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ORIGINAL RESEARCH

Comparison of a ketamine-propofol combination and etomidate for anaesthesia induction on haemodynamic parameters in patients undergoing coronary artery bypass grafting

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Objective: To compare the haemodynamic response of both a ketamine-propofol (ketofol) combination and etomidate for anaesthesia induction in patients undergoing coronary artery bypass grafting (CABG).

Methods: This randomised study was conducted in 120 patients (n = 60 for each group) who were scheduled for elective CABG surgery. Patients in group K received ketofol (a ketamine and propofol combination [1:1]) and group E received etomidate, until loss of verbal response. Baseline haemodynamic variables including heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), cardiac output (CO), cardiac index (CI) and systemic vascular resistance (SVR) were measured for all patients at 1, 2 and 3 minutes post induction. Serum cortisol and blood sugar levels were also compared before induction, after cardiopulmonary bypass (CPB) and at 24 hours postoperatively.

Results: Statistically significant reduction occurred in HR, SAP, DAP and MAP from baseline until 3 minutes post induction in both groups ($p < 0.001$), but intergroup comparison was comparable. Maximum fall in CO and CI from baseline at 3 minutes were greater in group E than in group K (38.18% and 22.36%, and 34.16% and 19.86%, respectively). Maximum fall in SVR at 3 minutes post induction was greater in group K than in group E and was statistically significant ($p < 0.05$). Significant increase in cortisol levels occurred within group K from baseline until 24 hours postoperatively. Significant fall in serum cortisol levels occurred after weaning off CPB within group E, which returned to almost baseline at 24 hours. Blood glucose levels rose from baseline until 24 hours postoperatively in both groups, but peaked more in group K after weaning from CPB than in group E ($p < 0.05$).

Conclusion: We concluded that both ketofol and etomidate produced stable haemodynamics in patients undergoing CABG.

Keywords: Ketamine-propofol combination, etomidate, cardiopulmonary bypass, haemodynamic response, cardiac anaesthesia

Introduction

The most critical period in cardiac patients undergoing coronary artery bypass graft (CABG) surgery is the anaesthesia induction.[1] Various factors that affect anaesthetic induction in cardiovascular surgery include haemodynamic stability, balance between myocardial oxygen demand and supply, and minimising the intubation stress response.[2] A multitude of induction agents are used either alone or in different combinations, including thiopentone, etomidate, propofol, midazolam and ketamine.[2] Etomidate is a cardio stable drug and is preferred as an induction agent for anaesthesia in patients undergoing CABG surgeries.[3] Etomidate does not depress sympathetic tone or myocardial contractility, hence its induction doses produce minimal changes in blood pressure and heart rate (HR).[4] Adrenocortical suppression (lasting up to 72 hours) and myoclonus, however, are undesirable effects of etomidate.[5] Ketamine is a fast-acting anaesthetic agent with dissociative properties but has unique cardiovascular effects. It provides intense analgesia, hypnosis and amnesia. It also causes less respiratory depression than other intravenous anaesthetics at clinically-relevant doses. Ketamine causes stimulation of the cardiovascular system which is usually associated with an increase in blood pressure, HR and cardiac output (CO), thus making it useful for patients with impaired cardiac function.[1,6] Propofol is the most widely used induction agent in general anaesthesia and has several advantages which include rapid onset, short duration and smooth emergence. Vasodilation is seen in both arterial and venous circulation, leading to reduced preload and afterload. It has cardiovascular depressive effects that can cause a sudden decrease in HR and blood pressure, hence propofol can lead to severe haemodynamic instability during induction of anaesthesia in patients with cardiovascular risk factors.[7]

To search for an ideal intravenous anaesthetic agent, various drug combinations have been examined like ketamine-propofol, etomidate-midazolam and thiopentone-midazolam. Of these various anaesthetic combinations that have been investigated, the ketamine-propofol combination (ketofol) is a popular choice because of the specific properties intrinsic to each drug. Drug combinations reduce the dose needed of each individual drug, leading to a decrease in adverse effects.[7] Ketofol ensures better haemodynamic stability in patients, especially in those undergoing cardiovascular surgery. We studied the comparison of combination of ketamine and propofol (in a 1:1 ratio) and etomidate for anaesthesia induction in patients undergoing CABG.

Methods

After obtaining approval from the Institutional Ethics Committee as well as written informed consent, 120 patients within

the age group of 30–70 years, fulfilling criteria of the American Society of Anaesthesiologists (ASA) Grade II and III, and scheduled for CABG surgery, were included in this prospective randomised comparative study. Patients who were excluded from this study include those with a known history of adrenal insufficiency, who received steroid therapy during the preceding six months, with left ventricular ejection fraction (LVEF) < 40%, with renal or hepatic insufficiency, with known allergies to any of the study drugs, and who used propofol, ketamine or etomidate one week prior to surgery.

The primary objective of this study was to compare haemodynamic parameters, including HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), CO, cardiac index (CI) and systemic vascular resistance (SVR), using either a ketamine and propofol combination (1:1) or etomidate for anaesthesia induction in patients undergoing CABG. The secondary objective was to assess serum cortisol and blood sugar levels in patients who received either a ketamine and propofol combination (1:1) or etomidate.

The total of 120 patients were randomly allocated to either group K or group E through the lottery method. The proposed study population consisted of two groups of 60 participants each.

Participants in group K received a combination of ketamine and propofol in a ratio of 1:1 (5 mg/ml) each, while participants in group E received etomidate.

A detailed pre-anaesthetic checkup and relevant investigations were done. Patients were premedicated with injection morphine (0.1 mg/kg intramuscular) half an hour before moving them to the operating theatre (OT). Upon arrival in the OT, standard monitoring including non-invasive blood pressure (NIBP), pulse-oximetry and electrocardiogram (ECG) monitoring were attached. After securing a peripheral venous line with an 18 G cannula, a fentanyl (1 µg/kg) injection was given and 7 ml/kg of Ringer's lactate solution was infused over a 20-minute period. Intra-arterial radial cannulation was achieved under local infiltration. Baseline values of HR, oxygen saturation (SpO_2), invasive SAP, DAP, MAP, CO, CI and SVR were recorded with a FloTrac device and labelled as baseline before induction of anaesthesia (T0). A fentanyl (4 µg/kg) injection was given intravenously after intra-arterial cannulation. Patients were pre-oxygenated with 100% oxygen for 3 minutes. After 3 minutes, anaesthesia was induced with an injection of either ketofol (1:1) or etomidate until loss of verbal response. After checking their ventilation, each patient received intravenous vecuronium bromide (0.2 mg/kg) for muscle relaxation. Patients were then ventilated with 100% O_2 using a face mask and a semi-closed system with a circle absorber for 3 minutes. All the parameters were recorded post induction (T1) at 1, 2 and 3 minutes (T1-1, T1-2 and T1-3). Endotracheal intubation was performed with an appropriate size endotracheal cuffed tube. If MAP fell below 55 mmHg, intravenous phenylephrine was administered in an aliquot of 20 µg every 30 seconds until MAP was above 55 mmHg again.

Blood samples were measured for serum cortisol and blood sugar levels before anaesthesia induction, after CPB and 24 hours postoperatively. At the end of surgery, patients were moved to the cardiac intensive care unit (ICU) with an endotracheal tube in situ after an adequate dose of muscle relaxant and opioid analgesic.

Statistical analysis

Categorical variables for groups K and E were presented as numbers and percentages (%) while continuous variables were presented as mean ± standard deviation (SD) and median. Normality of data was tested by the Kolmogorov–Smirnov test. Quantitative variables were compared using the independent t-test/Mann–Whitney test between the two groups. Qualitative variables were compared using the chi-square test/Fisher's exact test. A p-value of < 0.05 was considered statistically significant. The data was entered into a Microsoft Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) (version 21.0) (IBM, New York, USA).

A study done by Baradari et al.[1] observed a percentage change in MAP in the ketofol group of 34 ± 17 and in the etomidate group of 26 ± 14. Taking these values as reference, the sample size was determined between the two groups with 80% power of study and 5% level of significance. The sample size, therefore, was 56 patients in each study group. To reduce margin of error, the total sample size was determined as 120 patients (60 patients per group).

Results

Both the groups were comparable in terms of demographic parameters (age, gender, height and weight), ASA grading and the type of elective surgery (p-value > 0.05). Intragroup comparison between group K and group E resulted in statistically significant reduction in HR, MAP and SVR from baseline at 1, 2 and 3 minutes post induction (p-value < 0.0001).

The maximum fall in HR in group K (T0 – 79.88 ± 13.03 to T1-1–3 – 63.58 ± 7.67) was 19.8 ± 4.98%, while in group E (T0 – 83.02 ± 14.58 to T1-1–3 – 67.1 ± 10.52) was 18.77 ± 4.77% at 3 minutes post induction (p = 0.387) (Figure 1). The maximum fall in MAP in group K (T0 – 92.57 ± 6.67 to T1-1–3 – 72.57 ± 4.11) was 21.46 ± 3.41%, while in group E (T0 – 92.67 ± 7.61 to T1-1–3 – 71.85 ± 4.18) was 22.22 ± 4.46% at 3 minutes post induction (p = 0.396) (Figure 2). Intergroup comparison revealed that the fall in HR and MAP from baseline until 3 minutes post induction were statistically and clinically insignificant in both groups. The maximum fall in SVR in group K (T0 – 1220.31 ± 181.65 to T1-1–3 – 1151.89 ± 166.87) was 5.51 ± 3.48%, while in group E (T0 – 1236.11 ± 194.71 to T1-1–3 – 1191.74 ± 183.18) was 3.5 ± 3.03% at 3 minutes post induction (p = 0.001) (Figure 3). This was statistically significant and clinically relevant as perioperative hypotension episodes were more prevalent in group K compared to group E. Of the patients in group K, 5% (3/60) had significant hypotension episodes requiring fluid/vasopressor administration until 3 minutes post induction.

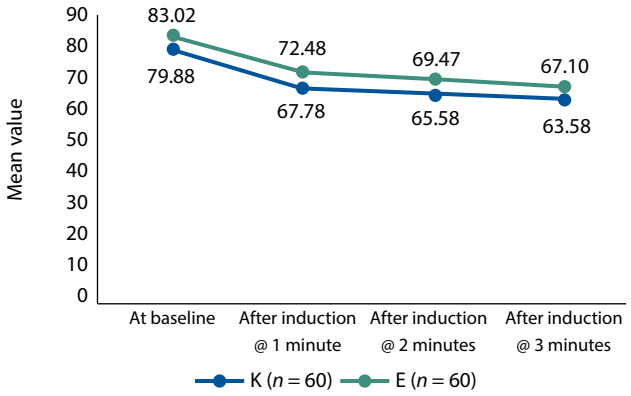

Figure 1: Comparison of trend of heart rate (bpm) at different time intervals between group K and group E

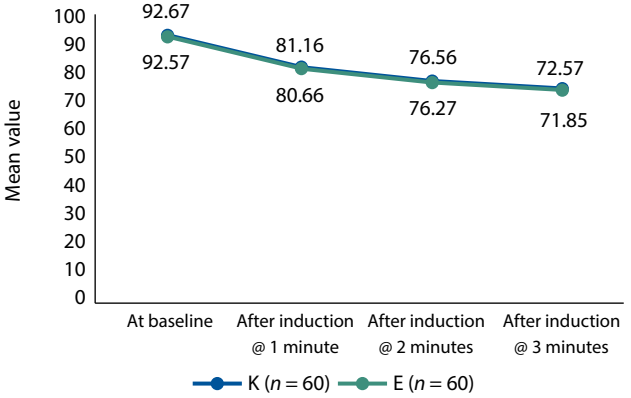

Figure 2: Comparison of trend of mean arterial pressure (mmHg) at different time intervals between group K and group E

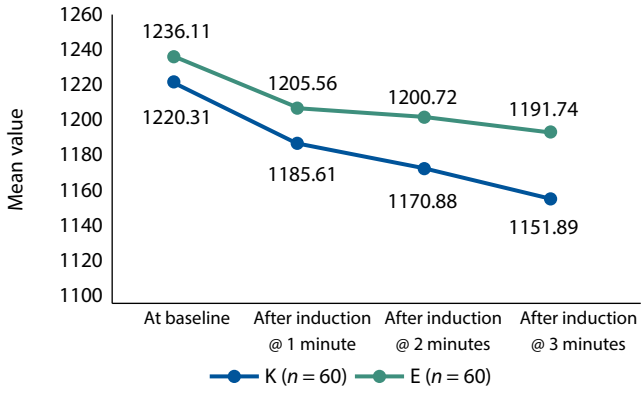

Figure 3: Comparison of trend of systemic vascular resistance (dynes/sec./cm^2) at different time intervals between group K and group E

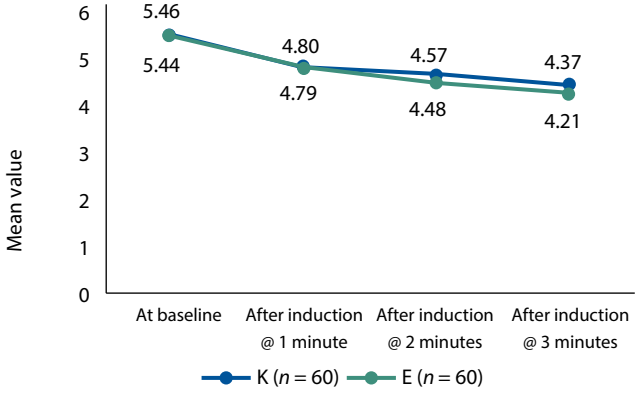

Figure 4: Comparison of trend of cardiac output (litres/minute) at different time intervals between group K and group E

Induction with either ketofol or etomidate resulted in statistically significant reduction in CO and CI from baseline at 1, 2 and 3 minutes post induction (p-value < 0.0001). The maximum significant fall in CO group K (T0 – 5.46 ± 0.85 to T1-1–3 – 4.36 ± 0.64) was 19.86 ± 4.52%, while in group E (T0 – 5.44 ± 0.89 to T1-1–3 – 4.21 ± 0.69) was 22.36 ± 4.64% at 3 minutes post induction (p = 0.003) (Figure 4). The maximum significant fall in CI in group K (T0 – 3.45 ± 0.52 to T1-1–3 – 2.25 ± 0.37) was 34.16 ± 10.17%, while in group E (T0 – 3.47 ± 0.68 to T1-1–3 – 2.1 ± 0.36) it was 38.18 ± 11.11% at 3 minutes post induction (p = 0.021) (Figure 5). Fall in CO and CI was greater in group E than in group K at 3 minutes post induction and was statistically significant (p-value

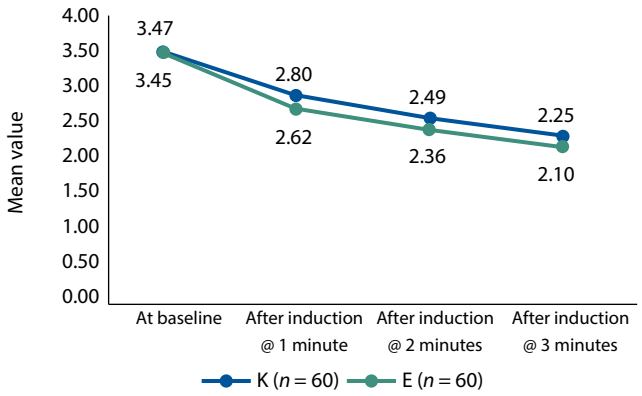

Figure 5: Comparison of trend of cardiac index (litres/min/m^2) at different time intervals between group K and group E

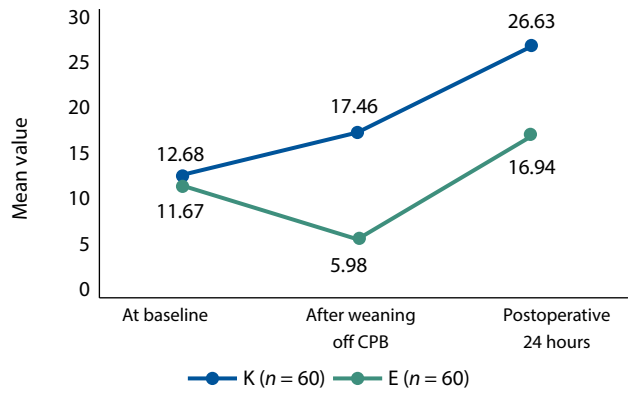

Figure 6: Comparison of trend of serum cortisol levels (µg/dl) at different time intervals between group K and group E

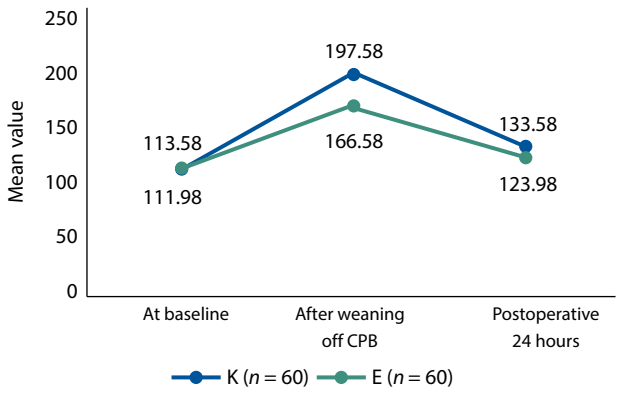

Figure 7: Comparison of trend of blood glucose levels (mg/dl) at different time intervals between group K and group E

< 0.05) but not clinically relevant as the patients remained haemodynamically stable.

There was significant fall in cortisol levels in group E from baseline until weaning off CPB (11.66 ± 4.07 to 5.98 ± 1.59) and it rose during the postoperative period as measured at 24 hours (16.94 ± 4.11). In group K, however, there was rise in serum cortisol levels from baseline until 24 hours postoperatively (12.68 ± 5.37 to 26.63 ± 10.48) (Figure 6). Also, there was a rise in blood glucose levels from baseline until 24 hours postoperatively (111.98 ± 10.25 to 133.58 ± 18.6 and 113.58 ± 17.99 to 123.98 ± 23.26 in groups K and E, respectively). The blood glucose levels peaked higher in group K (197.58 ± 35.59) after weaning off CPB than in group E (166.58 ± 26.92), which was statistically significant (*p*-value < 0.0001) (Figure 7). This could be because of the brief suppression of the hypothalamic-pituitary axis and decreased cortisol levels caused by etomidate. Fall in cortisol secretion also suggested less rise in blood sugar levels in group E.

Discussion

Cardiovascular stability is a crucial requirement of any anaesthetic agent used for induction of anaesthesia in patients undergoing CABG surgery, especially in patients with a poor cardiovascular reserve.[6,8] We compared a ketamine-propofol combination (1:1) with etomidate for anaesthesia induction on haemodynamic response in patients undergoing CABG.

Intragroup comparison of baseline haemodynamic parameters showed a significant decrease from baseline in HR, SAP, DAP and MAP in both group K and group E until 3 minutes post induction ($p < 0.001$). Intergroup comparisons for these variables, however, showed no statistical or clinical difference. Baradari et al.[1] showed that there was a decrease in all haemodynamic parameters (HR, SAP, DAP and MAP) which was greater in the ketofol (1:1.5) group than in the etomidate (0.2 mg/kg) group. The ephedrine requirement in their study due to haemodynamic changes was 24.4% (10 patients) and 5% (2 patients) in the ketofol group and the etomidate group, respectively. This is compared to our present study, where the phenylephrine requirement in group K (ketofol 1:1) was 5% (3 patients) and in group E was nil. Baradari et al.[1] concluded that etomidate provided better haemodynamic stability in patients with left ventricular dysfunction undergoing CABG surgery under general anaesthesia compared to ketofol (1:1.5). The difference could be explained by the fact that our study used ketofol in a 1:1 ratio which led to more stable haemodynamics compared to the ketofol ratio of 1:1.5.

Aghdaii et al.[8] also demonstrated haemodynamic responses similar to our study in patients with left ventricular dysfunction undergoing CABG after induction with either an etomidate-midazolam (EM) (0.2:0.06) or a propofol-ketamine (PK) (1:1) combination. There was considerable decrease in SVR and CI from baseline after induction in both of these groups. The fall in SVR was greater in the PK group than the EM group, while the CI fell more in the EM group than the PK group,[8] similar to our study.

Comparison between a propofol-fentanyl (PF) (1.5:2) and propofol-ketamine (PK) (1:1) combination during induction of anaesthesia by Bajwa et al.[9] resulted in greater fall in arterial pressures within the PF group than the PK group. The above results emphasised that a propofol-ketamine combination was haemodynamically more stable due to the antagonistic properties of propofol (decrease in blood pressure) and ketamine (increase in blood pressure) when used in a ratio of 1:1.[9]

ELZayyata et al.[10] found that a combination of ketamine and propofol (1:1) was effective and haemodynamically safe for anaesthesia induction of critically ill rheumatic cardiac parturients undergoing caesarean section. Low-dose ketamine combined with propofol in a ratio of (1:1) led to better preservation of MAP compared with propofol alone, as shown in our present study.[11,12]

In their meta-analysis, Yao et al. suggested that anaesthesia induction with etomidate in cardiac surgical patients lead to reversible and transient lower cortisol levels as well as a higher adrenal insufficiency incidence, but the outcome of the patient was not affected.[13]

Etomidate causes adrenocortical suppression by inhibiting the hypothalamic-pituitary axis. This results in a decrease in plasma cortisol levels lasting up to 72 hours which may cause a decrease in blood pressure under anaesthesia and may result in a decrease in blood glucose levels. In the majority of patients, these changes are clinically insignificant.

A study conducted by Morel et al.[3] stated that a single bolus of etomidate (0.3 mg/kg) blunted the hypothalamic-pituitary-adrenal axis response for more than 24 hours in patients undergoing elective cardiac surgery, but this was not associated with an increase in vasopressor requirements. The incidence of relative adrenal insufficiency was higher in the etomidate group at 12 hours (100%) and 24 hours (85%) ($p = 0.001$) compared to propofol (0.5 mg/kg) which was 40% at 12 hours and 25% at 24 hours.[3] Our study found significant fall in serum cortisol levels with group E after weaning off CPB which almost returned to baseline after 24 hours without any increase in vasopressor requirements, but there was significant increase in cortisol levels in group K after weaning off CPB and postoperatively at 24 hours. Our results were similar to the study done by Kaushal et al.[14] who found a rise in serum cortisol levels after weaning off CPB with propofol but reduction in serum cortisol levels with etomidate.

Our study showed that blood glucose levels significantly increased after weaning off CPB and 24 hours postoperatively in both group K and group E compared to baseline. These results were also similar to the study done by Kaushal et al.[14] The rise was less in group E due to the decreased stress response because of inhibition of cortisol synthesis. At 24 hours postoperatively, the blood glucose values decreased but remained greater than the baseline values.

Myoclonus, allergic reactions and pain on injection was not seen with either of the studied drugs.

Limitations of the study

There were a few limitations in this study. Firstly, the study was carried out at a single hospital from which all patients undergoing CABG surgery were selected. Patients on antihypertensive drugs and other multiple comorbidities were not excluded, which may be a confounding factor. Also, the sample size for the investigation of these patients might not be large enough.

Conclusion

The study concluded that both the ketamine-propofol combination (1:1) and etomidate produce satisfactory induction conditions with minor haemodynamic fluctuations in patients undergoing CABG surgery. Ketofol (1:1) can be used safely, though a certain subset of patients, perhaps from an older age group or those on antihypertensives, may require treatment with vasopressors. Adrenocortical suppression caused by etomidate was not found to be clinically significant since serum cortisol levels reached baseline at 24 hours postoperatively. Blood glucose rose until 24 hours postoperatively in both study groups but it peaked less in group E.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethics Committee approval was obtained from the Government of India VMMC and Safdarjung Hospital Institute Ethics Committee, serial no. IEC/VMMC/SJH/THESIS/OCTOBER/2018-159.

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