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Original Research Article

THE EFFECT OF SINGLE DOSE ETOMIDATE AND PROPOFOL ON SERUM CORTISOL LEVEL IN CARDIAC PATIENTS UNDERGOING CARDIAC SURGERY ON CARDIOPULMONARY BYPASS: A PROSPECTIVE COMPARATIVE STUDY

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Abstract

Background: Cardiovascular patients are highly prone for hemodynamic perturbation and exaggerated stress response during induction and cardio pulmonary bypass. Induction agents used for same should have minimum hemodynamic variation and maintains myocardial oxygen supply demands during procedure. Propofol and etomidate are well known anesthestic agents used for induction including all cardiovascular surgery. **Materials and Methods:** After getting approval from institutional ethical committee, the study was conducted in department of anaesthesiology and critical care with the collaboration of cardiovascular surgery department. For these sixty patients of either sex, aged between 20-80 years of age, ASA grade II to IV were enrolled for this prospective, randomized, clinical trial. After preanesthetic check-up all enrolled patients were randomly allocated into two group of 30 each. Group I received 0.4 mg/kg etomidate and group II received 2 mg/kg as induction along with 2 microgram/kg fentanyl. Serum cortisol level were measured at baseline, 6 hour and 24 hours postoperatively after induction. **Result:** Serum cortisol level were increased in both group from baseline and mean increment at 6 hours was more marked in etomidate group (105.85±182.83 nmol/L) than propofol (153.22±150.54 nmol/L that was statistically significant. At 24 hours although serum cortisol was increased in etomidate group but was statistically insignificant. It shows adrenocortical suppression was more in etomidate group means less stress response. **Conclusion:** Etomidate can be safely used as induction agent in patients of cardiac surgeries with compromised LV function for cardiac surgeries under cardio-pulmonary bypass without serious cortisol suppression.

INTRODUCTION

Anaesthetic concerns of patients with coronary artery disease include hemodynamic stability, attenuate stress response to intubation and maintenance of balance between myocardial oxygen demands and supply.[1] Although numerous intravenous anaesthetic agents have been used for induction purpose for cardiac surgeries; Conventionally propofol is very common aesthetic agents used as induction and recently we also started practicing with etomidate, a relatively newer induction agent. The two drugs however have different induction properties.[2]

Propofol is a non-opioid, non-barbiturate, sedative hypnotic agent. It is 2,6-Diisopropylphenol, is a short-acting induction that results in a diminished level of consciousness and amnesia through GABA receptor.[3] It is used for induction as well as maintenance of general anesthesia, monitored anaesthesia care, sedation in ICU. It has sympathetic inhibition property, impairment of baroreceptor reflex, direct negative inotropic effect and decrease in systemic vascular resistance leads to dose

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dependent fall in blood pressure.[4]This effect may be provoked in inadequate hydration due to fasting condition and also in pt with poor left ventricular contractility. One beneficial effect is that there is no reflex tachycardia, so myocardial oxygen demand supply is maintained.

Etomidate is a carboxylate imidazole agent which is very short acting has a better cardiovascular profile. [5,6] than propofol, minimal respiratory depression action and cerebro-protective properties without effect on sympathetic nervous system, baroreceptor reflex regulating system. A surplus feature is that it maintains coronary perfusion even in patients poor cardiac reserve,[7,8] so leads a trend for using in cardiac as well non-cardiac surgeries in cardiac patients. It does not have significant effect either on the peripheral and pulmonary vascular bed. Common side effects are nausea and vomiting, pain on injection, thrombophlebitis and myoclonus,[9] that can be attenuated by new fat emulsion but incidence of myoclonus after injection is not reduced. A notable side effect is reduction in serum cortisol levels by causing reversible inhibition of 11-betahydroxylase enzyme, even after single dose, leading to reduced cortisol levels for up to twenty-four hours.[10]

This study was conducted to see the effect of single dose of propofol and etomidate on stress response by corelating it with the serum cortisol level in cardiac patients undergoing coronary artery bypass grafting and valvular surgery on cardio pulmonary bypass.

Aims and objectives

Primary objective- To evaluate the effects of single dose Etomidate and Propofol on serum cortisol level in cardiac patients undergoing CABG, valvular replacement surgery on cardio pulmonary bypass.

Secondary objective- To observe any associated side effects.

MATERIALSANDMETHODS

After getting approval from ethical committee, this prospective, randomized clinical study was carried out in operation theatre of cardio-thoracic-vascular surgery department, KGMU, Lucknow. Sixty patients for coronary artery bypass graft (CABG) or valvular heart replacement surgery, aged of 20 to 80 years, ASA grade II to IV wereenrolledfor the study. Valvular surgery includes aortic valve replacement(AVR), mitral valve replacement (MVR) and double valve replacement (DVR). After obtaining a written and informed consent, they were randomly allocated into two groups of 30 patients each. Patients having systolic blood pressure < 80 and >200mm of Hg, heart rate <45 and >130, ejection fraction <40%,undergoing emergency surgery, having congestive cardiac failure,renal dysfunction,patients on mechanical ventilation, on long term steroid therapy and known adrenal or endocrine dysfunction were excluded from the study.

All enrolled patients had undergone through a proper preanesthetic check-up and blood sample for serum cortisol were taken considered as a baseline for all patients. Randomization were done by applying a computer derived random number sequence and sealed opaque envelope into two groups. Group I received 0.4 mg/kg etomidate and group II received 2 mg/kg as induction along with 2 microgram/kg fentanyl. In the operation room peripheral line was and basic monitors like noninvasive blood pressure, pulse oximetry, electrocardiogram and temperature were connected. A peripheral line with large bore cannula and arterial line were secured and IV fluid of ringer lactate were started. Inj. midazolam 2 mg followed by preoxygenation for 3 minutes and then patients were induced as per group.

After induction all patients were given vecuronium 0.1 mg/kg as intubating dose to facilitate endotracheal intubation. Femoral artery and central venous catheterization were done ananaesthesia was maintained with O2 N2O, isoflurane and intermittently with vecuronium as per standard protocol. Vital parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure(MAP), oxygen saturation and capnography monitoring done continuously till surgery is finished and patient shifted to ICU. Patients were observed postoperatively for any adverse effects. Injection dexamethasone 16mg intravenously was given routinely in priming fluid of cardio pulmonary bypass machine in both the groups.

Serum cortisol values were measured at 3 time points: day before operation (baseline), after 6 hours of induction of anesthesia and after 24 hours from time of induction (postoperative). The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

RESULTS

Median age of patients of Group I was 39 years while that of Group II was 41 years. Difference in mean age of patients of Group I (38.47±12.06 years) and Group II (42.46±16.94 years) was not found to be statistically significant (p=0.281).

Table 1: Age Profile of Study Population

Group	No. of patients	Min.	Max.	Median	Mean	S.D.
Group I	30	21	65	39	38.47	12.06
Group II	30	20	69	41	42.46	16.94
Total	60	20	69	40	40.53	14.73

‘t’ = 1.089; p=0.281

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Table 2: Gender Profile of Study Population

Gender	Group I (n=30)		Group II (n=30)		Total (N=60)	
	No.	%	No.	%	No.	%
Female	8	26.67	15	50.00	23	38.33
Male	22	73.33	15	50.00	37	61.67
Male: Female	1:0.36		1:1		1:0.62	
	χ^2=3.455 (df=1); p=0.063					

Results shows male: female ratio in Group I was 1:0.36 while in Group II was 1:1 but difference in gender of patients of above two groups was not found to be statistically significant (p=0.063).

Number of patients undergoing DVR (33.33%) of Group I was higher as compared to Group II (6.67%). Proportion of patients of Group II was higher as compared to Group I for rest of the procedures – AVR (13.33% vs. 6.67%), CABG (26.67% vs. 16.67%) and MVR (53.33% vs. 43.33%). Difference in operating procedure among patients of Group I and Group II was not found to be statistically significant (p=0.072).

Table 3: Comparison of Operating Procedure of Study Population

Operating Procedure	Group I (n=30)		Group II (n=30)		Total (N=60)	
	No.	%	No.	%	No.	%
AVR	2	6.67	4	13.33	6	10.00
CABG	5	16.67	8	26.67	13	21.67
DVR	10	33.33	2	6.67	12	20.00
MVR	13	43.33	16	53.33	29	48.83
	χ^2=7.003 (df=3); p=0.072					

Table 4: Comparison of S. cortisol levels at of Study Population

	Group	No. of patients	Min.	Max.	Median	Mean	S.D.
Pre-Operative S. cortisol levels	Group I	30	112.0	386.3	221.55	231.58	74.19
	Group II	30	109.8	374.6	204.4	203.00	65.82
	Total	60	109.8	386.3	211.2	217.28	71.01
	't' = 1.578; p=0.120						
after 6 hours of induction	Group I	30	116.0	750.60	286.35	337.43	171.51
	Group II	30	161.8	814.30	338.80	356.22	130.53
	Total	60	116.0	814.30	320.65	346.83	151.41
	't' = 0.478; p=0.635						
post-operative S. cortisol levels	Group I	30	202.60	896.00	309.20	367.90	165.69
	Group II	30	206.70	487.80	304.70	312.24	71.52
	Total	60	202.60	896.00	308.60	340.07	129.59
	't' = 1.689; p=0.097						

Mean serum cortisol levels of patients at preoperative of Group I (231.58±74.19nmol/L) was found to be slightly higher than that of Group II (203.00±65.82 nmol/L), however the difference was not found to be statistically significant (p=0.120).

Mean serum cortisol levels of patients of Group II (356.22±130.53nmol/L) was found to be higher than that of Group I (337.43±171.51 nmol/L) after 6 hrs. of induction, however the difference was not found to be statistically significant (p=0.635).

Mean post-op. serum cortisol levels of patients of Group I (367.90±165.69 nmol/L) was found to be higher than that of Group II (312.24±71.52nmol/L), however the difference was not found to be statistically significant (p=0.097).

Table 5: Intra group change in S. Cortisol levels at different intervals

	Group I					Group II				
	Mean Change	SD	% Change	't'	'p'	Mean Change	SD	% Change	't'	'p'
Before induction & 6 h post induction	105.85	182.83	45.71	3.171	0.004	153.22	150.54	75.48	5.575	<0.001
6h post induction. & post-op.	30.47	177.81	9.03	0.356	0.938	-43.98	155.81	12.35	-1.546	0.133
Before induction & post-op.	136.32	169.44	58.86	4.407	<0.001	109.24	91.49	53.81	6.540	<0.001

In group I intragroup change in S. cortisol levels before induction and 6 hrs post induction was 105.85±182.83nmol/L, an increase of 45.71% from baseline serum cortisol levels was observed, this change was found to be statistically significant (p <0.004). In group II intragroup change in S. cortisol levels was 153.22±150.54nmol/L, an increase of 75.48% from baseline was observed at 6 hours post-

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induction, this change was found to be statistically significant(p<o.oo1).

In group I intragroup change in S. cortisol levels before induction and postoperative was 136.32±169.44nmol/L, an increase of 58.86% from baseline was observed, this change was found to be statistically significant(p<0.001). In group II intragroup change in S. cortisol levels was 109.24±91.49nmol/L, an increase of 53.81% from baseline was observed, this change was found to be statistically significant(p<0.001).

In group I intragroup Change in Serum cortisol during 6 hours post induction to post-operative (9.03%) was not found to be statistically significant (p=0.938) In group II Change in Serum cortisol at 6 hours post induction (9%) and post-op. (12.35%) was not found to be statistically significant (p=0.133).

DISCUSSION

Induction of general anaesthesia is still a challenge for cardiac disease patient for non-cardiac surgery, CABG and valve replacement surgery on cardio-pulmonary bypass. Anaesthesia concerns of these surgery are maintaining hemodynamic stability and keep balance of oxygen supply demand. Various drugs had been used for this purpose like thiopentone, propofol, ketamine, etomidate, fentanyl and midazolam alone or in combination preferably.

Surgical stimulus and anaesthesia during surgery initiates stress response which severity can be corelated with some biochemical and inflammatory marker like serum cortisol, interleukin-6 (IL6), white blood cells, c-reactive protein etc.[11]Baseline cortisol levels in the human body peak between 07.00 and 08.00 hrs and range from 140 to 700 nmol/l, the levels decline by 16.00 hrs and range between 80 to 350nmol/l.[12,13]

The demographic variables were comparable in the two groups and they did not have any impact on the result of our study. The demographic profiles of patient enrolled reflects the demographic profiles of community at the risk for coronary artery disease and valvular heart disease.

Mean serum cortisol levels of patients at period of 6 hours after induction and 24 hr after induction (post operative) of propofol Group and etomidate group were higher from base line. On comparing this level although were comparable.

In our study change in mean serum cortisol level from baseline (preoperative) to 6 hr after induction, in group II (propofol) were more significant (p<0.001) than group I (etomidate) (p=0.004). This shows that stress response was more in propofol group than etomidate group.It shows that there could be adreno-cortical suppression in etomidate group as the increase in serum cortisol at 6 hours was much lesser as compared with propofol group. In our study change in serum cortisol level from baseline to postoperative was statistically significant in both groups. (p<0.001).

Cortisol is a catabolic hormone and mobilises carbohydrates, proteins and fats to ultimately cause rise in the blood glucose levels, which is sometimes resistant to control by insulin. Increased cortisol also causes a reduction in the inflammatory response, by stabilizing lysosomal membranes, decreasing capillary permeability, reduced migration of white blood cells to the inflamed area and phagocytosis of damaged cells as it is 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.

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. Using a continuous infusion may be detrimental and may lead to increased mortality.[14]

In our study increase of cortisol level rather than decrease of cortisol level may be due to stress response of Cardiopulmonary bypass by means of stimulation of the sympathetic adrenal system as a result of which plasma levels of sympathomimetic amines such as epinephrine, nor-epinephrine and cortico-steroids may increase several times.[15] Though there was a statistically significant increase in serum cortisol at 6 hours post induction in the etomidate group but this increase was much lesser as compared to the increase in serum cortisol in propofol group (45.71% vs 75.48%). This could be due to adreno cortical suppressant effect of etomidate which prevent higher rise in serum cortisol level.

Several studies by Velissaris T et al,[16] Maggio M et al,[17] Hoda MR et al,[18]have reported a rise in serum cortisol level at the end of surgery that persisted in the early post operative period with peak values reaching 4-6 hours post operative. This was followed by return towards near normal levels at 24 hours. Etomidate by suppressing cortisol levels during and post CPB, actually turns out to be beneficial, as seen in our study in which serum cortisol level on weaning from CPB was lesser as compared with propofol group.

Morel J et al,[19] studied the effect of single bolus dose of etomidate on cortisol synthesis and vasopressor requirement in elective cardiac surgery patients and observed that it blunted the hypothalamic – pituitary –adrenal axis response for more than 24 hours as opposed to our results, but this was not associated with an increase in vasopressor requirements which is similar to our study.

Some adreno cortical suppression which is transient and reversible with etomidate may not be good for induction of anesthesia in non-cardiac surgery for patients with normal cardiac function, where other regular anesthetic agents like propofol, midazolam, fentanyl and thiopentone sodium do very well. But in cardiac disease patients with compromised cardiac function where induction of anesthesia with

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regular anesthetic agent causes significant hemodynamic instability, etomidate can act as a good alternative with its cardio stable properties.

CONCLUSION

Etomidate with fentanyl is good anaesthetic agent combination for induction of anaesthesia in cardiac disease patients with compromised cardiac function undergoing cardiac surgery on bypass. Etomidate can also be used for induction of anaesthesia in patients with compromised cardiac function fornon-cardiac surgery.

REFERENCES

1. Moffitt EA, Sethna DH. The coronary circulation and myocardial oxygenation in coronary artery disease: effects of anesthesia. Anesthesia& Analgesia. 1986;65(4):395-410.
2. Stoelting Robert, Simon C. Hiller Pharmacology and Physiology in Anesthetic practice. 4th Ed. Philadelphia: Lippincott Williams and Wilkins publishers; 2006. pp. 159–60.
3. Krasowski MD, Jenkins A, Flood P, Kung AY, Hopfinger AJ, Harrison NL. General anesthetic potencies of a series of propofol analogs correlate with potency for potentiation of γ-aminobutyric acid (GABA) current at the GABAA receptor but not with lipid solubility. Journal of Pharmacology and Experimental Therapeutics. 2001;297(1):338-51.
4. Hoşten T, Solak M, Kılıçkan L, Özdamar D, Toker K. The Effects of Etomidate and Propofol Induction on Hemodynamic and Endocrine Response Undergoing CABG Surgery. Balkan Medical Journal. 2007;2007(2).
5. Criado A, Maseda J, Navarro E, Escarpa A, Avello F. Induction of anaesthesia with etomidate: haemodynamic study of 36 patients. BJA: British Journal of Anaesthesia. 1980;52(8):803-6.
6. Riou B, Lecarpentier Y, Viars P. Effects of etomidate on the cardiac papillary muscle of normal hamsters and those with cardiomyopathy. Anesthesiology. 1993;78(1):83-90.
7. Morel J, Salard M, Castelain C, Bayon MC, Lambert P, Vola M, Auboyer C, Molliex S. Haemodynamic consequences of etomidate administration in elective cardiac surgery: a randomized double-blinded study. British journal of anaesthesia. 2011 ;107(4):503-9.
8. Paris A, Philipp M, Tonner PH, Steinfath M, Lohse M, Scholz J, Hein L. Activation of α2B-adrenoceptors mediates the cardiovascular effects of etomidate. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2003 ;99(4):889-95.
9. Nyman Y, Von Hofsten K, Ritzmo C, Eksborg S, Lönnqvist PA. Effect of a small priming dose on myoclonic movements after intravenous anaesthesia induction with Etomidate-Lipuro in children. British journal of anaesthesia. 2011 ;107(2):225-8.
10. Zurick AM, Sigurdsson H, Koehler LS, Sethna DH, Gupta MK, Rojc K, Licata AA, Easley K, Estafanous FG. Magnitude and time course of perioperative adrenal suppression with single dose etomidate in male adult cardiac surgical patients. Anesthesiology. 1986 ;65(3A): A248.
11. Watt, D. G., Horgan, P. G., & McMillan, D. C. (2015). Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery, 157(2), 362–380.
12. Stewart PM, Newell-Price JDC. The adrenal cortex. In: Melmed S, Polonsky KS, Larsen PR, KronenbergHM, eds. Williams Textbook of Endocrinology. 13th ed. Philadelphia, PA: Elsevier Saunders; 2016: chap 15.
13. Chernecky CC, Berger BJ. Cortisol-plasma or serum. In: Chernecky CC, Berger BJ,eds. Laboratory Tests and Diagnostic Procedures. 6th ed. Philadelphia, PA: Elsevier Saunders; 2013:388-389.
14. Duthie DJ, Fraser R., Nimmo WS Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. Br J Anaesth. 1985;57:156-159.
15. Seravalli L, Pralong F, Revelly JP, Que YA, Chollet M, ChioleroR.Adrenal function after induction of cardiac surgery patientswith etomidate: a retrospective study. Ann Fr Anesth Reanim2009; 28: 743–716.
16. VelissarisT,TangAT,MurrayM,MehtaRL,WoodPL,HettDA,Ohri SK: A prospective randomised study to evaluate stress response during beating heart and conventional coronary revascularisation.annthoracsurg 2004,78:506-512.
17. Maggio M,CedaGP,DeCicco G, CattadoriE,VisoliS,AblondiF,Beghi C :acute change in circulating hormones in older patientswith impaired ventricular function undergoing on pump coronary artery bypass grafting .J Endocrinol Invest 2005,28:711-719.
18. Hoda MR, EL-Achkar,H, Schmitz E, Scheffold T, Vetter HO, De Simone R : systemic stress hormone response in patients undergoing open heart surgeries with or without cardio pulmonary bypass.Annthoracsurg 2006,82:2179-2186.
19. Morel J, Salard M, Castelain C, Bayon MC, Lambert P, Vola M, et al. Haemodynamic consequences of etomidate administration in elective cardiac surgery: A randomized double-blinded study. Br J Anaesth.2011;107:503–9.

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