

# Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass

Ram Prasad Kaushal, Ajay Vatal, Radhika Pathak

Department Anesthesiology, Gandhi Medical College, Bhopal, Madhya Pradesh, India

## ABSTRACT

**Introduction:** The concerns for induction of anaesthesia in patients undergoing cardiac surgery include hemodynamic stability, attenuation of stress response and maintenance of balance between myocardial oxygen demand and supply. Various Intravenous anaesthetic agents like Thiopentone, Etomidate, Propofol, Midazolam, and Ketamine have been used for anesthetizing patients for cardiac surgeries. However, many authors have expressed concerns regarding induction with thiopentone, midazolam and ketamine. Hence, Propofol and Etomidate are preferred for induction in these patients. However, these two drugs have different characteristics. Etomidate is preferred for patients with poor left ventricular (LV) function as it provides stable cardiovascular profile. But there are concerns about reduction in adrenal suppression and serum cortisol levels. Propofol, on the other hand may cause a reduction in systemic vascular resistance and subsequent hypotension. Thus, this study was conducted to compare induction with these two agents in cardiac surgeries. **Methods:** Baseline categorical and continuous variables were compared using Fisher's exact test and student's t test respectively. Hemodynamic variables were compared using student's t test for independent samples. The primary outcome (serum cortisol and blood sugar) of the study was compared using Wilcoxon Rank Sum test. The P value less than 0.05 was considered significant. **Results:** Etomidate provides more stable hemodynamic parameters as compared to Propofol. Propofol causes vasodilation and may result in drop of systematic BP. Etomidate can therefore be safely used for induction in patients with good LV function for CABG/MVR/AVR on CPB without serious cortisol suppression lasting more than twenty-four hours.

**Key words:** Cardiac anesthesia; Etomidate; Propofol, CPB

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## INTRODUCTION

The considerations for induction of anesthesia in patients undergoing cardiac surgery include hemodynamic stability, attenuation of the stress responses and maintenance of balance between myocardial oxygen demand and supply. Various intravenous (IV) inducing agents like thiopentone, etomidate,

propofol and midazolam have been used for anesthetising these patients.<sup>[1-5]</sup> Various authors have expressed concerns regarding induction of anesthesia with agents such as thiopentone, midazolam, ketamine.

Propofol and etomidate are well-known anesthetic agents routinely used for the induction of anesthesia for cardiac

**Address for correspondence:** Dr. Ram Prasad Kaushal, Rose-22, Green Meadows, Arera Hills, Bhopal, Madhya Pradesh, India.  
E-mail: [rpkashal1@rediffmail.com](mailto:rpkashal1@rediffmail.com)

surgeries.<sup>[6-10]</sup> The two drugs however have different induction characteristics.

Etomidate, first introduced in the seventies, was withdrawn, because of anaphylactic reactions to Cremaphore EL. There were also concerns about reductions in the serum cortisol levels,<sup>[9,11,12]</sup> which lasts for up to 24 h. However, It has a very stable cardiovascular profile<sup>[1,13,14]</sup> and has been reintroduced in India. Etomidate is recommended for induction in patients with poor left ventricular (LV) function. While, propofol may cause a reduction in systemic vascular resistance (SVR).

Hence, this study was conducted to compare the effect of anesthetic induction with single dose etomidate versus propofol on serum cortisol levels and hemodynamics.

## MATERIALS AND METHODS

After obtaining Institutional Ethics Committee approval and written informed consent from the patients, 60 patients (age: 20–60 years, weight: 40–70 kg) of American Society of Anesthesiologists Grade II and III scheduled for elective coronary artery bypass grafting (CABG)/mitral valve replacement (MVR)/aortic valve replacement (AVR) on cardiopulmonary bypass (CPB) were enrolled in this prospective randomized study.

Patients undergoing emergency surgery, having congestive cardiac failure, renal dysfunction (serum creatinine >2 mg/dl), on mechanical ventilation or on long-term steroid therapy, known adrenal or endocrine dysfunction were excluded from the study.

Proper preanesthetic check-up and all relevant investigations were done for all patients.

The patients were randomly divided into two groups of 30 patients each.

Propofol was chosen as other inducing agents like thiopentone and ketamine are not routinely used in MVR and CABG surgeries.

Group I: Injection propofol (P) group (2 mg/kg) IV.

Group II: Etomidate (E) group (0.2 mg/kg) IV.

Randomization was done by opening a sealed envelope just before entry to operating room.

In the operation theater, pulse oximeter, noninvasive blood pressure (BP) apparatus and five lead electrocardiogram (ECG) were connected to the patient.

Swan ganz catheter placement under local infiltration is done as routine in our Institution and to measure pre-induction values, i.v. Premedication in our Institution is done after the arrival of patient in OT. After peripheral IV cannulation and intra-arterial radial cannulation, central venous line and pulmonary artery/swan Ganz catheter placement under local infiltration, patient was premedicated with injection glycopyrrolate 0.2 mg IV, injection midazolam 2 mg, injection ranitidine 50 mg and injection ondansetron 4 mg.

After stabilization period of 5 min, the baseline values of heart rate, systolic and diastolic BP (SBP and DBP) (invasive BP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), pulmonary capillary wedge pressure (PCWP), SVR, peripheral vascular resistance (PVR), SpO<sub>2</sub>, were recorded and ECG was monitored.

All patients were induced between 8 and 9 am and samples for baseline values of serum cortisol and blood sugar were obtained before induction.

Intravenous fentanyl 2 mcg/kg was given 3 min prior to induction.

After preoxygenation, Group I received 2 mg/kg propofol and Group II received 0.2 mg/kg etomidate for induction.

After the loss of eyelash reflex in both groups, again HR, SBP, DBP, MAP, CVP, PCWP, CO, CI, SVR, PVR were recorded. Injection vecuronium bromide 0.1 mg/kg IV was given, and endotracheal intubation was performed. Again the readings for HR, SBP, DBP, MAP, CVP, PCWP, CO, CI, PVR and SVR were recorded. Intraoperative analgesia was provided with injection fentanyl up to total dose of 20 mcg/kg as intermittent bolus doses. Anesthesia was maintained with isoflurane (0.2–2%) and injection 0.1 mg/kg vecuronium was administered as IV bolus followed by 0.02 mg/kg every 30–40 min. Femoral artery catheterization was done. Five min postintubation again HR, SBP, DBP, MAP, CVP, PCWP, CO, CI, SVR, PVR recorded. Patients received IV antibiotics after test dose and IV methylprednisolone 30 mg/kg in divided doses through central venous catheter.

Heparin in the dose of 300–400 units/kg was administered prior to initiation of CPB during CPB. Serum cortisol values and blood sugar levels were again measured while the patient was on CPB.

Heparin was reversed with protamine in the dose of 4.5 mg/kg after weaning the patient from CPB. Again serum cortisol and blood sugar were measured after heparin reversal.

At the end of surgery, patient was shifted to the cardiac ICU with an endotracheal tube *in situ* after adequate dose of muscle relaxant and opioid analgesic.

Patients were observed postoperatively for any adverse effects.

HR, IBP, NIBP, CVP, PCWP, CO, CI, SVR, PVR were recorded:

- Baseline/before induction
- After the induction (loss of eyelash reflex and verbal response)
- Immediately after intubation
- After 5 min of intubation.

#### Endocrine response

Serum cortisol values and blood sugar were measured at 4 time points:

- Baseline before induction of anesthesia
- During CPB
- After bypass/protamine reversal of heparin after termination of CPB and
- At 24 h.

Data were summarized as the number (%) or mean  $\pm$  standard deviation/median (range) as appropriate. Baseline categorical and continuous variables were compared between the groups using Fisher's exact test and Student's *t*-test respectively. Hemodynamic variables were compared between the groups using Student's *t*-test for independent samples. The primary outcome (serum cortisol and blood sugar) of the study was compared between the groups using Wilcoxon Rank Sum test since the data was non-normal.  $P < 0.05$  was considered as significant.

## OBSERVATIONS AND RESULTS

There was no significant difference in CO between both the groups though there was significant fall from baseline value in P group after induction [Tables 1-12]. The values remained below baseline even 5 min after intubation

**Table 1: Patients characteristics and operation details**

Variable	Group I (P) (n=30)	Group II (E) (n=30)	P
Age (years)	33.96 $\pm$ 10.88	36 $\pm$ 12.33	0.499
Sex (male/female)	15/15	16/14	
Weight (kg)	47.7 $\pm$ 8.15	46.26 $\pm$ 6.93	0.463
Height (cm)	161.1 $\pm$ 7.7	162.8 $\pm$ 8.3	0.414
ASA Grade II	22	19	
ASA Grade III	8	11	
Duration of surgery (in h)	5.25 $\pm$ 1.11	5.4 $\pm$ 1.02	0.587
Surgical procedure			
MVR	23	22	
AVR	4	6	
CABG	3	2	

Values expressed as mean $\pm$ SD. \* $P < 0.05$  considered significant statistically. ASA: American Society of Anesthesiologists, MVR: Mitral valve replacement, AVR: Aortic valve replacement, CABG: Coronary artery bypass grafting, SD: Standard deviation

**Table 2: Baseline hemodynamic parameters between the two groups**

Baseline parameters	Group I (n=30)	Group II (n=30)	P
HR	91.03 $\pm$ 20.7	80.66 $\pm$ 23.53	0.0714
SBP	117.63 $\pm$ 15.66	111.56 $\pm$ 16.005	0.143
DBP	73.93 $\pm$ 11.41	72.5 $\pm$ 8.16	0.586
MAP	88.38 $\pm$ 12.01	85.08 $\pm$ 10.50	0.2619
CVP	6.73 $\pm$ 1.38	7.43 $\pm$ 1.47	0.062
PCWP	6.63 $\pm$ 1.65	8.86 $\pm$ 1.19	<0.001*
CO	4.35 $\pm$ 0.76	4.06 $\pm$ 0.65	0.117
CI	2.41 $\pm$ 0.42	2.26 $\pm$ 0.38	0.15
SVR	1889.4 $\pm$ 396.1	1798.4 $\pm$ 310.21	0.32
PVR	141.66 $\pm$ 30.4	155.4 $\pm$ 30.3	0.08

Values expressed as mean $\pm$ SD. \* $P < 0.05$  considered significant statistically. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, CVP: Central venous pressure, PCWP: Pulmonary capillary wedge pressure, CO: Cardiac output, CI: Cardiac index, SVR: Systemic vascular resistance, PVR: Peripheral vascular resistance, SD: Standard deviation

which was significant. Baseline values were comparable in both the groups and no significant changes were observed in etomidate group after induction.

Unlike Group E, Group P showed significant fall in CI after induction which continued till 5 min after intubation as compared to baseline values.

#### Observations

##### Hemodynamic parameters

There was no significant difference in between the groups with respect to HR, CVP and PCWP. There was significant decrease in SBP, DBP and MAP between the groups after induction, after intubation and 5 min postintubation. There was significant decrease in CO

**Table 3: Hemodynamic responses between the two groups**

	Group I (P) (n=30)	Group II (E) (n=30)	P
HR			
Baseline	91.03±2.07	80.66±23.53	0.0714
After induction	88.53±18.20	80.6±12.92	0.056
After intubation	96.93±20.34	85.83±23.53	0.0501
5 min after intubation	92.8±14.91	87.46±10.99	0.119
SBP			
Baseline	117.63±15.66	111.56±16.005	0.143
After induction	80.63±8.63	98.5±14.73	<0.001*
After intubation	86.53±15.65	103.4±12.286	<0.001*
5 min after induction	95.86±3.51	103.7±6.22	<0.001*
DBP			
Baseline	73.93±11.41	72.53±8.16	0.586
After induction	59.7±7.28	69.4±8.26	0.007*
After intubation	64.6±6.46	71.43±7.37	0.0015*
5 min after intubation	66.6±4.41	71.26±4.83	0.0003*
MAP			
Baseline	88.38±12.01	85.08±10.50	0.261
After induction	67.97±5.79	80.54±9.39	<0.001*
After intubation	72.79±5.54	82.07±7.09	<0.001*
5 min after intubation	76.46±3.47	82.05±3.92	<0.001*

Values expressed as mean±SD. \*P<0.05 considered significant statistically. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SD: Standard deviation

**Table 4: CVP comparison between two groups**

	Group P (n=30)	Group E (n=30)	P
Baseline	6.73±1.38	7.43±1.47	0.062
After induction	6.60±1.10	7.23±1.38	0.0554
After intubation	7.86±0.93	7.4±1.24	0.109
5 min after intubation	7.63±1.09	7.4±1.06	0.418

Values expressed as mean±SD. \*P<0.05 considered significant statistically. CVP: Central venous pressure, SD: Standard deviation

**Table 5: Pulmonary capillary wedge pressure**

PCWP	Group P (n=30)	Group E (n=30)	P
Baseline	7.43±1.38	9.06±1.57	<0.001*
After induction	6.63±1.65	8.86±1.19	<0.001*
After intubation	8.6±1.67	9.16±1.64	0.195
5 min after intubation	8.76±1.13	9.06±1.25	0.38

Values expressed as mean±SD. \*P<0.05 considered significant statistically. PCWP: Pulmonary capillary wedge pressure, SD: Standard deviation

and CI in propofol group when compared to baseline values after induction, after intubation and 5 min after intubation, but not in etomidate group. SVR was

**Table 6: Cardiac output**

CO	Group P (n=30)	Group E (n=30)	P
Baseline	4.35±0.76	4.06±0.65	0.117
After induction	3.72±0.74	3.88±0.7	0.393
After intubation	3.85±0.68	3.91±0.56	0.71
5 min after intubation	3.87±0.60	3.8±0.5	0.625

Values expressed as mean±SD. \*P<0.05 considered significant statistically. CO: Cardiac output, SD: Standard deviation

**Table 7: Cardiac index**

CI	Group P (n=30)	Group E (n=30)	P
Baseline	2.41±0.42	2.26±0.38	0.15
After induction	2.06±0.41	2.15±0.32	0.38
After intubation	2.13±0.37	2.17±0.31	0.65
5 min after intubation	2.14±0.33	2.10±0.28	0.61

Values expressed as mean±SD. \*P<0.05 considered significant statistically. CI: Cardiac index, SD: Standard deviation

**Table 8: Systemic vascular resistance**

	Group P (n=30)	Group E (n=30)	P
Baseline	1889.4±396.1	1798.4±310.21	0.32
After induction	1587.267±123.53	1613.5±369.5	0.71
After intubation	1822.56±130.011	1733.133±293.9	0.132
5 min after intubation	1604.3±142.45	1920.2±259.09	<0.001*

Values expressed as mean±SD. \*P<0.05 considered significant statistically. SVR: Systemic vascular resistance, SD: Standard deviation

**Table 9: Pulmonary vascular resistance between two groups**

	Group P (n=30)	Group E (n=30)	P
Baseline	141.66±30.4	155.4±30.3	0.08
After induction	125.46±25.12	138.5±25.9	0.052
After intubation	140.5±21.48	147.8±16.65	0.146
5 min after intubation	136.63±18.6	144.7±13.5	0.059

Values expressed as mean±SD. \*P<0.05 considered significant statistically. PVR: Pulmonary vascular resistance, SD: Standard deviation

significantly decreased after induction in both the groups while the value continued to decrease at 5 min postintubation in the propofol group and increased significantly above baseline in the etomidate group. Values in PVR were significantly decreased after induction in both groups and increased to near baseline levels by 5 min postintubation.

#### Myoclonus and hypotension

Myoclonus was not seen as the drug was injected slowly. hypotension occurred post induction with propofol, it was defined as fall of MAP of more than 10% on the base line.

**Table 10: Serum cortisol and blood glucose values between two groups**

	Group P (n=30)	Group E (n=30)	P
Serum cortisol values			
Baseline/before induction	11.7±1.95	12.2±2.94	0.44
During bypass	14.8±1.62	9.36±3.04	<0.001*
After bypass/after protamine reversal of heparin	23.26±3.14	7.66±2.91	<0.001*
At 24 h postoperatively	28.3±2.97	24.23±3.62	<0.001*
Blood glucose levels			
Baseline	97.43±15.66	93.83±15.9	0.380
During bypass	158.03±38.62	138.53±33.5	0.041*
After protamine reversal/ weaning off CPB	159.03±39.91	136.9±35.24	0.0265*
At 24 h postoperatively	106.06±28.15	98.86±15.9	0.227

Values expressed as mean±SD. \*P<0.05 considered significant statistically. SD: Standard deviation, CPB: Cardiopulmonary bypass

**Table 11: Associated adverse outcomes between two groups**

Adverse reactions	Group P	Group E
Postoperative nausea and vomiting	None	None
Allergic reaction	None	None
Excitatory effects like myoclonus, dystocia or tremor	None	None
Adrenal depression	None	None
Pain on injection	None	None
Hypotension perioperatively	None requiring vasopressor support	None requiring vasopressor support

**Table 12: Different doses of the two drugs used**

Drug	Author	Dose (mg/kg)
Propofol	Patrick <i>et al.</i> (1985) <sup>[3]</sup>	1.5
	Vermeyen <i>et al.</i> <sup>[16]</sup>	1.5
	Kaplan <i>et al.</i> <sup>[17]</sup>	2.5
	Boer <i>et al.</i> <sup>[7]</sup>	2
	Boer <i>et al.</i> <sup>[1]</sup>	2
	Singh <i>et al.</i> <sup>[4]</sup>	1.5
	Pandey <i>et al.</i> <sup>[11]</sup>	2
Etomidate	Gooding <i>et al.</i> <sup>[10]</sup>	0.3
	Colvin <i>et al.</i> <sup>[13]</sup>	0.3
	Boer <i>et al.</i> <sup>[1]</sup>	0.3
	Yunqi <i>et al.</i> <sup>[18]</sup>	0.3
	Singh <i>et al.</i> <sup>[4]</sup>	0.2
	Morel <i>et al.</i> <sup>[19]</sup>	0.3
	Pandey <i>et al.</i> <sup>[11]</sup>	0.2
	Rahman <i>et al.</i> <sup>[15]</sup>	0.2

#### Effects on serum cortisol levels

There was significant fall in the cortisol values in etomidate group during bypass and further significant fall

after weaning off CPB as compared to the propofol group. The average cortisol value was reduced to approximately 50% at the time of weaning in etomidate group while it increased to almost double in the propofol group.

The serum cortisol level at 24 h was higher as compared to baseline values in both the groups. In the etomidate group, the serum cortisol returned to normal levels which were however almost twice the baseline values. In the propofol group, the serum levels remained high and were about two and a half times the baseline value.

#### Effects on blood glucose levels

There was significant increase in blood glucose value during bypass and when weaning off CPB in both groups compared to baseline and between the two groups, but the rise was less in etomidate group due to decreased stress response because of inhibition of cortisol synthesis. After 24 h of surgery, however the values returned to baseline with no significant differences between the groups.

#### DISCUSSION

The deleterious effects of anesthetic agents in patients suffering from coronary artery disease are well-known. Induction of general anesthesia may be a critical period during CABG and valve replacement surgery, especially in presence of LV dysfunction. There is a paucity of literature regarding the choice of suitable agent to avoid deleterious effects in such patients. Anesthetic induction techniques for cardiovascular surgery are based on considering hemodynamic stability and effects on myocardial oxygen supply and demand.

Various authors have concern regarding induction of anesthesia with agents such as etomidate, thiopentone, propofol, ketamine and midazolam. However, the use of etomidate and propofol has been considered superior to other IV anesthetic agents in these group of patients.<sup>[5-9]</sup>

#### Selection of inducing agent

Etomidate (Lipuro. B Braun. Melsungen. Germany) is a short acting IV anesthetic agent used for the induction of general anesthesia. It was introduced as an IV agent in 1972 in Europe and in 1983 in United States. It has a rapid onset of action, a safe cardiovascular risk profile, and lack of histamine release and therefore is less likely to cause a significant drop in BP than other induction agents. It is an ideal induction agent for patients who

are hemodynamically unstable. The normal adult serum cortisol levels are 5–25 mcg/dl. Etomidate suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting 11-beta-hydroxylase, an enzyme important in adrenal steroid production leading to primary adrenal suppression. The cortisol suppression induced by a single dose of etomidate is almost always limited to 24 h, and therefore does not pose any threat of prolonged adrenocortical suppression. The cortisol levels in our study also returned to normal levels at 24 h postinduction with etomidate.

Propofol is a short-acting, intravenously administered hypnotic agent. Propofol has been proposed to have several mechanisms of action, both through potentiation of GABA receptor activity, thereby slowing the channel-closing time, and also acting as a sodium channel blocker. Recent research has also suggested that the endocannabinoid system may contribute significantly to propofol's anesthetic action and to its unique properties. Propofol causes vasodilatation and may result in transient fall in systemic BP.

Various studies have shown stable cardiovascular profile of etomidate like studies by Gooding *et al.*, Sun (1991), Yunqi *et al.*, Hosten *et al.*, Pandey *et al.* Some other authors have found propofol to be effective in patients with good LV function and combined with some analgesic as shown in the studies by Patrick *et al.*, Stephan *et al.*, Vermeyen *et al.*, Kaplan *et al.*

#### Selection of dose for etomidate and propofol induction

Following authors have used different dosages of propofol and etomidate for induction in patients undergoing cardiovascular surgery [Table 12].

Based on above studies, we selected an induction dose of 2 mg/kg for propofol and 0.2 mg/kg for Etomidate for our study.

#### CONCLUSION

- Etomidate provides more stable hemodynamic parameters when used for induction of anesthesia as compared to propofol in patients with poor LV function
- There is a rise in serum Cortisol levels on the initiation of CPB after induction of anesthesia with propofol in our study. This was not present in the etomidate group, where the serum Cortisol levels reduced. Serum Cortisol levels returned to near

normal range at 24 h without any untoward effects. The values though were almost twice the baseline”

- Etomidate can therefore be safely used as an anesthetic induction agent in patients with poor LV function for CABG/MVR/AVR on CPB without serious cortisol suppression lasting more than 24 h
- No untoward incidence was seen with either etomidate or propofol induction.

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