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CHANGES IN SERUM CORTISOL LEVELS AND HEMODYNAMIC RESPONSES: COMPARISON OF ETOMIDATE AND THIOPENTONE FOR INDUCTION OF GENERAL ANAESTHESIA IN ELECTIVE SURGERIES

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ABSTRACT:
Background: Etomidate offers a clear benefit of improved cardiovascular stability with reduced risk of hypotension during anaesthesia.(6)Even though it has a highly favourable cardiovascular profile, the use of etomidate had dramatically decreased since 1983 until 2001.This was because its use was associated with adrenal suppression, which some believe is associated with poor outcome, particularly in critically ill patients and those with sepsis(7,8).The effect on serum cortisol levels with the newer preparation of etomidate has still not been studied in ASA I/II patients. Hence, this study was designed to compare the effects of induction with a single bolus dose of intravenous etomidate and thiopentone on serum cortisol levels.
Methods: In this prospective, randomized study 64 patients, 20-65 years of age, undergoing general anaesthesia for elective surgeries were randomly assigned to one of the two groups receiving either thiopentone 5 mg kg−1 (Group T) or etomidate 0.3 mg kg−1 (Group E) for induction of anaesthesia. Serum cortisol levels were measured preoperatively, 4 hours and 24 hours after induction. Hemodynamic parameters and adverse effects were also assessed.
Results: In patients receiving etomidate, mean serum cortisol levels decrease from 17.86 ± 2.97 µg/dl (baseline) to 14.02 ± 2.91 µg/dl 4 hrs after induction. By 24 hours, the mean serum cortisol levels had returned to baseline values (17.71 ± 3.06 µg/dl). The decrease in mean serum cortisol levels at 4 hrs was statistically significant, though it remained within the normal reference range (6-25µg/dl). In group T, mean serum cortisol levels did not show any significant change (from 18.85 ± 2.85 µg/dl to 19.53 ± 3.28 µg/dl) 4 hrs after induction and remained near the baseline at 24 hrs postoperatively.
Conclusion: To conclude though both etomidate and thiopentone have a stable hemodynamic profile in ASA I/II patients, the use of etomidate is associated with a decrease in serum cortisol levels and a high incidence of myoclonus.
Categories: Medical Education, Endocrinology/Diabetes/Metabolism, Anesthesiology

KEYWORDS: adrenal suppression, cortisol, etomidate, lipid emulsion, myoclonus

INTRODUCTION

Etomidate offers a clear benefit of improved cardiovascular stability with reduced risk of hypotension during anaesthesia [1]. Even though it has a highly favorable cardiovascular profile, the use of etomidate had dramatically decreased since 1983 until 2001.This was because its use was associated with adrenal suppression, which some believe is associated with poor outcome, particularly in critically ill patients and those with sepsis [2,3]. In each of the prospective etomidate studies documenting adrenocortical suppression without associated clinical sequelae, a conclusion of safety was not forthcoming. The reason was that these studies did not address high-stress procedures, in which the benefit of a high cortisol level in response to a major stress could be desirable, thereby implying that the body's ability to respond to a high surgical stress was still intact despite high doses of etomidate [4]. Any negative clinical outcome associated with etomidate induction, despite its rampant use in western countries, has however not been reported. After etomidate induction, the cortisol levels usually remains in the low-normal range, and the adrenocortical suppression is a short-lived phenomenon. High-stress surgery can overcome the temporary adrenocortical suppression caused by etomidate and no study has reported any adverse outcomes secondary to short-term adrenocortical suppression [4].

These facts suggest that the issue of temporary adrenocortical suppression after perioperative induction doses of etomidate is not clinically significant. With the introduction of the new preparation of etomidate in lipid emulsion, it has again gained some popularity since the adverse effects e.g. pain on injection, thrombophlebitis and hemolysis associated with the original preparation in propylene glycol has been abolished [5]. Excitatory effects such as spontaneous movements, myoclonus, dystonia and tremors are still seen in 50 - 80% patients at the time of induction [6].

On reviewing the literature, we found that though there are several studies regarding the effect of etomidate on serum cortisol levels in critically ill patients, there are very few studies in healthy patients (ASA I &II) in recent literature.

Scarcity of studies especially in Indian population comparing the effects of intravenous etomidate and thiopentone on serum cortisol levels.
Hence, a randomized study was designed to compare the effects of induction with a single bolus dose of intravenous etomidate and thiopentone on serum cortisol levels.

MATERIALS AND METHODS

This study was conducted with the objective to study the changes in serum cortisol levels when etomidate and thiopentone are used for induction of general anaesthesia in ASA grade I and II patients undergoing elective surgeries. It was designed as a randomised controlled study and carried out over the course of two years after receiving approval from the ethical committee. The patients with ASA grades I and II who were 20-65 years of age and posted for elective surgery under general anaesthesia were included in the study, while the patients with anticipated difficult airway, emergency surgical procedure, h/o steroid therapy within last months, surgery lasting >2 hours or h/o allergy to any drug were excluded from the study.
A total of 64 patients were included in the study. Patients were randomly allocated into two groups of 32 each. In group E (Etomidate) , anaesthesia was induced with Etomidate 0.3 mg/kg while in group T (Thiopentone), Thiopentone 5mg/kg was used.
In all patients, blood samples (2ml) were withdrawn for evaluation of serum cortisol levels preoperatively (baseline values at 9 am), 4 hrs after induction and at 24 hrs postoperatively (9 am next day). Evaluation was done by the chemiluminiscence technique using Beckmann Coulter Access 2.0 cortisol assay.
Hemodynamic parameters - Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) were monitored before induction (baseline), after induction (0 min), after intubation (5 min), and thereafter every 15 minutes till the end of the surgery. ECG, SpO2 and EtCO2 will be continuously monitored. Any side effects were also noted.
Statistical Analysis: Quantitative study was done using PAIRED STUDENT T TEST / ANOVA TEST to compare the effect on hemodynamics and serum cortisol levels. Qualitative study was done using CHI-SQUARE TEST / FISHER EXACT TEST - side effects· Results were presented as mean ± S.D or percentage. P value of <0.05 was considered as significant.

RESULTS

All the patients were between 20 years and 65 years. The obtained demographic data (i.e., mean age, weight, sex, and type of surgery) of the two groups were comparable.
As shown in Table 1, In group E (etomidate), baseline mean serum cortisol levels was 17.86 ± 2.97 µg/dl and in the group T (thiopentone), it was 18.85 ± 2.85 µg/dl. The baseline values in both the groups were comparable. At 4 hours after induction, there was a significant decrease in the mean serum cortisol levels (14.02 ± 2.91 µg/dl) in group E whereas in group T, mean serum cortisol levels slightly increased from the baseline value to 19.53 ± 3.28 µg/dl. This difference in mean cortisol levels at 4 hours after induction was statistically significant.
In group E, mean serum cortisol levels returned to baseline values (17.71 ± 3.06 µg/dl) 24 hours postoperatively. Twenty four hours postoperatively mean serum cortisol levels was 19.32 ± 2.83 µg/dl in group T. At 24 hours there was no statistically significant difference in mean cortisol levels in group E & group T.
At all times of observation, mean cortisol levels in both the groups remained within the normal range.

TABLE 1: Mean Serum Cortisol Levels

Time		**Baseline**	**4hrs after induction**	**24hrs (postoperative)**
GRP *E	Mean serum cortisol levels (±SD) (µg/dl)	17.86 ± 2.97	14.02 ± 2.91	17.71 ± 3.06
	p-value	-	0.000*	0.384
Mean serum cortisol levels (±SD) GRP ^T	(µg/dl)	18.85 ± 2.85	19.53 ± 3.28	19.32 ± 2.83
p-value		-	0.032	0.099
p-value (E Vs. T)		0.089	0.000*	0.066

*E: etomidate group, ^T: thiopentone group
The hemodynamic parameters taken into consideration were heart rate and blood pressure (systolic and diastolic). The other parameters that were studied included SpO2, respiratory rate (RR), and end tidal carbon-dioxide (EtCO2) levels. The corresponding data were comparable between the two groups.
Myoclonus was observed in 31 out of 32 patients who received etomidate (96.88%) whereas none of the patients (0%) receiving thiopentone had myoclonus. None of the patients in group E had pain during injection of etomidate. However, 3 patients (9.38%) who received thiopentone had pain during injection. None of the patients in either group had nausea or vomiting in the postoperative period (Table 2).

TABLE 2: Incidence of Side Effects

Side effects	GRP *E		GRP ^T		p-value
	n	%	n	%	
Myoclonus	31	96.88%	0	0.00%	0.000*
Pain on injection	0	0.00%	3	9.38%	0.005*
Nausea & vomiting	0	0.00%	0	0.00%	0.000*

*E: etomidate group, ^T: thiopentone group

DISCUSSION

Adrenal suppression with etomidate has been a recognized entity for many years since the use of etomidate increased for giving sedation in critical care setting. Though there are several studies regarding the effect of etomidate on serum cortisol levels in critically ill patients, there are very few studies in ASA I/II patients in recent years, especially with its newer preparation in lipid emulsion. Interpretation of the literature has confounded significant limitations regarding the use of single dose of etomidate for induction purposes in current anaesthesia practice.

In our study, at 4 hours after induction, there was a statistically significant decrease in mean serum cortisol levels in group E (14.02 ± 2.91 µg/dl). However, in group T, mean serum cortisol levels showed no such fall (19.53 ± 3.28 µg/dl). This difference between the two groups was statistically significant. Similar to our observations, Fragen RJ et al [7], Wanscher M et al [8], Borner U et al [9] and Hildreth AN et al [10] observed a significant decrease in mean serum cortisol levels in the patients receiving etomidate 4 hours after induction. Though there was a statistically significant fall in the levels, they were within the normal range. They also observed that cortisol values returned to baseline levels in 12 to 24 hours just like our study.

In contrast, Allolio B et al [11] observed a marked fall in the etomidate group from 14.54 ± 3.9µg/dl preoperatively to 1.6 ± 0.5µg/dl 3.5 hrs after induction which was below the normal range of serum cortisol (6-25µgdl). Wagner RL et al [12], De Coster and Helmers [13], Crozier TA et al [14], Vanacker B et al [5], Vinclair M et al [15] and Schenarts CL et al [16] found that response to ACTH stimulation test (CST) in patients receiving etomidate was suppressed, thus implying that cortisol secretion following exogenous ACTH administeration was blunted. Schenarts et al [17] also found that there was maximum suppression to CST at 4 hours that returned to normal by 12-24 hours.

In all the studies quoted above, there was no hemodynamic instability or clinical impairment associated with the fall in serum cortisol levels with the single dose of etomidate (0.2-0.4mg/kg).

In our study, myoclonus was observed in 31 out of 32 patients (96.88%) who received etomidate whereas none of the patients (0%) receiving thiopentone had myoclonus. All patients received fentanyl 2µg/kg. This was similar to the study done by Suttman H et al [18] who found that myoclonus occurred in all the cases who received etomidate and there was no difference between the two preparations of etomidate (etomidate in propylene glycol and etomidate in lipid emulsion) on the incidence of myoclonus.

In contrast, Geise JL et al [19] (51%), Toklu S et al [20] (20%) and Kaur S et al {[21] 16%) reported a lower incidence of myoclonus with etomidate.

None of the patients in either group had nausea or vomiting in the postoperative period. Geise JL et al [19] found an equal incidence of postoperative nausea and vomiting in both groups (thiopentone and etomidate).All patients in our study underwent laparoscopic procedures and had received anti emetic in the perioperative period. This could account for the absence of nausea and vomiting in our study.

CONCLUSIONS

From the present study, it can be concluded that a single dose of etomidate used for induction led to a decrease in serum cortisol levels at 4 hours. Serum cortisol levels returned to baseline values by 24 hours. Even at 4 hours, the levels remained within the normal reference range. There was no clinically significant change in mean HR, mean SBP, mean DBP and mean arterial pressure in either group E or group T.

To conclude though both etomidate and thiopentone have a stable hemodynamic profile in ASA I/II patients, the use of etomidate is associated with a decrease in serum cortisol levels and a high incidence of myoclonus.

Additional Information

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ethics Committee for Human Research, LHMC, New Delhi issued approval LHMC/ECHR/46. The thesis protocol titled "CHANGES IN SERUM CORTISOL LEVELS AND HEMODYNAMIC RESPONSES: COMPARISON OF ETOMIDATE AND THIOPENTONE FOR INDUCTION OF GENERALANAESTHESIA IN ELECTIVE SURGERIES" was discussed in IEC meeting and was approved for conduct. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1. Fragen RJ, Caldwell N, Brunner EA. Clinical use of etomidate for anesthesia induction: a preliminary report. Anesth Analg. 1976;55(5):730-733. doi:10.1213/00000539-197609000-00026. PMID: 987734.
2. Wanscher M, Tønnesen E, Hüttel M, Larsen K. Etomidate infusion and adrenocortical function: a study in elective surgery. Acta Anaesthesiol Scand. 1985;29(5):483-485. doi:10.1111/j.1399-6576.1985.tb02238.x. PMID: 4036533.
3. Borner U, Gips H, Boldt J, Hoge R, von Bormann B, Hempelmann G. Effect of an introductory dose of etomidate, methohexital and midazolam on adrenal cortex function before and after ACTH-stimulation. Dtsch Med Wochenschr. 1985;110:750-752.
4. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. J Trauma. 2008;65(3):573-579. doi:10.1097/TA.0b013e31818255e8. PMID: 18784570.
5. Allolio B, Stuttmann R, Leonhard U, Fischer H, Winkelmann W. Adrenocortical suppression by a single induction dose of etomidate. Klin Wochenschr. 1984;62:1014-1017.
6. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310(22):1415-1421. doi:10.1056/NEJM198405313102202. PMID: 6325910.
7. De Coster R, Helmers JH, Noorduin H. Effect of etomidate on cortisol biosynthesis: site of action after induction of anaesthesia. Acta Endocrinol (Copenh). 1985;110(4):526-531. doi:10.1530/acta.0.1100526. PMID: 3004088.
8. Crozier TA, Beck D, Wuttke W, Kettler D. Relation of the inhibition of cortisol synthesis in vivo to plasma etomidate concentrations. Anaesthesist. 1988;37(5):337-339. PMID: 3261141.
9. Vinclair M, Broux C, Faure P, Brun J, Genty C, Jacquot C, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. Intensive Care Med. 2008;34(4):714-719. doi:10.1007/s00134-007-0970-y.
10. Schenarts CL, Burton JH, Riker RR. Adrenocortical dysfunction following etomidate induction in emergency department patients. Acad Emerg Med. 2001;8(1):1-7. doi:10.1111/j.1553-2712.2001.tb00537.x. PMID: 11136139.
11. Suttmann H, Doenicke A, Kugler J, Laub M. A new formulation of etomidate in lipid emulsion—bioavailability and venous provocation. Anaesthesist. 1989;38(8):421-423. PMID: 2675669.
12. Toklu S, Iyilikci L, Gonen C, Ciftci L, Gunenc F, Sahin E, et al. Comparison of etomidate-remifentanil and propofol-remifentanil sedation in patients scheduled for colonoscopy. Eur J Anaesthesiol. 2009;26:370-376. doi:10.1097/EJA.0b013e328318c666.
13. Kaur B, Kaur T, Gupta P. Comparative evaluation of haemodynamic response during induction of general anaesthesia and incidence of myoclonus with etomidate and propofol: a randomised controlled trial. J Clin Diagn Res. 2018;12(10):UC13-UC16. doi:10.7860/JCDR/2018/30183.12160.