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

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ABSTRACT

**Introduction:** The considerations 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 a 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

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.[1-5] 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...
surgery. 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, which lasts for up to 24 h. However, it has a very stable cardiovascular profile 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 gantz catheter placement under local infiltration is done as routine in our Institution and to measure pre-induction values, i.e., 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), SpO₂, 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 ± 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 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 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 post-intubation. There was significant decrease in CO.

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

| Variable       | Group I (P) (n=30) | Group II (E) (n=30) | P    |
|----------------|-------------------|---------------------|------|
| Age (years)    | 33.96±10.88       | 36±12.33            | 0.499|
| Sex (male/female) | 15/15             | 16/14               |      |
| Weight (kg)    | 47.7±8.15         | 46.26±6.93          | 0.463|
| Height (cm)    | 161.1±7.7         | 162.8±8.3           | 0.414|
| ASA Grade II   | 22                | 19                  |      |
| ASA Grade III  | 8                 | 11                  |      |
| Duration of surgery (in h) | 5.25±1.11 | 5.4±1.02 | 0.587|

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

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

Values expressed as mean±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 3: Hemodynamic responses between the two groups

|                    | Group I (P) (n=30) | Group II (E) (n=30) | P       |
|--------------------|--------------------|--------------------|---------|
| HR                 | 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        | 85.63±23.53        | 0.0501  |
| 5 min after intubation | 92.8±14.91         | 87.46±10.99        | 0.119   |
| SBP                | 117.63±15.66       | 111.56±16.006      | 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 intubation | 95.86±3.51         | 103.7±6.22         | <0.001* |
| DBP                | 73.93±11.41        | 72.53±8.16         | 0.586   |
| After induction    | 59.7±7.28          | 69.4±8.26          | 0.007*  |
| After intubation   | 64.3±6.46          | 71.43±7.37         | <0.005* |
| 5 min after intubation | 66.6±4.41          | 71.26±4.83         | 0.0003* |
| MAP                | 88.38±12.01        | 85.0±10.50         | 0.261   |
| After induction    | 67.97±5.79         | 80.5±4.39          | <0.001* |
| After intubation   | 72.79±5.54         | 82.07±7.09         | <0.001* |
| 5 min after intubation | 76.4±3.47          | 82.05±3.92         | <0.001* |

Values expressed as mean±SD. *P<0.05 considered significant statistically. HR: Heart rate, 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 | 7.6±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

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 | 2.1±0.33      | 2.1±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

| PVR              | 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±130.11 | 1733.13±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. PVR: Systemic vascular resistance, SD: Standard deviation

Table 9: Pulmonary vascular resistance between two groups

| PVR              | 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

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 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.
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.

**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

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

| Group     | Serum cortisol values | Blood glucose levels |
|-----------|-----------------------|----------------------|
|           | Baseline/before induction | During bypass | After bypass/after protamine reversal of heparin | At 24 h postoperatively | Baseline | During bypass | After protamine reversal/weaning off CPB | At 24 h postoperatively |
| Group P  | 11.7±1.95             | 14.8±1.62           | 23.26±3.14                  | 28.3±2.97               | 97.43±15.66 | 158.03±38.62 | 159.03±39.91                  | 106.06±28.15           |
| Group E  | 12.2±2.94             | 9.36±3.04           | 7.66±2.91                   | 24.23±3.62              | 93.83±15.9  | 138.53±33.5  | 136.9±35.24                   | 98.86±15.9             |
| P         | 0.44                  | <0.001*             | <0.001*                     | <0.001*                 | 0.380      | 0.041*        | 0.0265*                       | 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 et al. (1985)[3] | 1.5          |
|        | Vermeyen et al.[16] | 2.5          |
|        | Kaplan et al.[17] | 2.5          |
|        | Boer et al.[7] | 2            |
|        | Boer et al.[1] | 2            |
|        | Singh et al.[4] | 1.5          |
|        | Pandey et al.[11] | 2            |
|        | Gooding et al.[10] | 0.3          |
|        | Colvin et al.[5] | 0.3          |
|        | Boer et al.[1] | 0.3          |
|        | Yunqi et al.[18] | 0.3          |
|        | Singh et al.[4] | 0.2          |
|        | Morel et al.[16] | 0.3          |
|        | Pandey et al.[11] | 0.2          |
|        | Rahman et al.[19] | 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.
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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