



RESEARCH ARTICLE

TO COMPARE EFFICACY AND SAFETY BETWEEN ETOMIDATE AND FENTANYL-MIDAZOLAM AS AN INDUCTION AGENTS IN PATIENTS UNDERGOING ADULT VALVULAR OPEN HEART SURGERIES

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ABSTRACT

Background: Valvular Heart disease patients are always have other system involvement due to their complications. In such kind of high risk patients if haemodynamic instability occurs during induction, intubation then it will be hazardous to the patients. Hence the ideal anesthetic induction agents if used will be helpful to these patients. Hence we decided to study effects of etomidate and Fentanyl –Midazolam combination as induction agents as well as their effects on stress response of Intubation and cardiopulmonary bypass.

Aim: To study the effects of induction dose of etomidate and Fentanyl Midazolam on stress response of intubation and Cardiopulmonary Bypass in adult cardiac valvular surgeries

Materials and methods: After approval from the institutional review board, 60 patients undergoing cardiac valvular surgeries using cardiopulmonary bypass were enrolled in the study. Patients were randomized to receive either Etomidate or fentanyl-midazolam for induction of anaesthesia. Anaesthesia was maintained in both the groups with fentanyl 2 mcg/kg/hr, midazolam 0.02 mg/kg/hr, vecuronium 0.05 mg/kg/hr and Desflurane till the end of surgery.

Results: Baseline demographic and hemodynamic variables and cortisol levels were comparable in both the groups. Cortisol and blood sugar levels decreased in etomidate group on cardiopulmonary bypass and significant difference was found between etomidate and fentanyl-midazolam group. Cortisol levels 24 hours after the surgery showed no significant difference.

Conclusion: Etomidate induction results in significantly decreased cortisol and blood sugar levels on cardiopulmonary bypass as compared to fentanyl-midazolam group, and thus, decreasing the stress response elicited by cardiopulmonary bypass. 24 hours after surgery cortisol levels in both the groups were comparable without any untoward effects.

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INTRODUCTION

Cardiac patients are high risk patients and always have threat to life as they have comorbidities because of either complication of disease or associated problems. Hence any event causing tachycardia are deleterious. Also Cardiopulmonary bypass during cardiac surgeries evokes a well described stress response which results into increase in plasma cortisol levels. Adult patients who experience increased hormonal and metabolic responses may have greater incidence of post-operative complications. The cortisol levels rise significantly in early postoperative phase, with a partial recovery towards baseline values observed at 24 hours postoperatively. We hypothesized that depression of cortisol levels by etomidate could reduce the stress response triggered

by CPB. Thus we compared fentanyl-midazolam induction with etomidate induction to find out the efficacy of later to reduce the stress response to intubation and also stress response of CPB in terms of haemodynamics and blood sugar and cortisol levels. We aimed to compare the stress response to cardiopulmonary bypass between etomidate and high dose fentanyl-midazolam, and, to study the hemodynamic effects of etomidate during induction.

MATERIALS AND METHODS

After obtaining approval from Institutional review board for the study we included 60 patients who underwent elective cardiac surgery with cardiopulmonary bypass. A written informed consent taken from every participant after which patients were divided by computerized randomization into 2 groups of 30 each. Exclusion criteria were- patients <18 years

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age, patient refusal to participate in the study, congenital heart diseases or intracardiac shunt, patients known to have bleeding diathesis, systemic infections, any history of CNS disease including convulsions and emergency procedures. The study was conducted over a period of 6 months at Seth. G.S. Medical College & King Edward Medical Hospital. The patients were either first or second on a morning operative list to avoid any diurnal variation of hormonal concentrations. Comparisons between the two groups used Student's t-test for quantitative variables and Chi square test for qualitative variables. Statistical significance was regarded as $p < 0.05$. Statistical analysis was done using N-master version 1.0. Anaesthesia was induced, in fentanyl group with Inj.Fentanyl 15mcg/kg and Inj.Midazolam 0.1 mg/kg intravenous, and in Etomidate group with Inj.Etomidate 0.3 mg/kg, Inj. Fentanyl 5mcg/kg and Inj.Midazolam 0.05mg/kg intravenous. In both the group induction was followed by relaxation with Inj. Rocuronium. 1mg/kg Intravenous and intubation done with appropriate sized cuffed endotracheal tube. Maintenance of anaesthesia in both the groups was done with infusion of Inj. Fentanyl 2 mcg/kg/hr Midazolam 0.02mg/kg/hr- Vecuronium 0.05mg/kg/hr and Desflurane till the end of surgery. During the surgery patients were ventilated with Oxygen: Air (50:50). Unfractionated heparin (300 IU/Kg) was administered before CPB initiation to obtain an activated clotting time of >400 sec. After surgery patients were shifted to postoperative intensive care unit. Blood samples for plasma cortisol and blood sugar levels were collected before induction of anaesthesia, after aortic cross clamping on CPB and 24 hours postoperatively.

RESULTS

During study period 60 patients were enrolled with 30 each in etomidate and fentanyl-midazolam group respectively. Patient characteristics were comparable between the two groups. All patients were undergoing cardiac valvular surgery. No significant difference was seen in the duration of cardiopulmonary bypass (CPB) or aortic cross clamping between groups. Mean arterial pressure was not significantly different between both the groups during intraoperative and postoperative periods. Heart rate was comparable with no significant difference in both the groups. No significant difference was there between baseline cortisol levels, mean (sd), in etomidate 12.46(9.24) mcg/dl and fentanyl-midazolam 10.52 (9.30) group. A significant difference was observed in cortisol levels, in etomidate 9.36 (4.69) and fentanyl-midazolam 32.28 (12.77) group after aortic cross clamping. Cortisol levels 24 hours after surgery showed no significant difference. A baseline blood sugar level was comparable in both the groups with no significant difference. It was found that mean (SD) levels were higher in fentanyl-midazolam 140 (14) group as compared to etomidate group 108 (10) on CPB 30 minutes after aortic cross clamping, with a significant difference in both the groups. There was no significant difference in blood sugar levels among the groups 24 hours after surgery.

Table 1. Demographic Variables

Induction Agent	Age (in years)	Gender (M/F)	BMI (Kg/m ²)	Aortic clamp time (mins)	CPB time (mins)	Ejection fraction (%)
Etomidate	52 ± 10	21/9	26 ± 4	52 ± 24	86 ± 30	58 ± 12
Opioids	49 ± 9	20/10	28 ± 3	56 ± 27	88 ± 32	59 ± 11

Table 2. Cortisol levels

Induction agents	Cortisol levels (Baseline)	On CPB	24hrs
Etomidate	15.46 ± 7.42	12.52 ± 7.10	0.1296
Opioid	10.36 ± 4.69	32.28 ± 12.77	0.0001

Table 3. Blood Sugar Levels

Induction agents	Cortisol levels (Baseline)	On CPB	24hrs
Etomidate	15.46 ± 7.42	12.52 ± 7.10	0.1296
Opioid	10.36 ± 4.69	32.28 ± 12.77	0.0001

Table 4. Hemodynamic Variables

Induction agents	HR	5mins	10mins	30mins	Off CPB	Postop	BP	5mins	10mins	30mins	OFF CPB	Post OP
ETOMIDATE	82 ± 10	80±10	84±10	78 ± 10	84±14	84±16	79±12	78±10	80±10	74±10	86±14	70±12
OPIOIDS	80 ± 14	76±10	72 ± 10	74±10	82±16	82±14	81±14	78±10	76±14	70±10	84±16	64±14

Table 5.

Induction agent	SPO2 (baseline)	5 mins	10mins	30 mins	Off CPB	Postop
ETOMIDATE	100	100	99	100	98±2	100
OPIOID	100	99	98	100	99±10	100

Table 6. Lactic acid levels

Induction agent	Lactic acid on CPB(mmol/l)	Norepinephrine requirement (mcg/kg/min)
Etomidate	1.8±0.8	0.04±0.03
Opioids	2.4±1.0	0.03±0.03

Cortisol and Blood sugar levels

It was observed that nor epinephrine requirements, mean (SD), post-surgery in etomidate group was 0.04 (0.03) mcg/kg/min and in fentanyl-midazolam group it was found to be 0.03 (0.03) mcg/kg/min with no significant difference among both groups.

DISCUSSION

Etomidate (Lipuro. B Braun. Melsungen. Germany) is a short acting intravenous anesthetic agent used for the induction of general anesthesia (Wagner *et al.*, 1984). It was introduced as an intravenous agent in 1972 in Europe and in 1983 in United States (Schenarts *et al.*, 2001). It has a rapid onset of action and a safe cardiovascular risk profile, and therefore is less likely to cause a significant drop in blood pressure than other induction agents (Malerba *et al.*, 2005; Den Brinker *et al.*, 2008; Zurick *et al.*, 1986). It is an ideal induction agent for patients who are haemodynamically unstable (Zurick *et al.*, 1986). The normal adult serum cortisol levels are 05 mcg/dl to 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 (Pandey *et al.*, 2012). Using a continuous infusion may be detrimental and may lead to increased mortality (Robert *et al.*, 2005). The cortisol suppression induced by a single dose of etomidate is almost always limited to 24 hours (Wagner *et al.*, 1984), and therefore does not pose any threat of prolonged adrenocortical suppression. The cortisol levels in this study also returned to normal levels at twenty hours. The results of this study shows that etomidate induction in patients undergoing valvular heart surgeries is associated with decreased cortisol and blood sugar levels on CPB and hence stress response. Many studies have been conducted for stress response on CPB in paediatric cases but only limited data is available for adult population. Cardiopulmonary bypass is associated with well described changes in the neurohormonal environment which are characterized by activation of the sympathetic axis and a generalized stress endocrine response. The initiation of CPB increases blood concentration of norepinephrine, epinephrine and cortisol (Reves *et al.*, 1982). Cardiopulmonary bypass has often been compared with the pathophysiologic changes occurring in sepsis or systemic inflammatory response syndrome (SIRS) (Kinet, 1989; Wan *et al.*, 1997) Several studies have reported a rise in cortisol levels at the end of surgery that persisted in the early postoperative period with peak values reached 4-6 hours postoperatively. This is followed by a return towards near normal levels at 24 hours [Velissaris *et al.*, 2004; Maggio *et al.*, 2005; Hoda *et al.*, 2006; Iribarren *et al.*, 2010]. Cardiopulmonary bypass is known to produce a stress response by means of stimulation of the sympathetic adrenal system. Plasma levels of sympathomimetic amines such as epinephrine and nor-epinephrine may increase several thousand folds in response to CPB (Anand and Hickey, 1992). This may lead to systemic inflammatory response (SIRS), a catabolic state and may delay patient recovery after CPB. Etomidate by suppressing cortisol levels during and post CPB actually turns out to be beneficial in such patients. 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 (Wagner *et al.*, 1984). Adrenal suppression in humans with induction doses of etomidate has been shown in several studies (Wagner *et al.*, 1984; Schenarts *et al.*, 2001; Malerba *et al.*, 2005; Den Brinker *et al.*, 2008) suggesting suppression persisting for at least 24 hours following cardiac surgery (Zurick *et al.*, 1986). The cortisol suppression induced by a single dose of etomidate is almost always limited to 24 hours (Zurick *et al.*, 1986), and therefore does not pose any threat of prolonged adrenocortical suppression. Cortisol is a catabolic hormone and mobilises carbohydrates, proteins and fat to ultimately cause a marked rise in the blood glucose levels, which is resistant to control by insulin. Cortisol being the precursor for catecholamine synthesis in the body, it is postulated that reduction in levels would have a negative impact on the mounting of the stress response to CPB by the body (Pandey *et al.*, 2012). Cortisol stimulates gluconeogenesis by the liver as much as tenfold, reflecting principally mobilization of amino acid from extra hepatic sites and transfer to the liver for conversion to glucose. This increased rate of gluconeogenesis in addition to moderate decrease in the rate of glucose use caused by cortisol, results in increased blood glucose concentration (Robert *et al.*, 2005). Even though etomidate, known for its adrenocortical suppression property, may have beneficial effects in cardiac valvular surgeries using CPB, by reducing stress response by means of reduction in cortisol levels and blood sugar levels during intraoperative and postoperative period which is a critical time period post cardiac surgery. It is also observed in this study that hemodynamic is well maintained in etomidate group post induction as compared to opioids. The cortisol and blood sugar levels gradually returns towards normal values at the end of 24 hours and thus does not causes any alteration in hemodynamic response post-surgery. The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function (Miller *et al.*, 2009) and capacity to bind and stimulate peripheral alpha-2B adrenergic receptors with a subsequent vasoconstriction. (Craig *et al.*, 2010)

Conclusion

Etomidate as well as Fentanyl combination are good induction agents as well as they are safe in terms of reducing stress response to Cardiopulmonary Bypass.

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