International Journal of Drug Research in Clinics

International Journal of Drug Research in Clinics, 2023, 1, e1
10.34172/ijdrc.2023.e1
http://ijdrug.com

Editorial

The Magical Role of Vitamin C on Adrenal Insufficiency Subsequent to Etomidate Administration: Ongoing Challenges in the Management of Trauma Patients

Hassan Soleimanpour[1*]

[1]Emergency and Trauma Care Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

***Corresponding Author:** Hassan Soleimanpour, Emails: soleimanpourh@tbzmed.ac.ir, h.soleimanpour@gmail.com

Received: January 21, 2023, **Accepted:** February 2, 2023, **ePublished:** February 6, 2023

Etomidate is a non-barbiturate short-acting, sedative-hypnotic drug that is often used for the induction of general anesthesia during rapid sequence intubation (RSI) in critically ill patients. The onset of its effect is 5-15 seconds, and its effects last 5-15 minutes with an outstanding hemodynamic profile and a low risk of peri-intubation hypotension.[1] It has been effectively used as an anesthesia induction agent since the mid-1970s in Europe and since 1983 in the United States.[2] This drug binds to γ-aminobutyric acid type A (GABAA) receptors, strengthening the effects of GABA. In addition, etomidate is a central α2-receptor agonist, indicating that it preserves the vascular tone and myocardial contractility after an induction dose.[3] Etomidate motives a dose-dependent prohibition of 11β-hydroxylase that converts 11-deoxycortisol to cortisol, thus reducing the levels of cortisol. This synthetic pathway accounts for about 80% of circulating cortisol. Cortisol is the most plentiful endogenous glucocorticoid and increases vascular response to catecholamines and angiotensin II.[4]

The use of etomidate is controversial in critically ill patients since some studies have reported an association with a higher mortality rate in patients with sepsis. In patients with suspected clinical sepsis requiring emerg ency intubation in the emergency department, etomidate was related to increased risks of initial vasopressor use following intubation.[5] Single-dose etomidate for RSI in severe trauma patients is related to increased incidence of hospital-acquired pneumonia, multiple organ dysfunction syndrome, acute respiratory distress syndrome, as well as increased duration of intensive care and hospital stay in part because of the effect of etomidate on decreasing the circulating cortisol concentrations and influencing inflammatory response.[6,7] The inhibition of steroidogenesis is a probable fatal side effect of etomidate, which is highly potent and can arise even at doses below the essential dose for general anesthesia. Intravenous etomidate is an effective adrenal steroid synthesis suppressor which reduces the levels of cortisol in patients for 72 hours after a single injection. The administration of an intravenous dose of 0.2-0.4 mg/kg etomidate for intubation increases the risk of adrenal insufficiency by 12-fold. In general, it is recognized that adrenal insufficiency is related to increased mortality in sepsis. Adrenal insufficiency, whether caused by etomidate or secondary to corticosteroid insufficiency associated with critical illness, is a common problem in the intensive care unit.[8] Studies have demonstrated that nearly 50% of critically ill patients (e.g., those with traumatic brain injury) have adrenal insufficiency, which is associated with age, the severity of the injury, and the administration of etomidate. High doses of cortisol should not be prescribed in severe sepsis. Numerous studies recommend that replacement therapy with low doses of hydrocortisone decreases the severity of the systemic inflammatory response to sepsis and the duration of shock and can influence survival in catecholamine-dependent patients.

Vitamin C is a water-soluble vitamin with anti-inflammatory, antioxidant, and microvascular effects. The presence of extremely high levels of vitamin C in the adrenal gland along with its release in response to adrenocorticotropic hormone (ACTH) recommends that this vitamin has a role in cortisol synthesis. Studies

Author's Biosketch

Hassan Soleimanpour (M.D.) Professor of Anesthesiology and Critical Care, Subspecialty in Intensive Care Medicine (ICM), Clinical Fellowship in EBM, Fellowship in Trauma Critical Care and CPR, Emergency and Trauma Care Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

have shown that vitamin C, which is a cofactor for the production of catecholamines and cortisol needed for the survival of shock, is depleted during sepsis.[9] Vitamin C is a cofactor necessary for the synthesis of norepinephrine, whereas cortisol increases epinephrine biosynthesis from norepinephrine. Corticosteroids have a significant role in blocking beta-adrenergic receptors' down-regulation and preserving vasopressors' responsiveness of the vascular bed in septic shock.[10] High-dose vitamin C in severe sepsis and septic shock could maintain the endogenous synthesis of catecholamines and consequently ameliorate the necessity for exogenously administered vasopressors.[11]

Vitamin C was introduced as a selective treatment to reduce etomidate-induced adrenal suppression by Boidin. Nevertheless, the effects of vitamin C on the inhibition of adrenal insufficiency caused by etomidate remain controversial. This vitamin aids to sustain the normal function of the adrenal and supports cortisol formation, particularly in the final phase of the 11-deoxycortisol conversion to cortisol.[12] Supplementation with vitamin C prevents adrenal insufficiency by etomidate through stimulating the rate of 11-β–hydroxylase turnover, thus increasing cortisol formation. Vitamin C deficiency leads to declined hydroxylation in the cytochrome P450 monooxygenase system and results in the suppression of cortisol.[13]

In rabbits, pretreatment with vitamin C suppresses the etomidate-induced inhibition of adrenocortical function and leads to considerably increased serum cortisol concentration and greatly decreased concentration of ACTH. The effects of vitamin C on etomidate-induced adrenocortical insufficiency are dose-dependent and can be diverse at different time points. The protective effects of vitamin C were found to continuously increase within 6 hours of etomidate injection.[14]

Preoperative oral vitamin C (500 mg two times daily for 7 days) could prevent etomidate-induced adrenal insufficiency in cardiac patients referred for elective cardiac surgery undergoing cardiopulmonary bypass. Therefore, etomidate may be a suitable alternative for anesthesia induction in patients with heart disease with pretreatment with vitamin C.[11] In another study, the administration of 1 g of intravenous vitamin C to patients 1 hour before surgical induction could reverse etomidate effects and preserve serum cortisol at the pre-operative level.[15]

It is evident that the injection of vitamin C before the etomidate administration in the induction phase of RSI can inhibit adrenal insufficiency. It was also demonstrated that vitamin C could inhibit the reduction of the serum levels of cortisol induced by etomidate. Due to the minor side effects of etomidate, it remains the selected drug in unstable trauma patients. Consequently, vitamin C supplementation returns the levels of cortisol to normal following the etomidate use. Vitamin C treatment regimens were accompanied by decreased mortality and vasopressor requirement in sepsis. However, there is little evidence regarding the investigation of this area. The effects of vitamin C on cortisol levels begin to decrease over a prolonged time. Further, adrenal suppression induced by etomidate diminishes over time. Therefore, these factors need further investigation.

Acknowledgements
I would like to appreciate the cooperation of the Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran in conducting this research.

Conflict of interests declaration
The author declares that he has no competing interests.

Consent for publication
Not applicable.

Data availability statement
All data generated or analyzed during this study are included in this published article.

Ethics statement
Not applicable.

Funding
Not applicable.

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