

## Original Article

## Effect of Vitamin C on Serum Cortisol after Etomidate Induction of Anesthesia

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### Abstract

**Background:** Etomidate is suitable for induction of anesthesia, especially in elderly patients and patients who have cardiovascular compromise. Vitamin C has been introduced as a treatment option to decrease Etomidate induced adrenal insufficiency but its actual effect is still controversial. Objective is to determine the effect of vitamin C on reduction of serum cortisol after Etomidate induction of anesthesia.

**Materials and Methods:** In a randomized clinical trial, 40 patients of the American Society of Anesthesiologists (ASA) class I and II, aged between 25 to 70 years old, candidate for elective laparotomy were selected. One hour before induction of surgery, 1 gram of intravenous vitamin C were administered to the patients in vitamin C group. Two blood samples were obtained 5 minutes before induction and then another sample 4 hours after induction with Etomidate after surgery. All samples were measured for serum free cortisol, ACTH, and C-reactive protein (CRP).

**Results:** There were no significant differences between duration of surgery, pre-operative and post-operative blood pressure and heart rate in two groups ( $p > 0.05$ ). Serum cortisol was significantly declined in control group from  $16.2 \pm 6.3$   $\mu\text{g/dl}$  in pre-operative to  $8.5 \pm 4.2$  in post-operative ( $p = 0.0005$ ), but not in vitamin C group from  $17.5 \pm 5.6$  in pre-operative to  $16.8 \pm 6.4$  in post-operative ( $p = 0.75$ ). ACTH levels increased non-significantly from pre-operative to post-operative period in both vitamin C (pre-operative:  $52.1 \pm 15$  vs. post-operative:  $56.4 \pm 18$   $\text{pg/ml}$ ) ( $p = 0.48$ ) and in control group (pre-operative:  $50.5 \pm 16$  vs. post-operative:  $56.2 \pm 20$ ).

**Conclusion:** Etomidate could significantly decrease post-operative serum free cortisol and induce adrenocortical suppression and CRP increase. This effect could be reversed by using vitamin C premedication to maintain serum cortisol at pre-operative level.

**Keywords:** ACTH, Cortisol, Etomidate, Vitamin C

**Please cite this article as:** Nooraei N, Fathi M, Edalat L, Behnaz F, Mohajerani SA, Dabbagh A. Effect of Vitamin C on Serum Cortisol after Etomidate Induction of Anesthesia. J Cell Mol Anesth. 2016;1(1):28-33.

### Introduction

Etomidate is an imidazole derivative used primarily for induction of anesthesia, especially in

elderly patients and patients who have cardiovascular compromise. These beneficial properties led to widespread use of Etomidate for induction, for

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Received: October 28, 2015  
Accepted: November 20, 2015

maintenance of anesthesia, and for prolonged sedation in critically ill patients (1). The major advantage of Etomidate is its minimal effect on the cardiovascular and respiratory systems. The hemodynamic stability seen with Etomidate may be due partly to its unique lack of effect on the sympathetic nervous system and on baroreceptor function (2).

Anesthesiologists' enthusiasm for Etomidate was tempered, however, by reports that the drug can cause temporary inhibition of steroid synthesis after single doses and infusions (3). This effect, combined with other minor disadvantages such as myoclonus led to several editorials questioning the role of Etomidate in modern anesthetic practice (4). Because minor adrenocortical suppressive effects were shown to follow even single bolus doses, concerns about the use of Etomidate for anesthetic induction arose (5, 6). Etomidate administration was associated with a trend toward a relative increase in mortality (7).

The specific endocrine effects manifested by Etomidate are a dose-dependent reversible inhibition of the  $11\beta$ -hydroxylase which converts 11-deoxycortisol to cortisol, and a relatively minor effect on  $17\alpha$ -hydroxylase (8). This activity results to increase in ACTH.

Temporary adrenocortical suppression, as measured by a reduced response to ACTH stimulation, was documented for 6 hours post-operative and returned to normal by 20 hours post-operative. Boidin *et al.* introduce vitamin C as a treatment option to decrease Etomidate induced adrenal insufficiency. However, vitamin C effect on prevention of adrenal suppression induced by etomidate is still controversial. The main objective of this study was to determine the effect of vitamin C on reduction of serum cortisol after Etomidate induction of anesthesia.

## Methods

The study was reviewed and approved by the University Review Board and hospital ethics committee and been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki. Also, the study was registered in IRCT.ir with this ID: [IRCTIRCT201511252804N10](https://www.irct.ir/trial/201511252804N10). Information about trial was given comprehensively both orally and in written

form to the patients. All patients gave their written informed consents prior to their inclusion in the study according to University Hospital Ethics Board Committee.

Patient's selection: in a randomized clinical trial, 46 patients of the American Society of Anesthesiologists (ASA) class I and II, aged between 25 to 70 years old, candidate for elective laparotomy were selected. Patients were excluded if they had severe disabling illness, Addison or Cushing disease, septic shock or severe sepsis, trauma, history of corticosteroid intake at a dose that could suppress corticopituitary-adrenal, and duration of surgery longer than 4 hours or extreme changes in hemodynamics during surgery. Pre-operative visit was performed before the surgery. Six patients were excluded from the study.

Forty six patients enrolled and 6 were excluded; 40 patients were randomly (accidental numbers) assigned to one of control or vitamin C groups (Figure1). Randomization was performed before the surgery. Anesthesiologist administering drugs were blind to the group of patients and the syringes contain (concealment allocation).

Vitamin C administration: patients were randomly assigned to group vitamin C or Control. All patients entered operating room (OR) at 8 o'clock in the morning. Then, 1 hour before induction of surgery, 1 gram of intravenous vitamin C were administered to the patients in vitamin C group. Control group received the same volume of normal saline in the same color syringes.

Monitoring and Anesthesia: all patients were monitored for standard monitoring including ECG, Oxygen saturation pulse oximetry, non-invasive blood monitoring, and end-tidal CO<sub>2</sub> monitoring.

Patients were pre-oxygenated with 5 lit/min 100% O<sub>2</sub> for 3 to 5 min. Anesthesia was induced by the same method in all patients. For premedication, fentanyl 5  $\mu$ g/kg and midazolam 0.02 mg/kg was administered. Three minutes later the anesthesia was induced by Etomidate 0.3 mg/kg and Lidocain 1.5 mg/kg and cisatracurium 0.2 mg/kg. Intubation was performed under smooth direct laryngoscopy after 60-90 seconds when TOF=0. Endotracheal tube size was selected after laryngoscopy under direct visualization. Anesthesia was maintained with 1 minimum alveolar

anesthetic concentration (MAC) isoflurane and 50% nitrous oxide/50% oxygen. Extubation was performed using the same method in both groups. After surgery, when TOF>0.7 and patient was fully awaked, neuromuscular block was reversed (Neostigmin 0.05 mg/kg+Atropin=0.02 mg/kg) and extubated. In recovery, patients only had O2 5 lit/min via face mask.

Fluid therapy was performed using standard method. Patients were covered with 3 layers of surgical drapes. The ambient temperature was measured by a wall thermometer and room temperature was maintained at 23°C.

**Blood Sampling:** two blood samples were obtained from patients including one sample 5 minutes before induction with etomidate and then another sample 4 hours after induction with Etomidate after surgery in recovery or ward. All samples were measured for serum free cortisol, ACTH, and C reactive protein (CRP). Blood pressure, heart rate, and oxygen saturation were recorded before surgery and every 2 hours after anesthesia.

**Statistical Analysis:** statistical calculations were conducted using SPSS 18 (Chicago, IL, USA). The parametric variables were presented as mean±SD and were analyzed by student t-test; nonparametric variables were analyzed by Chi-Square or Mann-Whitney U-test. P<0.05 was considered as statistically significant. Sample size was estimated using sample size calculator software with 95% confidence interval, p=0.05 and power of 80% and difference between two groups of 70% in primary outcome based on pilot study.

## Results

In this randomized clinical trial, 46 patients were enrolled in the study, in which 6 were excluded and 40 of them randomly assigned to one of groups. Twenty of them received vitamin C and 20 patients received normal saline. Age, sex, and body mass index (BMI) were not significantly different between two groups of study (p>0.05) (Table1).

**Hemodynamics:** there were no significant differences between duration of surgery between two groups (p>0.05). Pre-operative and post-operative blood pressure and heart rate were not significantly

different in two groups of study (p>0.05; Table2).

**Serum Cortisol, ACTH and CRP:** serum cortisol was significantly declined in control group from 16.2±6.3 in pre-operative sample to 8.5±4.2 in post-operative (p=0.0005). However, cortisol did not decrease significantly in vitamin C group from 17.5±5.6 in pre-operative sample to 16.8±6.4 in post-operative sample (p=0.75) (Figure2).

ACTH serum levels increased non-significantly from pre-operative to post-operative period in both vitamin C group (pre-operative:

**Table 1:** Comparison of demographic characteristics of patients in two groups.

	Vit C	Control	p-value
Age (years)	52.4±	54.7±14.6	0.56*
	15.6		
Sex (Male/Female)	10/5	12/3	0.62¥
BMI	24.6±	23.7±4.56	0.39*
	4.3		
ASA Class			
I	64%	60%	0.56¥
II	36%	40%	
Type of surgery			
Gastrectomy	21%	18%	
(partial/total)	18%	22%	
Cholecystectomy	22%	19%	NA
Intestine resection	11%	12%	
Splenectomy	12%	14%	
Urinary System-	16%	15%	
Kidneys			
Others			

BMI: Body mass index; ASA: American Society of Anesthesiology

\*t-test; ¥ Chi-Square

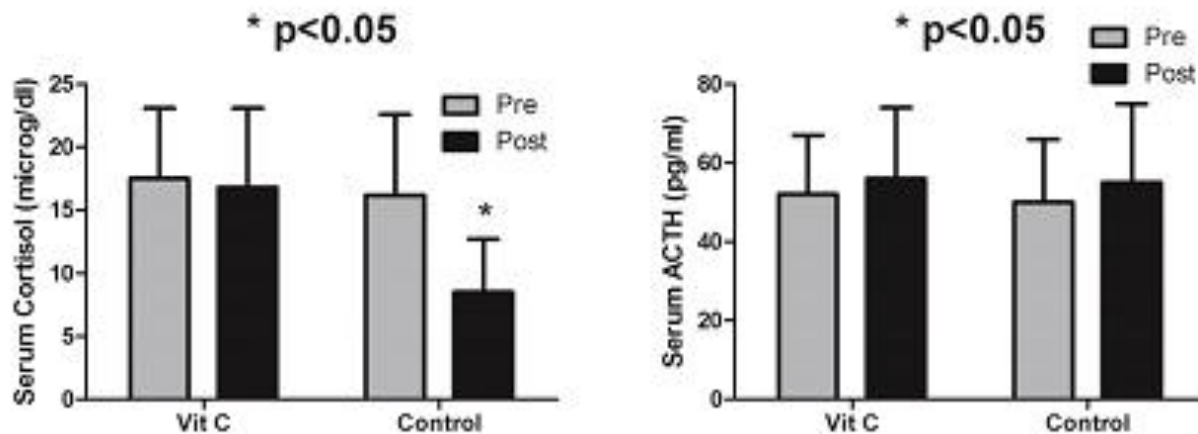
**Table 2:** Comparison of duration of surgery and hemodynamic of patients in two groups.

	Vit C	Control	p value*
Duration of Surgery (hours)	2.7±1.34	2.89±1.27	0.54
Mean arterial pressure (mmHg)	95.7±17.5	94.6±15.5	0.78
Pre-operation	94.5±14.3	92.6±14.7	0.58
Post-operation			
Heart rate			
Pre-operation	87.5±16.5	84.3±13.8	0.38
Post-operation	85.3±13.6	83.9±15.8	0.69

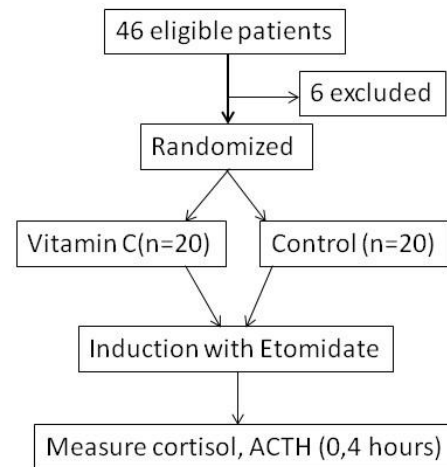
\*t-test

52.1±15 vs. post-operative: 56.4±18) (p=0.48) and in control group (pre-operative: 50.5±16 vs. post-operative:56.2±20; p=0.39) (Figure 2).

Serum CRP was significantly increased in control group from pre-operative (0.97±0.8) to post-operative (2.32±1.25), p value was p=0.0015, while it did not significantly increased in vitamin C group from pre-operative (0.92±0.75) to post-operative (1.1±0.80) with p value p=0.52 (Figure 3).



**Fig. 2.** Comparison of serum CRP between pre and postoperation in Vitamin C and control groups.

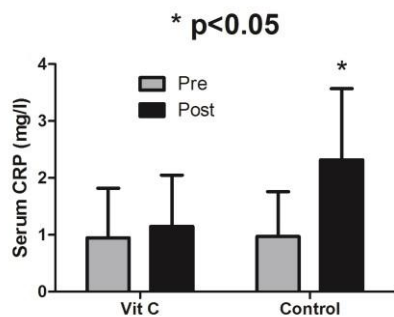


**Fig. 1.** Consort chart of the study.

## Discussion

Our study showed that Etomidate induction reduces serum cortisol in control group but not when vitamin C premedication is administered. On the other hand, Etomidate did not decrease ACTH secretion. However, ACTH secretion was not sufficient to increase cortisol due to inhibition of 11-β-hydroxylase (11).

In our study, cortisol level significantly decreased in control group after Etomidate induction but in vitamin C group free serum cortisol did not significantly decreased. Although this is not in contrast to other studies when evaluating Etomidate induction doses; none reported adverse outcomes



**Fig. 3.** Comparison of serum CRP between pre and post-operation in Vitamin C and control groups.

secondary to short-term adrenocortical suppression. In other studies documenting Etomidate induced adrenocortical suppression without associated clinical sequela; 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, and blockade of the response to ACTH by Etomidate could be detrimental. Etomidate could induce a potential risk for patients with high risk surgeries and frail patients with trauma, cardiac surgery (12) or septic shock (13) and should be avoided (14). Administration of Etomidate for rapid sequence intubation is associated with higher rates of adrenal insufficiency and mortality in patients with sepsis (15).

In our study, mean cortisol levels in the vitamin C group did not decreased significantly postoperatively. The blockade of  $11\beta$ -hydroxylase seems to be related to the free imidazole radical of Etomidate-binding cytochrome P-450 (16). This results in inhibition of ascorbic acid re-synthesis, which is required for steroid production in humans. Blockade of the cytochrome P-450 dependent enzyme  $11\beta$ -hydroxylase also results in decreased mineralocorticoid production particularly in critically ill patients (17). Therefore, vitamin C supplementation could restore cortisol levels to normal after the use of Etomidate. However few research contradict this effect that vitamin C given before anesthesia achieved by Etomidate is not sufficient for the prevention of surgical stress response (18).

Our experiment suggests that the issue of

adrenocortical suppression after perioperative induction doses of Etomidate will be reversed by vitamin C after laparotomies. Duthie and his colleagues showed that in otherwise healthy patients undergoing minor peripheral surgery, plasma cortisol levels were slightly depressed from the pre-induction levels for 1 hour postoperatively and the nadir of mean cortisol levels did not fall out of the normal range (19). However, high-stress surgery can overcome the temporary adrenocortical suppression caused by Etomidate to induce a clinically significant level of cortisol deficiency and adrenocortical suppression. Vitamin C premedication could reverse Etomidate induced adrenocortical suppression phenomenon. Other studies showed no evidence of a clinically relevant attenuating effect of ascorbic acid or xylitol on Etomidate-induced adrenocortical suppression (20, 21).

## Conclusion

Etomidate could significantly decrease post-operative serum free cortisol and induce adrenocortical suppression and CRP increase. This effect could be reversed by using vitamin C premedication to maintain serum cortisol at pre-operative level. This would be of paramount importance in fragile patients and high-stress surgeries.

## Acknowledgment

The authors would like to acknowledge the kind efforts of the operating room physicians and nurses of Modarres Hospital, Tehran, Iran for their cooperation and kind help.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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