 DOI: 10.18231/2394-4994.2017.0071

# Comparison of hemodynamic and serum cortisol levels in response to anesthetic induction with Etomidate or Propofol in patients undergoing CABG surgery

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## Abstract

**Introduction:** To compare the effects of induction agent etomidate and propofol on hemodynamic and serum cortisol levels in patients undergoing coronary artery bypass graft surgery on cardiopulmonary bypass.

**Materials and Method:** After approval from the Institute Ethics committee sixty patients of-ASA grade II or III were enrolled in study. Patients were randomized to receive either propofol or etomidate for anesthesia induction.

**Result:** Hemodynamically, etomidate was more stable than propofol, because propofol causes significant fall in SBP and SVR but after intubation there was significant increase in HR and SBP($P > 0.05$) in etomidate group. Baseline serum cortisol values were within normal limits in both the groups. The cortisol level in the etomidate group decreased after weaning from cardiopulmonary bypass (CPB) upto 60% of baseline while in the propofol group it increased twice than baseline. The values were close to double the baseline at twenty-four hours after induction, but statistically not significant.

**Conclusion:** The surge in serum cortisol levels on the initiation of CPB seen after propofol is prevented by the use of etomidate. Serum cortisol levels in both groups was raised above the baseline after twenty-four hours. Etomidate group shows stable hemodynamic parameters during induction of anesthesia compared to propofol group but after intubation there is more hemodynamic variation in etomidate group because etomidate does not inhibit sympathetic stimulation by laryngoscopy and suggest that some agents should be used to attenuate laryngoscopy response with etomidate.

**Keywords:** Propofol; Etomidate; Coronary Artery Bypass Grafting (CABG); Cardiopulmonary Bypass (CPB); Coronary artery disease(CAD)

**Received:** 14th December, 2016 **Accepted:** 4th March, 2017

## Introduction

Patients having CAD and those posted for CABG constitute a high risk group of patients among the all cardiac surgery patients. Hemodynamic stability, attenuation of the sympathetic responses to laryngoscopy and intubation and the maintenance of adequate balance between myocardial oxygen demand and supply are main concern during induction of anesthesia in patients with coronary artery disease.[1,2]

During surgery severe stress response evoked by cardiopulmonary bypass is well described including an increase in plasma cortisol levels.[3]

As, etomidate has minimal cardiovascular and respiratory depressant action and absence of histamine release, it is used in patients with compromised cardiopulmonary function.[2]

There is a reduction in serum cortisol levels after even a single dose of etomidate but it does not persist in the post operative period, when the body's circulatory response have to be intact for the hemodynamic balance.

Rapid return of consciousness along with negligible residual CNS effects is the most important advantage of propofol but it causes greater fall in blood pressure and systemic vascular resistance than comparative doses of Etomidate.[4]

This study was conducted to compare variation in serum cortisol level and haemodynamics after induction with etomidate and propofol.

## Materials and Method

The study was conducted in the Department of Anesthesiology, S.M.S. hospital and attached group of hospitals, Jaipur after approval from the institutional ethical committee and a written informed consent.

The study recruited sixty patients between the age of 25 to 60 years with triple vessel disease and left ventricular ejection fraction >45%; presenting for elective CABG surgery.

Patients with decompensated cardiac failure, renal dysfunction, bleeding and coagulation abnormalities, preexisting arrhythmias, on mechanical ventilation or on steroid therapy or undergoing emergency surgery, were excluded from the study.

Patients were then randomly allocated to one of the two groups (30 patients in each group)

**Group "A" (Etomidate Group)→** received Inj. Etomidate 0.3mg/kg intravenously.

**Group "B" (Propofol Group)→** received Inj. propofol 2mg/kg intravenously.

The randomization was done by chit in box method.

Patient consumed nothing by mouth 8 hrs preoperatively. Patient's consent and PAC was checked. 18 gauge peripheral venous cannula was inserted into any upper limb peripheral vein and ringer lactate solution was started in peripheral line in all patients.

As part of the institute protocol, all patients were premedicated with Injection morphine 0.1 mg/kg and injection promethazine 0.5 mg/kg intramuscularly half an hour prior to induction of anesthesia.

In operating room, 5-lead ECG, pulse oxymeter was connected, then right femoral artery cannulation was done for invasive blood pressure monitoring.. Central venous catheter was inserted into right internal jugular vein and pulmonary artery catheter was placed via internal jugular vein. All cannulation were performed under local anesthetics.

The patients were then given Inj. Fentanyl (4µg/kg); iv slowly over one minute and after a period of ten minutes, baseline parameters in the form of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI),systemic vascular resistance (SVR), systemic vascular resistance index (SVRI) ,pulmonary vascular resistance(PVR), pulmonary vascular resistance index(PVRI), serum cortisol level were recorded . Preoxygenation was done during these ten minutes, after which induction of anesthesia using either Inj. Etomidate (0.3mg/kg) or Inj. propofol (2mg/kg) was performed. The study drug will be administered in small doses over a period of 60-90 seconds, until there was loss of eyelash reflex and lack of response to vigorous voice commands and tactile stimuli. Muscle relaxation for intubation was facilitated by Inj.Rocuronium 1mg/kg. Positive pressure ventilation was done with 100% oxygen for a period of two minutes. HR. SBP, DBP, CVP, PCWP, CO, CI, SVR, SVRI, PVR, PVRI and serum cortisol level were recorded at 2 min after giving the study drug for induction.

Then endotracheal intubation was performed and ventilated with 100% oxygen. Intubation was done at 3 min after the induction. Again the HR, SBP, DBP, MAP, CVP, PCWP, CO, CI, SVR, SVRI, PVR, PVRI were recorded at 3 min after intubation. Surgery or any other manipulations were not allowed to commence till 3 minutes after intubation. Foley's catheter and ryle's tube were inserted, thereafter.

All patients were mechanically ventilated with 100% oxygen to maintain an end-tidal carbon dioxide between 35 and 40 mm Hg and anesthesia was maintained using intermittent doses of Inj. Midazolam 0.01 mg/kg, Inj. Fentanyl 1 mcg/kg and Inj. Vecuronium 0.02 mg/kg. Heparin in the dose of 4 mg/kg was administered prior to initiation of CPB. A hematocrit of at least 30% was maintained during CPB. Heparin was reversed with protamine in the dose of 5mg/kg after weaning the patient from CPB. Serum cortisol level measured at the time of weaning off CPB. At the end of surgery patients will be shifted to ICU. Serum cortisol level again measured 24 hours after surgery.

**Statistical Analysis:** Statistical programming software – SPSS version 19.0.0 (SPSS Inc., Chicago, Illinois, USA) was used. Quantitative data were summarized in the form of Mean and S.D. The difference between the means of both the groups were analyzed using appropriate statistical test (unpaired t test). The difference between the means within the groups were analyzed using appropriate statistical test (paired t test). The qualitative data were summarized in the form of no. and %. The difference in the qualitative data were analyzed using chi square test. The level of significance would be kept at 95% for all statistical analysis.

## Results

The two groups were comparable in terms of demographic data as there were no statistically significant differences between the groups in terms of age, sex and weight.(Table 1, 2)

**Table 1: Distribution of patients according to sex**

| Gender | ETOMIDATE | | PROPOFOL | | P-Value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Female | 2 | 6.7% | 7 | 23.3% | 0.0631 |
| Male | 28 | 93.3% | 23 | 76.7% | |
| Total | 30 | 100.0% | 30 | 100.0% | |

**Table 2: Distribution of patients according to age and weight**

| | Etomidate | | Propofol | | P-Value b/w groups |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age | 56.6 | 9.6 | 52.7 | 8.2 | 0.0919 |
| Wt | 61.3 | 11.9 | 61.7 | 10.0 | 0.8886 |

**Table 3: Comparison of mean serum cortisol level (mcg/dl) at various time intervals among the group**

| | ETOMIDATE | | | | PROPOFOL | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | P-Value from Base Line | P-Value from AFTER coming from bypass | Mean | SD | P-Value from baseline | P-Value from after coming from bypass | P-Value b/w groups |
| Baseline | 12.5 | 2.6 | | | 13.2 | 2.3 | | | 0.3266 |
| After coming from Bypass | 10.9 | 2.0 | 0.0036 | | 21.5 | 4.3 | 0.0000 | | 0.0000 |
| 24Hr after Surgery | 29.2 | 3.9 | 0.0000 | 0.0000 | 30.4 | 6.7 | 0.0000 | 0.0000 | 0.3954 |

**Table 4: Comparison of mean hemodynamic variables at various time intervals between both the groups**

| | | Etomidate | | | | Propofol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | P-Value from Base Line | P-Value from after 2 min Induction | Mean | SD | P-Value from baseline | P-Value from after 2 min Induction | P-Value b/w groups |
| Base Line | HR | 70.4 | 7.3 | | | 72.1 | 6.1 | | | 0.3318 |
| | SBP | 132.7 | 7.1 | | | 133.9 | 10.6 | | | 0.5997 |
| | DBP | 75.2 | 7.3 | | | 78.4 | 8.9 | | | 0.1280 |
| | CVP | 6.2 | 1.8 | | | 6.5 | 1.6 | | | 0.4928 |
| | PCWP | 6.9 | 1.7 | | | 7.0 | 2.1 | | | 0.8935 |
| | C.O. | 5.8 | 1.0 | | | 6.3 | 1.1 | | | 0.0522 |
| | C.I. | 3.5 | 0.7 | | | 4.0 | 1.3 | | | 0.0570 |
| | SVR | 1328.6 | 259.3 | | | 1415.3 | 274.5 | | | 0.2138 |
| | SVRI | 2432.0 | 323.5 | | | 2591.9 | 419.6 | | | 0.1039 |
| | PVR | 118.4 | 33.7 | | | 117.1 | 22.1 | | | 0.8571 |
| | PVRI | 245.8 | 53.7 | | | 259.6 | 41.3 | | | 0.2694 |
| After 2 min Induction | HR | 70.3 | 6.4 | 0.9340 | | 69.5 | 7.0 | 0.0928 | | 0.6737 |
| | SBP | 132.0 | 9.7 | 0.7841 | | 124.7 | 13.7 | 0.0007 | | 0.0214 |
| | DSP | 74.9 | 8.6 | 0.8789 | | 72.8 | 8.1 | 0.0371 | | 0.3329 |
| | CVP | 6.1 | 1.8 | 0.8804 | | 6.1 | 1.8 | 0.4378 | | 1.0000 |
| | PCWP | 6.8 | 1.9 | 0.7935 | | 6.6 | 1.5 | 0.5503 | | 0.7138 |
| | C.O. | 5.6 | 1.3 | 0.5481 | | 6.0 | 1.0 | 0.3444 | | 0.1415 |
| | C.I. | 3.5 | 1.1 | 0.9517 | | 3.8 | 0.8 | 0.4010 | | 0.2825 |
| | SVR | 1320.7 | 204.3 | 0.8963 | | 1247.4 | 296.2 | 0.0369 | | 0.2697 |
| | SVRI | 2432.1 | 264.1 | 0.9985 | | 2328.4 | 364.3 | 0.0120 | | 0.2120 |
| | PVR | 117.7 | 37.8 | 0.9438 | | 106.4 | 23.5 | 0.0985 | | 0.1719 |
| | PVRI | 243.7 | 54.7 | 0.8899 | | 238.7 | 49.3 | 0.0875 | | 0.7148 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 72.3 | 7.5 | 0.3582 | 0.2175 | 71.1 | 6.5 | 0.5218 | 0.3814 | 0.5110 |
| | SBP | 141.7 | 10.3 | 0.0013 | 0.0000 | 130.9 | 8.1 | 0.2099 | 0.0338 | 0.1150 |
| | DSP | 79.1 | 8.8 | 0.0991 | 0.0503 | 75.9 | 8.0 | 0.2915 | 0.1014 | 0.1418 |
| | CVP | 6.6 | 1.8 | 0.4176 | 0.2477 | 6.2 | 1.7 | 0.4525 | 0.9413 | 0.3874 |
| | PCWP | 7.4 | 1.9 | 0.3117 | 0.1638 | 6.9 | 1.8 | 0.8240 | 0.5038 | 0.2336 |
| | C.O. | 6.1 | 1.1 | 0.2442 | 0.1057 | 6.5 | 1.2 | 0.3580 | 0.1143 | 0.1588 |
| | C.I. | 3.9 | 0.8 | 0.0592 | 0.1354 | 4.2 | 1.1 | 0.6098 | 0.1494 | 0.2497 |
| | SVR | 1380.4 | 279.4 | 0.3701 | 0.3705 | 1402.3 | 232.2 | 0.8479 | 0.0609 | 0.7425 |
| | SVRI | 2490.3 | 328.7 | 0.4992 | 0.4373 | 2526.4 | 308.9 | 0.4560 | 0.0505 | 0.6628 |
| 3 Min after | PVR | 121.4 | 33.7 | 0.7608 | 0.5615 | 118.8 | 33.3 | 0.8051 | 0.1144 | 0.7651 |
| Intubation | PVRI | 255.8 | 53.7 | 0.5354 | 0.2211 | 245.8 | 52.1 | 0.1690 | 0.6205 | 0.4673 |

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), pulmonary vascular resistance(PVR), pulmonary vascular resistance index(PVRI)

The mean baseline serum cortisol level in group A was 12.5±2.6 mcg/dl. Group A showed significant fall in serum cortisol level just after coming off from cardiopulmonary bypass comparable to baseline (2 min after induction), while there was significant increase in serum cortisol level 24 hrs after surgery as compared to baseline. This increase serum cortisol level 24 hrs after surgery is also significant when we compare it with the level after coming off bypass.(Table 3)

The mean baseline serum cortisol level in group B was 13.2±2.3 mcg/dl. In Group B, there was significant rise in serum cortisol level just after coming off from cardiopulmonary bypass comparable to baseline (2 min after induction) and also show significant increase in serum cortisol level 24 hrs after surgery as compared to baseline. This increase serum cortisol level 24 hrs after surgery is also significant when we compare it with the level after coming off bypass.

Comparison of mean change in serum cortisol level was significant in the group but was also significant between both the groups only when we compared mean serum cortisol levels after coming from bypass. But levels of mean serum cortisol at baseline and 24 hours after surgery was not significant between both groups.

In group A the mean baseline heart rate was 70.4±7.3/min. After induction the rise of heart rate remained comparable to baseline, whereas after intubation the rise became significant compared to baseline. (Table 4)

In group B mean baseline heart rate was 72.1±6.1/min. After induction the heart rate decreased but not significantly, and heart rate increased 3 min after intubation but not much as compared to group A.

In group A mean baseline systolic blood pressure was 132.7±7.1 mmHg. After induction there was statistically non significant decrease in mean systolic blood pressure But 3 min after intubation the SBP increased significantly. The rise in heart rate after intubation much less in propofol group than in etomidate group.

In group B mean baseline systolic blood pressure was 133.9±10.6 mmHg. After induction there was a significant fall in SBP as compared to baseline. And 3min after intubation SBP increased significantly as compared to 2 min after intubation.

In group B, the DBP significantly decreased 2 min after induction but 3 min after intubation, there was a non significant increase in DBP.

The mean baseline Systemic Vascular Resistance in group A was 1328.6±259.3 Dyne/sec.cm-5. SVR was stable after induction but showed non significant increase as compared to baseline after intubation.

The mean baseline SVR in group B was 1415.3±274.5 Dyne/sec.cm-5. There was highly significant decrease in SVR as compared to baseline 2 min after induction but SVR increase 3 after intubation. Comparison of mean change in SVR between both the groups was non significant.

The mean baseline Systemic Vascular Resistance Index in group A was 2432.0±323.5Dyne/sec.cm-5/m². Group A showed non significant increase in SVRI as compared to baseline throughout the study.

The mean baseline SVRI in group B was 2591.9±419.6 Dyne/sec.cm-5/m². This group showed highly significant decrease in SVRI as compared to baseline at all points of study.

Comparison of mean change in SVRI between both the groups was highly significant at all points of study.

In group A, rest hemodynamic variables like CVP, CO, CI, PCWP, PVR and PVRI are relatively stable after induction and showed increasing trends after intubation. In group B these variables showed decreasing trends after induction and increasing trends after intubation but these changes were non significant.

## Discussion

There are various deleterious effects of anesthetic agents in patients suffering from coronary artery disease. Patient with compromised left ventricular function has higher risk.[2]

A wide variety of anesthetic drugs are available. The use of Etomidate and Propofol has been considered superior to other intravenous anesthetic agents in cardiac patients.[2]

Anaesthesia induction is associated with depression of the sympathetic system which causes decrease in cardiac output, stroke volume and a decrease in arterial blood pressure. This is due to while, sympathetic system activity is essential in patients with left ventricular dysfunction, careless anaesthesia induction may prove fatal and catastrophic.

Cardiopulmonary bypass is also a stressful situation in terms of sympathetic stimulation. CPB is associated with increase sympathomimetic amines i.e. epinephrine and, leading to systemic inflammatory response syndrome (SIRS) and delaying patient recovery.

Etomidate has a short lasting and rapid onset of action along with a safe cardiovascular risk profile. Therefore, it is an ideal induction agent for haemodynamically unstable patients. Etomidate has no effect on the sympathetic nervous system and on baroreceptor function.[5] An induction dose of etomidate causes almost no change in haemodynamic variables in cardiac patients. Etomidate does not inhibit sympathetic tone or myocardial function,[6] so does not block sympathetic responses to laryngoscopy and intubation.[7,8]

Etomidate reversibly inhibits 1-beta-hydroxylase in the adrenal cortex and causes cortical suppression. The cortisol suppression induced by a single dose of etomidate is almost always limited to 24 hours but

using a continuous infusion may lead to increased mortality.

In our study, one group found slightly depressed cortisol levels for a short duration postoperatively after a single dose of etomidate, but the levels never fell out of normal range. The cortisol levels also returned to levels equal to propofol group at 24 hours post induction.

There is currently no evidence of a clinically significant adverse outcome from single-dose etomidate. There are however retrospective studies which show that etomidate does not increase mortality in septic patients, in emergency room or in congenital heart disease.

Propofol is also a short-acting, intravenously administered hypnotic agent. It exerts its effect through potentiation of GABA receptor activity and also act as a sodium channel blocker. The endocannabinoid system may contribute significantly to propofol's anesthetic action. Propofol causes vasodilatation and transient fall in systemic blood pressure.

There was no statistically significant difference between both groups with regards to demographic data Therefore, nullified the effect of these confounding factors (age and ejection fraction) on the results (P-value>0.05).

The mean baseline HR, SBP, DBP, CVP, PCWP, CO, CI, PVR, PVRI, SVR and SVRI were comparable in both the groups (P-value > 0.05).

In Group A the heart rate remained comparable to baseline after induction, but after intubation it increased significantly as a result of sympathetic stimulation as it does not block sympathetic responses to laryngoscopy and intubation. Similar increase in heart rate, after intubation, was also noted by Carido et al[9] and Stockham et al.[8] In group B the heart rate decreased insignificantly after induction, but increased 3 min after intubation and then became comparable to baseline.

The SBP was significantly decrease in group B at 2 min after induction but relatively stable in group A .The SBP increase from the baseline at 3 minutes after intubation was significantly higher in group A, while the increase was insignificant in group B. The comparison of the mean change in SBP from the baseline in both the groups showed a significant difference at 2 min after induction.

According to Ebert et al[5] etomidate preserves both sympathetic outflow and autonomic reflexes. This is in accordance with our findings of increased heart rate and arterial blood pressure following intubation in etomidate group. However, this study and previous ones showed an initial small decrease in heart rate, and decrease in systemic blood pressure with propofol, although effects of these results were not significant electrocardiographically.

There was a significant decrease in SVR and SVRI in propofol group at 2 minutes after induction.

There was an insignificant fall in CVP which might be due to either inadequate intravenous fluid administration or intravenous vasodilators like Inj. Nitroglycerine. In Propofol group, fall in CVP might be a result dilatation of peripheral vasculature.

In group A the baseline cortisol levels decreased significantly (p value-0.0036) after the patient came from CPB. The cortisol levels also increased significantly 24 hrs after the surgery from the baseline and post CPB levels (p value-0.000).

In group B, the cortisol levels increased significantly as compared to the baseline when the patient came from CPB and 24 hrs after the surgery with p value of 0.00.The cortisol levels were significantly higher in group B as compared to group A post CPB(p value-0.000), while the two groups remained comparable at 24 hrs after the surgery.

Pandey et al[10] also observed a significant fall in serum cortisol levels after etomidate induction and significant increase in cortisol levels in the propofol group. Serum cortisol levels after 24 hr were also comparable in the groups.

These suppressed cortisol levels might be beneficial for patient during stress i.e. sternotomy, dissection around aorta, chest tube insertion and extubation. CAD patients have a diminished cardiopulmonary reserve and disturbed myocardial oxygen balance. High levels of stress, reflected by cortisol levels in the post-operative period may be detrimental to them. Therefore, etomidate ensures better patient tolerance to stressful stimuli post-operatively.

Both the groups showed an insignificant fall in CI after induction and an insignificant rise in CI after intubation as compared to baseline. Price et al[11] and Raveen et al (2) observed a decrease in cardiac index after induction. In our study the insignificant rise in CI in group A after intubation may be due to increase in CO as a result of maintained sympathetic reflexes by etomidate.

The hemodynamic effects of anesthetic induction agents in cardiac patients depend to a great extent–on the technique, skill, and experience of drug administration by the clinician (e.g., slow infusion vs. rapid bolus).Dose adjustment and speed of induction are probably more important than which individual drugs are used.

Adverse effect were seen like pain on injection (4 patients), severe hypotension (1 patient) and bradycardia (2 patients) in propofol group and myoclonus (2 patients) in etomidate group.

## Conclusion

Etomidate was less effective in minimizing the stress response, with a statistically significant increase from baseline in both heart rate (P = 0.001) and mean arterial pressure (P = 0.001), 3 minute after intubation. Baseline hemodynamic variables are more stable in etomidate group after induction but there was a

significant increase from the baseline after intubation, as it does not block sympathetic responses to larngoscopy and intubation. Intergroup comparison revealed non significant changes in these variables after induction and intubation except that SBP decreased significantly in propofol group after induction, as it causes vasodilatation and may result in transient fall in systemic blood pressure.

Serum cortisol level in the propofol group increased more than two fold, whereas the values in the etomidate group decreased close to 60%on weaning from bypass, although the values after 24 hour were close to double the baseline levels and also same in both groups, suggesting that Etomidate causes only transient fall(<24 hr) in serum cortisol level.

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