean BP after induction	73.71 ± 4.876	84.57 ± 4.192	85.00 ± 5.425	41.019	0.000
Mean BP 1min after intubation	81.67 ± 3.695	95.95 ± 4.082	92.77 ± 4.066	143.549	0.000
Mean BP 2mins after intubation	83.35 ± 3.927	91.70 ± 3.081	90.50 ± 3.555	88.266	0.000
Mean BP 3mins after intubation	86.20 ± 2.919	90.01 ± 2.484	89.35 ± 3.504	53.174	0.000
Mean BP 5mins after intubation	90.54 ± 2.453	88.44 ± 2.528	88.01 ± 3.830	28.420	0.000

**Table 5A:** Mean (Mean arterial BP) MAP (mmHg).

Time Interval	Group I vs. II	Group I vs. III	Group II vs. III
Baseline Mean BP	0.233	0.127	0.735
Mean BP pre induction	0.411	0.978	0.427
Mean BP after induction	0.000	0.000	0.715
Mean BP 1min after intubation	0.000	0.000	0.003
Mean BP 2mins after intubation	0.000	0.000	0.259
Mean BP 3mins	0.000	0.000	0.431
Mean BP 5mins after intubation	0.009	0.002	0.587

**Table 5B:** Group comparison mean (mean arterial BP).

In a study performed by Yağan Ö et al. [17], patients were randomly divided into three groups as group P (n=30, propofol 2.5 mg/kg), group E (n=30, etomidate 0.3 mg/kg) and group PE (n=30, propofol 1.25 mg/kg+etomidate 0.15 mg/kg). Measurement of the heart rate (HR) and mean arterial pressure values were defined as baseline, after the induction, before the intubation, immediately after the intubation and 1, 2, 3, 4, 5 and 10 minutes after the intubation. They found that Etomidate-propofol combination may be a valuable alternative when extremes of hypotensive and hypertensive responses due to propofol and etomidate are best to be avoided.

Another study reported that after anesthesia induction with etomidate (0.3 mg/kg) the ideal fentanyl dose was 5-10 mg/kg to prevent a hemodynamic response to laryngoscopy and intubation [18]. However, it can be predicted that use of such high dose of fentanyl may cause increased hypotension, nausea and vomiting.

In a study by Muriel et al. [19], a comparison was made of propofol (2 mg/kg), thiopental (5 mg/kg) and etomidate (0.3 mg/kg) in anesthesia induction. A statistically significant increase was determined in systolic and diastolic arterial pressure and HR in the etomidate and thiopental group after intubation and the highest rate of complication was reported in etomidate group.

Harris et al. [20] compared the hemodynamic response to tracheal intubation in 303 patients in whom anesthesia was induced with either

thiopentone 4 mg/kg, etomidate 0.3 mg/kg or propofol 2.5 mg/kg with or without fentanyl 2 µg/kg. After propofol alone, there was a significant decrease in arterial blood pressure, which did not increase above control value after intubation. Significant increase in arterial pressure followed intubation in patients induced with thiopentone or etomidate alone. Increases in heart rate occurred with all agents after laryngoscopy and intubation. The use of fentanyl resulted in arterial pressure lower than those after the induction agent alone and in an attenuation, but not abolition, of responses to laryngoscopy and intubation. We got similar results in our study with significant decrease in arterial blood pressure, after induction with propofol which did not increase above baseline value after intubation, while, with etomidate, there was significant increase in arterial pressure following intubation. Also, increase in heart rate occurred with all agents after laryngoscopy and intubation

Schmidt et al. [21] found in their study that, hypotension caused by propofol is due to the reduction of heart's preload and afterload, which are not synchronized with heart's compensatory responses such as increased cardiac output and increased HR. This hemodynamic drop would be intensified by high doses of the drug and high speed injection of the drug. In our study we got similar results in group I i.e. after induction with propofol there was hypotension and not synchronized with increased HR.

Mehrdad et al. [22] conducted a study including patients of 18-45 years of age that were admitted for elective orthopedic surgeries. patients were divided in two groups, their cardiovascular responses including: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and O<sub>2</sub> saturation (O<sub>2</sub> sat) were measured before the laryngoscopy, during the anesthesia induction with Etomidate (0.3 mg/kg) in group A and propofol (2-2.5 mg/kg) in group B and at 1, 3, 5, 10 min after the induction. They concluded that patients receiving Etomidate have more stable hemodynamic condition, if there would be no contraindications; it could be preferred over propofol for general anesthesia. Our study got similar results of better hemodynamic conditions with etomidate as compared to propofol.

In a study by Möller et al. [23] which used propofol and etomidate in general anesthesia induction accompanied by BIS monitoring, the MAP, cardiac index (CI) and systemic vascular resistance index (SVRI) values of 48 patients were compared. The hemodynamic data were found to be higher in the etomidate group up to 7 minutes after intubation. A significantly high level of hypotension incidence was

found in the propofol group and a significantly high level of hypertension incidence in the etomidate group. Compared with etomidate, the use of propofol was determined to have caused less hypertension and tachycardia after intubation. In the current study, the MAP values after induction in the propofol group were significantly lower than those of the other two groups. Following intubation, the MAP and HR values of the etomidate group were statistically significantly higher than those of the other two groups. These results confirm with those in literature.

There was added advantage of combining Etomidate with propofol for attenuating intubation reflex as compared to Etomidate alone, and had obvious advantage than using Propofol or Thiopentone alone.

Not using BIS to measure the depth of anesthesia is a major limitation of our study. Another limitation is not measuring plasma cortisol and adrenocorticotropic hormone level. But it has been reported that adrenal suppression after single dose of etomidate is transient and clinically unimportant [24].

## Conclusion

Induction with propofol alone is acceptable in patients with stable hemodynamics. However, propofol may cause hypotension in volume depleted patients. The combination of etomidate plus propofol has better hemodynamic stability than etomidate alone at 1 min after intubation, though etomidate was equally stable at other points of time. And, the combination proved to be significantly better than either propofol or etomidate alone.

## Conflict of Interest

There was no conflict of interest in this study.

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