Effect of Vitamin C on adrenal suppression following etomidate for rapid sequence induction in trauma patients: A randomized clinical trial

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Abstract

Background: Etomidate is an imidazol derivative which widely used in emergency department for Rapid Sequence Intubation (RSI). Although it has a safe hemodynamic profile but there are some concerns about its suppressant effects on adreno-cortical axis. Vitamin C as an antioxidant can play a protective role in this issue.

Method: In a controlled clinical trial, we studied adult traumatic patients who need RSI with etomidate. In one group underwent RSI with etomidate and cortisol level measured three hours later. In the other group we administrated one gram of vitamin C before etomidate administration and cortisol level measured three hours later.

Results: fifty-one patients has been studied. Serum cortisol level was significantly lower after RSI with etomidate in both groups. In Vitamin C group there was a significant higher cortisol level after RSI in comparison to control group.

Conclusion: Etomidate can suppress the cortisol level in traumatic patients underwent RSI. Vitamin C can reduce this suppressant effect of etomidate.

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Introduction

Rapid sequence induction/intubation (RSI) is the standard technic for airway management and intubation in emergency department (ED). This technic can reduce the risk of aspiration and intubation failure by using an anesthetic agent and a neuro-muscular blocking agent (1, 2). Using a safe and effective induction agent can maximize the intubation success and reduce the risk of adverse effects. Etomidate, an Imidazole derivative, is widely used as an induction agent for RSI in EDs. Its fast onset of action, safe hemodynamic profile, low respiratory depression effect and minimum histamine release made this drug a choice agent for RSI (3–5). Some studies showed that etomidate can cause an adrenal insufficiency by blocking 11-beta-hydroxylaze (5, 6). This suppression in cortisol level may cause a longer ventilatory support need, a longer intensive care unit (ICU) length of stay and a higher risk of acquired respiratory distress syndrome (ARDS) risk in traumatic patients (6, 7). Vitamin C is an anti-oxidant agent. It showed some prognosis improvement in patients suffering head trauma. It also plays a protective role against inflammation in hemorrhagic shock by inducing Hem-oxigenaze1 enzyme (8, 9). We conducted a clinical trial to investigate the effect of vitamin C on cortisol level in traumatic patients underwent RSI with etomidate.

Material And Method

This clinical trial conducted in Imam Reza General Hospital, a trauma referral hospital in Tabriz city, East Azarbaijan province, North West Iran.

Based on our center admission rate, we estimated to have 60 eligible patients to enroll in this trial in a six-month period of time (one eligible patient every three days). Patients with a history of trauma who needed airway management with RSI divided in two groups randomly. Sixty patients entered the study. Randomization was done by using random numbers table. Patients under 18-year-old, pregnant women, patients with a history of cardiac, renal or endocrine disorders and patients with a medication history of corticosteroids were excluded. In all patients a blood sample for serum cortisol level was obtained prior to RSI. In group I, patients underwent RSI with 0.3 mg/kg Etomidate (Aburaihan Pharmaceutical Co., Iran) and 1.5 mg/kg succinylcholine (Chandra Bhagat pharma Limited, India) and three hours later, serum cortisol level checked in these patients. As a placebo, these patients received 10 CC normal saline (two shots of 5 cc saline) intravenously. In group II, one-gram (500mg/5cc in two boluses) intravenous vitamin C (Sobhan darou Pharmaceutical Co., Iran) injected in pretreatment step of RSI and then patients underwent RSI with Etomidate and succinylcholine. Serum cortisol level checked three hours later. All patients received fentanyl (1 micg/kg) and midazolam (0.02mg/kg) for pretreatment. Figure 1 shows consort flowchart of the study.

The data was analyzed using SPSS Ver 22 software. The results were reported as frequency (percentage) and median (interquartile range). Kolmogorov-Smirnov test was used to test the normality of data distribution. To analyze the data, other methods of inferential statistics were used, such as the Chi-square test, Mann-Whitney U test, Wilcoxon signed rank (due to the non-normal nature of the data) and the covariance analysis method (to adjust the effect of the confounding variable). $P < 0.05$ was considered as the level of statistical significance. This study was approved by ethical committee of Tabriz University of Medical Sciences under the number of IR.TBZMED.REC.1397.925. Protocol of this clinical trial was submitted in Iranian registry of clinical trials under the ID of IRCT20090923002496N11.

Results

Sixty patients entered the study in two groups of 30 patients. Patients how died before 3 hours excluded. Fifty-one patients enrolled in trial. Twenty-four patients in group I and 27 patients in group II. In group I, 15 patients were male and 9 were female. In group II, 17 patients were male and 10 were female. There was no statistically difference in gender distribution between two groups.

The average age of patients in the group I was 64.5 years, with the lowest age being 18 years and the highest age being 89 years. The average age of patients in group II was 65 years, with the lowest age being 18 years and the highest age being 86 years. There was no statistically significant difference in terms of age between the two groups ($P = 0.770$) (Table 1). The median serum cortisol level of patients in group I, before induction, was 15.9 (with the lowest level of 5.7 and the highest level of 38.4). The median

serum cortisol level of patients in group II, before induction, was 40.8 (with the lowest level being 4.3 and the highest level being 59.9). Statistically significant difference was observed in terms of serum cortisol level before induction between two groups (P = 0.002) (Fig. 2). The median serum cortisol level of patients in group I, measured three hours after induction, was 15.05 with the lowest level being 5.8 and the highest level being 37.8. The median serum cortisol level of patients in group II, measured three hours after induction was 39.4 with the lowest level being 3.7 and the highest level being 1.61. A statistically significant difference was observed in terms of serum cortisol levels after injection between the two groups (P < 0.001). In the intra-group comparison (measurement after injection compared to before injection) of serum cortisol levels of patients in the group receiving etomidate without vitamin C injection, a statistically significant difference was observed (P = 0.005). In the intra-group comparison (measurement after injection compared to before injection) of serum cortisol levels of patients in the group receiving etomidate with vitamin C injection, no statistically significant difference was observed (P = 0.564) (Table 2). In investigating the effect of vitamin C on serum cortisol level after etomidate injection using the results of ANCOVA method, after removing the effect of the variable amount before the intervention, the effect of the group on the cortisol level measured after the intervention is statistically significant. (P = 0.019). In this way, it is found that the serum level of cortisol in the group of patients who received vitamin C is at a higher level than the patients who did not receive vitamin C (Table3).

Table 1
Demographic characteristics of patients

Variable		Group		P - Value
		Without Vit C n = 24 Frequency (percent)	With Vit C n = 27 Frequency (percent)	
Sex	Male	15 (62.5)	17 (63)	0.973
	Female	9 (37.5)	10 (37)	
age		64.5 (73.75–40.25)€	65 (77–46) €	0.770

€Median (Interquartile)

Table 2
Comparison of Cortisol levels between two groups, before and after etomidate injection

		Group		P - Value
		Without Vit C n = 24 Median (Interquartile)	With Vit C n = 27 Median (Interquartile)	
Cortisol level	Before injection	15.9 (25.37–8.17)	40.8 (47.9–14.3)	**0.002**
	After injection	15.05 (24.42–8.1)	39.4 (46.3–15.4)	**<0.001**
	P - Value	**0.005**	**0.564**	

Table 3
Evaluation of the effect of vitamin C on serum cortisol levels

Variables	Effect size	P-value
Group	0.112	0.019
Cortisol before induction	0.502	< 0.001
Group * Cortisol before induction	0.046	0.138

Discussion

Our study shows that in terms of serum cortisol levels before and after etomidate administration, there is a statistically significant difference between the two groups. The serum cortisol level after etomidate injection in the group of patients who received vitamin C is higher than the group of patients who did not receive vitamin C. Etomidate can suppress the adrenal response to major stress after trauma which can cause serious adverse events in trauma patients. Warner et al. showed a higher rate of acquired respiratory distress syndrome (ARDS) in patients with multiple trauma whom underwent RSI with etomidate (7). A study showed that vitamin C injection 20 minutes prior etomidate administration in rabbits significantly increases the serum cortisol level and prevents the inhibitory effect of etomidate on the adrenocortical axis (10). In human studies, vitamin C administration before cardiopulmonary bypass in cardiac surgery could prevents adrenocortical axis inhibition (11). Our results are consistent with study of Nooraei et al. They studied 40 patients underwent RSI with etomidate for elective laparotomy. Twenty patients received vitamin C before etomidate injection and 20 patients only received normal saline. Their study showed a reduction in cortisol level in control group but not in group receiving vitamin C. C-reactive protein (CRP) also had an increase in control group but not in vitamin C receiving patients (12). Deepanwita Das et al. studied oral vitamin C in seventy patients with elective cardiac surgery. Consistent with our study, patients with a one-gram oral daily vitamin C for seven days before surgery had a higher cortisol level than control group. Decrease in serum cortisol level was not only in first hour after RSI, but also for 24 hours after induction with etomidate (11). Contrary to the results of our study, Nathan et al.

did not find vitamin C as a protective agent against adrenal suppression. They studied a small group of patients (16 patients in two groups) and found a lower cortisol level in patients receiving vitamin C as premedication in RSI (13).

Limitation

This was a single center study with limited sample size. A larger sample size in a multicenter study could improve the power of study. We did not studied the effect of cortisol level on the outcome of patients and did not followed the final outcome of patients in two groups. Based on study protocol and method of randomization, we could not match our patients in term of admission time. Cortisol serum level has a circadian cycle and difference in admission time may cause significant differences in serum cortisol level. This caused a statistically significant difference in base line serum cortisol level between two groups in our study. We used ANCOVA method to remove the effect of this flaw.

Conclusion

Based on most of the studies conducted and our study, it is clear that vitamin C injection before the injection of etomidate in the induction stage of intubation with rapid sequence can prevent adrenal inhibition and decrease the serum cortisol level by etomidate. Although some studies have suggested other drugs such as midazolam instead of etomidate, but due to the minimal side effects of etomidate, this drug is still the drug of choice in unstable trauma patients.

To reduce the complication of adrenal suppression by etomidate in trauma patients, the use of methylprednisolone has also been mentioned, but due to the many complications of corticosteroids, more emphasis is placed on vitamin C, which, in addition to its antioxidant effects, can prevent adrenal inhibition by etomidate.

Abbreviations

ED
Emergency Department
RSI
Rapid Sequence Intubation

Declarations

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Authors' contributions: All authors have read and approved the manuscript. JRP, SPP, MRL and AV performed the data collection, literature review, and drafting of the manuscript. HS and KS undertook the major parts of the study design and performed the statistical analysis.

Availability of data and materials: The datasets generated during and analysed during the current study are not publicly available due to restriction of ethic committee of Tabriz University of Medical Sciences but are available from the corresponding author on reasonable request.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors declare they have no financial disclosure.

Consent for publication: The data presented in the manuscript and its supplemental files do not contain any details relevant to any individual patient and thus, no consent for publication was required

Ethics approval and consent to participate: This study was approved by the regional ethics committee with No. IR.TBZMED.REC.1397.925 ((2019-02-04) and registered in IRCT with IRCT registration number: IRCT20090923002496N11. Written informed consent was obtained from each patient' relatives.

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Figures

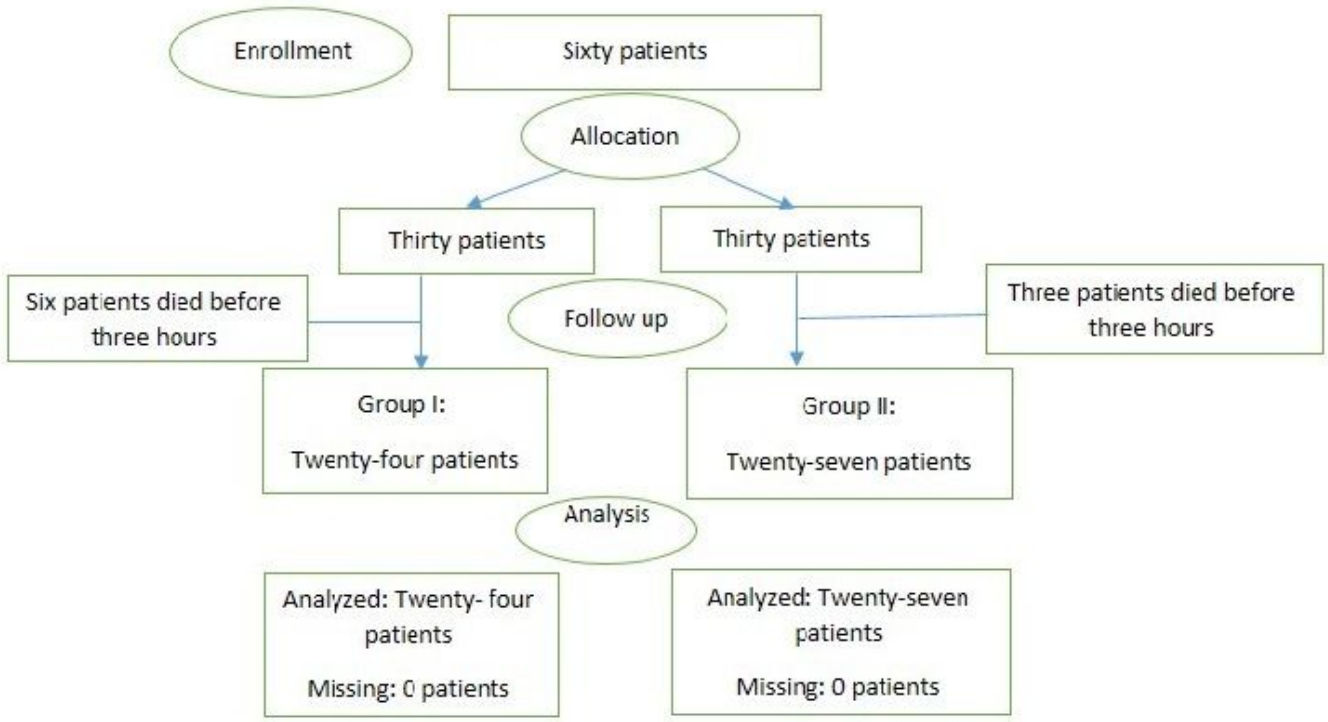

Figure 1

Flow chart of the study

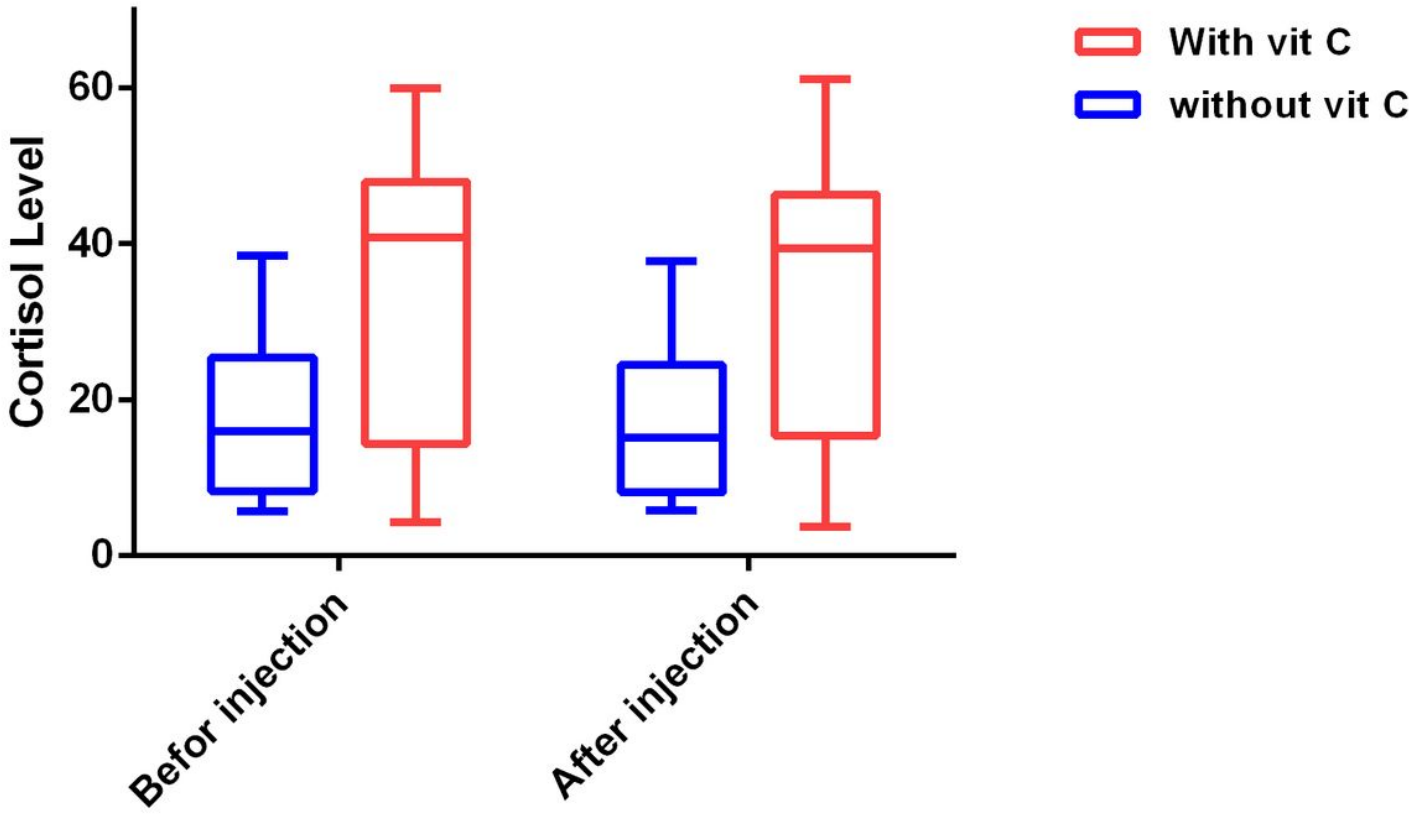

Figure 2

Cortisol level changes in both groups (Before and after etomidate injection)