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Research title

A comparative study regarding serum cortisol concentration before and after administration of Etomidate as inducing agent in abdominal surgeries .

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Abstract:

Introduction

Etomidate,a hypnotic agent, a carboxylated imidazole, activates GABA-A receptor containing B2 and B3 subunits, without analgesic activity. It is used as intravenous induction agent for general anaesthesia. The drug etomidate causes temporary inhibition of steroid synthesis after dose and infusion owing to its lack of effect on sympathetic nervous system and on baroreceptor, haemodynamic stability after administration of injection etomidate is observed. Etomidate is a short acting agent with rapid onset and recovery, good cardiovascular stability and so it is an acceptable induction agent for patients with poor cardiac functions. It causes primary adrenal cortical suppression by inhibiting 11-beta hydroxylase, the enzyme important for adrenal steroid production.

Aims and Objectives

The study is aimed to estimate the serum cortisol concentration before and after administration of inducing agent etomidate and its comparison and also to find out the side effects of etomidate like post-operative nausea and vomiting, myoclonic movements, pain at injection site, etc.

Materials and methods

40 patients were chosen who will undergo elective abdominal surgery under general anaesthesia (for e.g appendectomy, cholecystectomy).In the morning of the day of surgery at about 7AM and about 1 hour before surgery 3ml of venous blood was drawn with sterile technique.The patients were administered general anaesthesia following standard anaesthetic procedure for balanced anaesthesia. In the post-operative period the patient was shifted in the post anaesthesia care unit for 2 hours. After that the patient was shifted to post surgical care unit and was monitored there for next 2 days.

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Serum cortisol were estimated at 7AM and 1hour before surgery that is before induction with etomidate. And twice after 4 hours & 6 hours of administration of etomidate by taking 3ml venous blood each time.

Results

In this study, it was found that serum cortisol decreases after administration of etomidate and was more significant at 6 hours interval compared with 4 hours interval after the injection. Hence it is observed that in this study there was significant reduction of serum cortisol level following the administration of single bolus dose of etomidate injection.

Conclusion

There were significant reduction in cortisol levels after 4 hours & 6 hours interval from administration

Key Words : etomidate, general anaesthesia, serum cortisol, post-operative nausea and vomiting.

INTRODUCTION

Paul Janssen and his colleagues first described Etomidate in 1964 and given the name ‘hypnomidate’.

Etomidate is a short-acting agent used as a induction drug for administering general anaesthesia. Besides having a rapid onset and recovery it has got a good and safe cardiovascular profile and so is preferred for patients with poor cardiac functions(1,2). Etomidate is given as a bolus I.V dose of 0.4 mg/kg and has a half-life of about 75 minutes. It has a rapid onset of action of 30–60 seconds and a duration of action of 3–5 minutes. The R(+) isomer of Etomidate binds the GABA-A receptor containing Beta2 and Beta3 subunits. The B3 subunits of the transmembrane section of this receptor is involved in the anaesthetic action of etomidate by opening the chloride channels which results in cellular hyperpolarisation. Beta2 subunits in the receptor add to sedation. Etomidate is also central alpha2 receptor agonist maintaining myocardial contractility and vascular tone following induction resulting in maintainence of cardiovascular stability during induction(1,2). The active dextrorotatory isomer of etomidate is found in commercial preparations. Two formulations are available:

1)Etomidate in solution with 35% propylene glycol making it clear hypertonic and causes pain at the site of injection.

2)An aqueous emulsion of Etomidate with 10% soyabean oil, 2.25% glycerol and 1.25% egg phophatide causing it milky white and milky viscous.

Etomidate is highly protein bound (76%) and large non-ionised fraction at physiological PH (3) and has rapid onset of action.

Redistribution occurs and leads to decrease in plasma concentration. It is metabolized by the hepatic microsomal enzymes and plasma esterases to an active metabolite. The end products

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of etomidate hydrolysis are excreted in urine (78%) bile (22%). The half-life of the drug metabolism is 75 minutes. Onset of action is 30-60 seconds. The I.V. induction dose is 0.3 mg/kg of body weight. Peak effect is 1 minute. Etomidate causes temporary inhibition of steroid synthesis (4). Cortisol a steroid hormone is released during the "fight or flight" reaction usually the stress. This stress hormone release is controlled by hypothalamus-having peak level early in the morning and lowest level at midnight. Release of ACTH from the anterior pituitary in response to stress acts as the principal stimulus for cortisol production by the adrenal cortex.

Normal serum cortisol level : Ref. range in adults

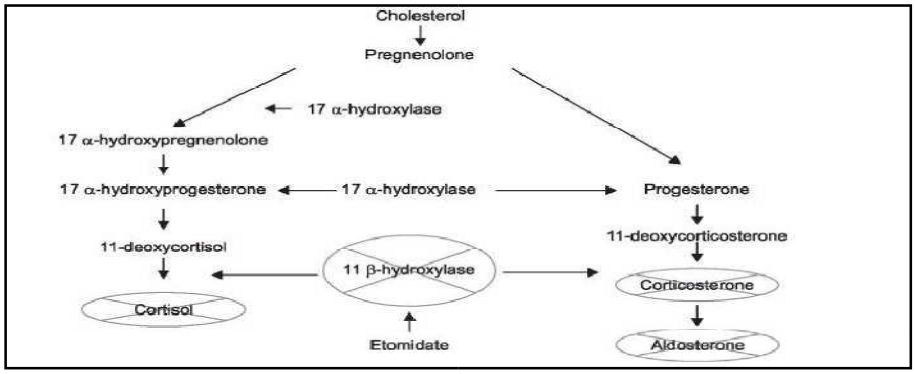
6AM to 12 noon = 5 to 25 microgram/dl or 140-690 mmol/l

4PM to 7 PM = 3 to 13 microgram/dl
8PM to 8AM = 0 to 10 microgram/dl or 0-276 mmol/l (6,7)

Surgical trauma may increase cortisol level from 400-1500 mmol/l in 4-6 hours depending on severity of surgical trauma (8).

Etomidate is a good induction agent for poor cardiac function patients (15). Primary adrenal suppression by etomidate is due to reversible inhibition of 11-beta hydroxylase enzyme , important for adrenal steroid production (9,10)

Mechanism of adrenal suppression:



AIMS & OBJECTIVES:

The aim of the study is to estimate the serum cortisol and its comparison before and after administration of etomidate as an induction agent.

MATERIALS AND METHODS:

Study Area: General surgery O.T., Post surgical ITU, Surgical ward of ESI-PGIMSR, Manicktala, Kolkata where the study was undertaken.

Study Population: Calculation of study population was done using the formula: N= 15.7*R*Q/(P1P2)^2

Before induction:

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First sample S1, second sample S2 in which mean S is taken as P1

After induction:

1st sample is T1, 2ND sample is T2 in which mean T taken as P2

P1 & P2 are the proportions of the two sample groups. R is the average of P1 & P2 and Q is 100-R.

Prior data indicate the difference in response of matched pairs is normally distributed with standard deviation 9.6. If the true difference in the mean response of matched pairs is 12.8, we will need to study 17 pairs of subjects to be able to reject null hypothesis that this response difference is zero with probability 0.99. The type 1 error probability with this test for null hypothesis is 0.01 (12).

Sample size = 40 ASA1 patients of age 20-45 years.

Inclusion criteria: 40 patients of 20-45 years of age of both sexes undergoing abdominal surgeries under general anaesthesia using standard procedure.

Exclusion criteria:-Patients not willing to participate in the study
-Age beyond the age group of 20-45 years.

-Patients with history of steroid intake and use.

-Any medical history suggestive of adrenocortical dysfunction.

-Patients with renal & hepatic dysfunction.

-ASA2 patients and above.

-Patients known to be allergic to etomidate.

-Patients taking adrenal androgens.

-Patients taking phenytoin.

-Patients who are taking OCP.

Study design: Prospective, Randomised, Observer blinded experimental studies.

Clinical: a) Serum cortisol estimation before and after administration of etomidate.

b) Systolic, diastolic and mean blood pressure.

c) Peripheral oxygen saturation

d) Respiratory rate, heart rate.

e) Side effects, if any

Study tools:

1) Random number table.

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2) Patient information brochure.
3) Consent form- informed.
4) I.V. cannula, infusion set, i.v. fluids.
5) 10ml, 5ml, 2ml syringes.
6) Anaesthesia work station with oxygen source and nitrous oxide. 7) Etomidate vial.
8) Emergency drugs and drugs to treat side effects.
9) Lab reports:
    a) Complete blood count
    b) Platelet count
    c) Blood sugar (FBS & PPBS),Serum urea,Serum creatinine
    d) L.F.T.
    e) E.C.G.
    f) Chest x-ray
    g) Viral serology
    h) Serum cortisol estimation

Study technique:

After approval of the college ethical committee, 40 ASA1 patients aged 20 to 45 years , planned for abdominal surgeries under general anaesthesia included in the study. Patients randomized in computer based tables.

The day before operation informed consent for the study has taken from each patient in the language he/she understands.

Overnight fasting (fasting from midnight at least 8 hours) on the day before operation for all 40 patients. On the day of operation each patient have received injection pantoprazole in the morning. At about 7a.m. and 1 hour before the surgery, 3ml of venous blood have drawn with sterile technique. After that the patient brought to the pre-recovery room where an IV line has been introduced and IV drip started. Pulse oxymeter , BP cuff, ECG leads attached with each patient.

Then the patient pre-oxygenated and general anaesthesia have been performed using injection Etomidate 0.3 mg/kg, injection fentanyl 2 mcg/kg , injection suxamethonium 1mg/kg and injection rocuronium 0.6-1 mg/kg. Maintainence has been done by 1.5-3% isoflurane and lungs ventilated with 33% oxygen and 66% nitrous oxide to maintain an endtidal carbon dioxide 35-45 mm Hg. Injection ondansetron has been given at a dose of 0.15mg/kg intravenously. After 4 hours and 6 hours of intubation, 3 ml of venous blood again drawn with sterile technique. After operation is over, the nasogastric tube was suctioned and removed. Reversal done by using injection neostigmine and injection glycopyrrolate. Before tracheal extubation , oral cavity and oro-pharynx suctionhas been done with suction catheter. In the post-operative period the patients have been monitored in post anaesthesia care unit for 30 minutes. After that the patient was shifted to postsurgical care unit and monitored for next 2 days.

Patient monitored for total 48 hours in the post-surgical intensive care unit. Sedation measured by modified Ramsay score along with other vitals like blood pressure, pulse rate, urine output, Spo2.

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Serum cortisol concentration was estimated at 7a,m. and 1 hour before the surgery. After the administration of 0.3mg/kg of etomidate as induction agent, again serum cortisol estimation done after 4 hours and 6 hours of administration of etomidate.

Results & Analysis:

Table: Distribution of mean Cortisol at 7 a.m. before etomidate injection,Cortisol 1hour before surgery,Cortisol after 4 hours of etomidate injection and Cortisol After 6 hours of etomidate injection

	Number	Mean	SD	Minimum	Maximum	Median
Cortisol before etomidate injection at 7 a.m	40	11.7038	3.1798	7.0900	20.1900	11.0600
Cortisol 1hour before surgery	40	15.1418	2.5547	11.4600	22.3700	14.9300
Cortisol after 4 hours of etomidate injection	40	10.5193	2.6915	4.3500	14.6500	11.0300`
Cortisol After 6 hours of etomidate injection	40	7.9053	2.3483	3.2500	11.6800	8.3350

$p<0.0001$, Statistical significant

Cortisol before etomidate injection at 7 a.m

In above table showed that the mean Cortisol before etomidate injection at 7 a.m (mean ±s.d.) of patients was 11.7038± 3.1798. Cortisol 1hour before surgery

In above table showed that the mean Cortisol 1hour before surgery (mean ±s.d.) of patients was 15.1418± 2.5547.

Cortisol after 4 hours of etomidate injection

In above table showed that the mean Cortisol after 4 hours of etomidate injection (mean ±s.d.)
of patients was 10.5193± 2.6915.

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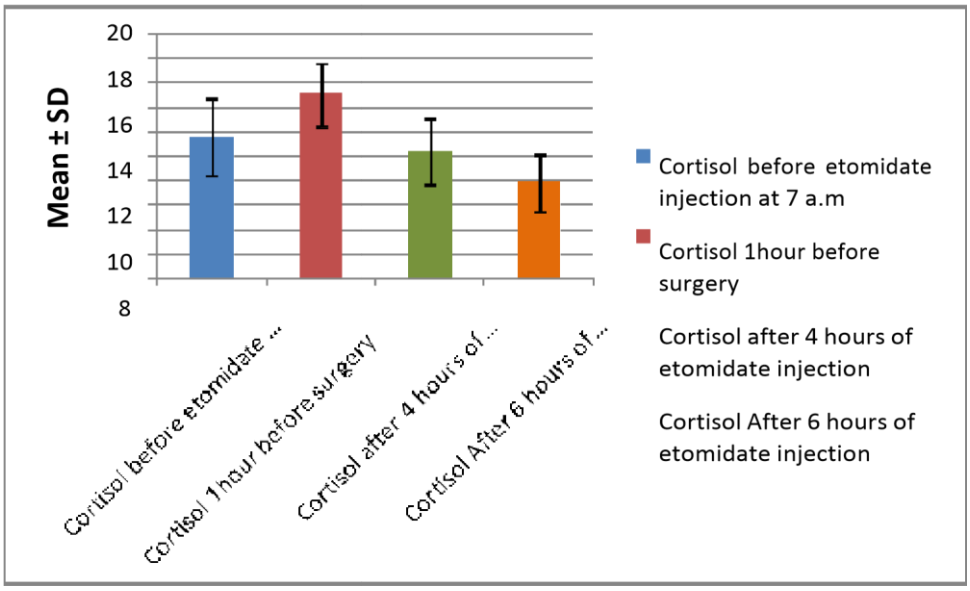
Cortisol after 6 hours of etomidate injection

In above table showed that the mean Cortisol after 6 hours of etomidate injection (mean ±s.d.) of patients was 7.9053± 2.3483.



Discussion

The first report of an effect of etomidate on plasma cortisol appeared in 1972 in Europe 7 1983 in U.S. This was followed by reports of increased mortality associated with low plasma cortisol level in patients receiving prolonged etomidate infusions for sedation (17,18).

Etomidate inhibits adrenal steroidogenesis by blocking two mitochondrial cytochrome P-450 dependent enzymes in the steroidogenic pathway- a) Cholesterol side-chain cleavage enzyme (17) & b) 11-beta hydroxylase (9,10). In some studies, it has been shown that the presence of an patients getting prolonged etomidate infusions. Abnormally high levels of 11-deoxycortisol was found in those patients after etomidate infusion were discontinued (14,22).

Etomidate was administered in the dosage of 0.3mg/kg of body weight. Serum cortisol was estimated before administration of etomidate at 7AM (Mean=11.7038) and 1 hour before surgery (Mean= 15.1418) differed with statistical significance ($p<0.0001$).

In a study S.chaurvi et al in 2020 found the reduction of cortisol levels by a bolus dose of etomidate in patients of ASA2 undergoing laproscopic cholecystectomy. In this study there is significant reduction in serum cortisol at 6 hours interval after the administration of etomidate. There was in vivo study on corticosteroid synthesis by subanaesthetic doses of etomidate (Diago et al 1988). They have shown that cortisol & aldesterone responses to ACTH were blunted & 11-deoxycortisol response were raised. D J Duthie et al in 1985 demonstrated biochemical effect of a single bolus dose of etomidate consistent with incomplete inhibition of adrenocortical mitochondrial 11-beta hydroxylase activity. D

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E Fry et al in 1984 found inhibition of 11- beta hydroxylation of cortisol by etomidate. The effect of sleep dose of etomidate on the plasma concentrations of cortisol, 11-deoxycortisol & 17 alpha- OH progesterone were investigated. The identity of 11-deoxycortisol was confirmed (21). The usual large increase of plasma cortisol levels associated with anaesthesia and surgery gets suppressed by etomidate induction (16,19). This suppression persist till at least 6 hours after the induction (17,18). Etomidate does suppress normal cortisol level following single induction dose of 0.3mg/kg in ASA1 patients. Some patients from the group had incidence of vomiting as side effect probably due to the drug etomidate which was not statistically significant.

In further studies, it has been found that prolonged usage of etomidate directly inhibits adrenal function & cortisol synthesis (20) & this suppression following etomidate infusion lasts for more than 24 hours (18).

In this study, it was found that serum cortisol decreases after administration of etomidate and was more significant at 6 hours interval compared with 4 hours interval after the injection. Hence it is observed that in this study there was significant reduction of serum cortisol level following the administration of single bolus dose of etomidate injection.

Conflicts of interest - None

Limitations

In this study, serum cortisol were estimated upto 6 hours after induction with etomidate. We could not do further estimation for more than 24 hours. Critically ill patients & patients of ASA2 & more had not been studied here. Other studies have shown increased incidence of mortality with etomidate induction in critically ill patients (5,11,13).

Conclusion

The study was conducted to assess the effect on cortisol levels following etomidate induction. There were significant reduction in cortisol levels after 4 hours & 6 hours interval from administration. No other complication following this drug has been found to occur.

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