Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

The Variation in Plasma Cortisol Levels in Response to Anaesthetic Induction with Etomidate and Ketamine in Paediatric Patients Undergoing Patent Ductus Arteriosus Ligation.

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ABSTRACT

Background: To compare the effect of anaesthetic induction with single dose etomidate versus ketamine on serum cortisol levels in paediatric patients posted for patent ductus arteriosus (PDA) ligation surgery. **Methods:** A total of 60 paediatric patients in the age group of 2 to 8 yrs posted for PDA correction in the department of cardiothoracic surgery in a tertiary care centre, was selected for prospective randomized control study trial and allocated randomly into 2 groups–group E and K. Anaesthetic induction was done using single dose etomidate (group E) and ketamine (group K) and serum cortisol levels were compared in paediatric patients posted for PDA ligation surgery.Statistical analysis done using SPSS 20 software. Baseline continuous variables were compared using student 't' test for independent samples. The primary outcome (serum cortisol) was compared using Wilcoxon Signed Ranks Test and student 't' test. The value less than 0.05 was considered significant. **Results:** The serum cortisol in group E was found to be significantly low 4 hour postoperatively compared to group K. However, serum cortisol increased 24 hour postoperatively in both groups and the increase was not found to be significant between the groups. **Conclusion:** Etomidate can be used for induction in paediatric cardiac surgery in patients without serious cortisol suppression lasting more than twenty four hours.

Keywords: Cardiac anaesthesia, etomidate, ketamine, paediatric PDA.

INTRODUCTION

The main considerations for induction of anaesthesia in paediatric patients undergoing cardiac surgery is to maintain haemodynamic stability, attenuation of stress responses and maintenance of balance between myocardial oxygen supply and demand. The intravenous (IV) inducing agents like thiopentone, etomidate, propofol, ketamine and midazolam have been used for anaesthetizing these patients. Various authors have expressed concerns regarding the use of these induction agents. Studies confirm that reduction of stress response in paediatric patients undergoing cardiac surgery helps improve postoperative morbidity. Etomidate[7-9] and ketamine are well known anaesthetic agents routinely used for induction of anaesthesia for paediatric cardiac surgeries.

Hence, the study was conducted to compare the effect of anaesthetic induction with single dose etomidate versus ketamine, in paediatric patients undergoing Patent ductus arteriosus (PDA) ligation, on serum cortisol levels.

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MATERIALS AND METHODS

After obtaining approval of institutional research and ethic committee, a total of 60 paediatric patients, of the American Society of Anaesthesiologists Grade 2 and 3, in the age group of 2 to 8 yrs posted for elective PDA ligation with left to right shunt in the department of Cardiothoracic surgery of a tertiary care centre, were selected and allocated randomly into 2 groups –group E and K. Written informed consent was obtained from parents of all the patients. The study design is that of prospective randomized control trial. Patients undergoing emergency surgery, patients having congestive cardiac failure, renal dysfunction, patients on mechanical ventilation or on long term steroid therapy, patients with known adrenal or endocrine dysfunction were excluded from the study.

Proper pre-anaesthetics check up and all relevant investigations were done for all patients. The patients were randomly divided into two groups of 30 patients each. Group E (Inj. etomidate 0.2 mg/kg IV) and Group K (Inj. ketamine 2 mg/kg IV). Ketamine and etomidate were chosen as inducing agents as other inducing agents like propofol and thiopentone were not routinely used in PDA surgeries as they cause decrease in SVR. The children were pre-medicated with oral promethazine 0.5mg/kg 1hour prior to surgery. In the operation theatre, pulse oximeter, noninvasive blood pressure apparatus and five lead ECG were connected to the patient. Intravenous lines were secured pre-operatively in wards. Patients were pre-medicated using Injection glycopyrrolate (0.05 mg/kg),

injection fentanyl (2 mcg/kg) and injection midazolam (0.05 mg/kg). Right femoral artery cannulation was done after local anaesthetic infiltration over the site. After stabilization period of 3 min, baseline values of heart rate (HR),systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), were recorded and electrocardiogram (ECG) were monitored. All patients were induced between 8 am and 9 am and sample of baseline value of serum cortisol was obtained before induction of the patient.
After preoxygenation, group E was induced with injection etomidate 0.2 mg/kg and group K were induced with injection ketamine 2 mg/kg. Injection rocuronium 1 mg/kg IV was given and endotracheal intubation was performed. Anaesthesia will be maintained using sevoflurane (1-2%) and injection rocuronium 0.25 mg/kg as intermittent doses. At the end of surgery, neuromuscular blockade was reversed using injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01mg/kg. Patients were extubated after full return of spontaneous respiration. Patients were observed postoperatively for any adverse outcome for 48 hours.
Blood samples for plasma cortisol were collected before induction of anaesthesia, after 4 hrs postoperatively and 24 hrs postoperatively. Plasma cortisol was measured with commercially available radioimmunoassay kit. Normal value for serum cortisol was 5 to 25 mcg/dl.
Serum cortisol was measured at 3 time points
-baseline/before induction
-4 hour postoperatively.
-24 hour postoperatively.
Statistical analysis done using SPSS 20 software. Baseline continuous variables compared using student ‘t’ test. The primary outcome (serum cortisol) was compared using wilcoxon signed ranks test and student ‘t’ test .The value less than 0.05 was considered significant.

RESULTS

The two groups were comparable in patient characteristics like age and weight and duration of surgery [Table 1].

Table 1: Patient characteristics and operation details.

Variable	Group E	Group K	P
Age (In Years)	5.017+/_1.75	5.017+/_1.81	0.682*
Weight (In Kg)	11.85+/_3.27	10.9+/_2.54	0.131*
Duration Of Surgery (in min)	101+/_9.64	103.67+/_9.37	0.889*

Values expressed in mean(SD) or median(range) and proportions applicable.
*independent t test,

There was a significant increase in the serum cortisol values in both groups 4 hour post-operatively compared to baseline values [Table 2]. But the serum cortisol values in etomidate group increase to be within normal limits (17.53+/_7.47) 4 hour postoperatively. The serum cortisol values increased to above normal values (58.003+/-2.65) in ketamine group, 4 hour post-operatively, which was approximately four and a half times the baseline values. When compared serum cortisol values 4 hour postoperatively between the groups, there was evident statistical significance (p=0.001) as the 4 hour postoperative serum cortisol values in group K showed approximately a three and a half times increase compared to group E.

Table 2: Comparison of serum cortisol levels between baseline and 4 hour postoperatively.

	Group E	Group K	P
Baseline	13.48+/_1.09	13.55+/_1.09	0.787
After 4 Hour	17.53+/_7.47	58.003+/_2.65	<0.001
	P <0.001#	P <0.001#	

Values expressed in mean (SD) or median(range) and proportions applicable.
*independent t test, #Wilcoxon Signed Ranks Test

The 24 hours postoperative serum cortisol values showed significant increase compared to baseline values in both groups [Table 3] (p=0.001). When compared between the groups, there was no statistical significance in the increase i n serum cortisol values 24 hours postoperatively. Both the groups showed an increase of approximately three times from the baseline values.

Table 3: Comparison of serum cortisol values between baseline and 24 hour postoperatively.

	Group E	Group K	P
Baseline	13.48+/_1.09	13.55+/_1.09	0.787*
After 24 Hour	43.96+/_5.19	43.96+/_5.27	1.00*
	P <0.001#	P <0.001#	

Values expressed in mean(SD) or median(range) and proportions applicable.
*independent t test, #Wilcoxon Signed Ranks Test

DISCUSSION

There is evidence that attenuating the stress response in paediatric patients undergoing cardiac surgery is of benefit.[1,2] The stress response to cardiac surgery in newborns is greater than that of adults.[1,2] Prevention of glucocorticoid response to surgery during the perioperative period is considered a therapeutic goal by most anaesthesiologist.
Ketamine is usually the agent of anaesthetic induction in paediatric patients with PDA as it causes increased SVR on reduction of right to left shunt and maintenance of cardiovascular stability in these patients.
Etomidate is drug of choice for induction of anaesthesia in paediatric patients with congenital heart disease who cannot tolerate haemodynamic

effects of other inducing agents. In comparative studies with other IV inducing agents, etomidate is described as cardio-stable drug with least effect on haemodynamics.[3-6] Etomidate first introduced in the seventies. It has a very stable cardiovascular profile.[7-9] Induction of anaesthesia with etomidate suppresses the usual large increases in plasma cortisol levels associated with anaesthesia and surgery.[10-12] Cortisol levels remain low at least 4 hrs after onset of anaesthesia.[10-12] It was concluded by Sebel et al that there was no difference in cortisol levels between anaesthetic inductions with thiopentone versus etomidate.[16] Fragen et al on the other hand found that etomidate induction depressed the blood cortisol compared to induction with thiopentone.[16]

Etomidate usage for a long duration directly affects adrenal function and inhibits cortisol synthesis.[13,14] Studies on the effect of a single bolus dose on cortisol suppression in paediatric patients are very less in number. Madhur et al have shown that etomidate and ketamine can be safely used in combination for short cardiac catheterization procedures, in paediatric patients with intra-cardiac shunts.[15]

The normal serum cortisol levels are 5 to 25 mcg/dl. Our study showed a significant increase in serum cortisol levels from the baseline, both 4 hrs and 24 hours postoperatively. However, the increase in etomidate group was within normal limits, unlike that in ketamine group, which increased above the normal limits to approximately four and a half times the baseline values and three and a half times the values of 4 hours postoperative etomidate group. This difference was due to the cortico-suppressive effect of etomidate. Cortico-suppressive effect of etomidate lasted for less than 24 hours as postoperative serum cortisol sample showed no significant difference in serum cortisol levels between the groups. In addition, there was a significant increase from baseline serum cortisol levels after 24 hours in etomidate group above normal range showing elimination of cortico-suppressive effect of etomidate within 24 hours. Serum cortisol levels in etomidate group had an increase in their levels over hours from 4 hrs to 24 hrs postoperative showing gradual elimination of cortico-suppressive effect of etomidate. 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. In our study, we also noticed that three patients in the etomidate group did not show any suppression of cortisol levels 4 hrs post-operatively which may be due to the incomplete inhibition of 11-beta hydroxylase. The cortisol suppression induced by a single dose of etomidate is almost always limited to 24 hrs and therefore, there is no concern of prolonged adrenocortical suppression. Myoclonus occurred in four of the patients induced with etomidate. This may be due to the rapid intravenous administration of the drug.

Ketamine was synthesised in 1962 by Stevens and was first used in humans in 1965 by Corssenand Domino. It was released for clinical use in 1970 and still used in a variety of clinical settings. Ketamine is different from other anaesthetic induction agents in that it has additional analgesic property. It does not depress cardiovascular and respiratory system but has a high incidence of postoperative psychological effects. It has unique cardiovascular effects as it causes an increase in blood pressure, heart rate and cardiac output. The increase in haemodynamic variables is associated with an increase in myocardial oxygen consumption. The haemodynamic changes with ketamine tend to be same in healthy patients and those with acquired or congenital heart disease. Patients with congenital heart disease do not have any significant changes in shunt direction or fraction or systemic oxygenation after ketamine induction of anaesthesia.

The timing of induction of anaesthesia in both groups was maintained between 8-9 am to avoid any effects of diurnal variation of cortisol levels in the study. As an institutional protocol, the paediatric patients are taken up as the first case in the morning.

Based on this study it can be concluded that etomidate can be used as an anaesthetic induction agent to attenuate the stress response associated with patent ductus arteriosus surgery in paediatric patients.

CONCLUSION

Etomidate can be used for induction in paediatric cardiac surgery in patients without serious cortisol suppression lasting more than twenty four hours.

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How to cite this article: Nayak K, Nitha CS. The Variation in Plasma Cortisol Levels in Response to Anaesthetic Induction with Etomidate and Ketamine in Paediatric Patients Undergoing Patent Ductus Arteriosus Ligation. Ann. Int. Med. Den. Res. 2016;2(3):71-4.

Source of Support: Nil, **Conflict of Interest:** None declared