v. 4, n. 73, 2024

International Journal of Health Science

INFLUENCE OF VITAMIN C ON ETOMIDATE-INDUCED ADRENAL SUPPRESSION: A LITERATURE REVIEW

Isadora Trindade Sobrinho
Student of medicine course at:
``Universidade Tiradentes``
Aracaju - Sergipe, Brazil
http://lattes.cnpq.br/3314100736812067
https://orcid.org/0009-0005-2089-4114

Rômulo Rodrigues de Souza Silva
Professor of the Department of Medicine at
``Universidade Tiradentes``
Aracaju - Sergipe, Brazil
http://lattes.cnpq.br/2234926783816364

Abstract: Introduction: The use of etomidate has been limited due to its ability to induce adrenal suppression, and cortisol is known to play a fundamental role in maintaining hemodynamic stability. Vitamin C appears to promote the formation of cortisol in patients with etomidate-induced adrenal suppression, since it plays an important role in the synthesis of endogenous cortisol. **Objectives:** To summarize the outcomes of clinical trials conducted to date to evaluate the influence of vitamin C administration on etomidate-induced adrenal suppression. **Methods:** This is a descriptive bibliographical research based on a free literature review. The articles and texts used for analysis were published in the last 10 years in the PubMED, Cochrane Library, Embase and Scielo databases, using the Boolean operators "AND" and "OR", and 13 works were selected. **Results:** Randomized clinical trials corroborate this finding, evaluating control groups (induced with etomidate) and intervention groups (induced with etomidate and administration of vitamin C), and finding statistically significant values ($p<0.01$) in serum cortisol levels. In addition, a recent meta-analysis associated the use of etomidate with mortality, and suggests that adrenal suppression is an important factor in this process. **Conclusion:** The administration of vitamin C appears safe and effective in maintaining serum cortisol levels, and it may be possible that it promotes a reduction in negative outcomes. However, some limitations, such as the low number of randomized clinical trials, make it difficult to consolidate the findings. The present study suggests that new clinical trials be conducted for elucidation purposes.

Keywords: Etomidate; Adrenal gland; Vitamin C

INTRODUCTION

The use of a safe and effective induction agent can maximize the success of orotracheal intubation and reduce the risk of adverse effects. Etomidate, an imidazole derivative, is widely used as an induction agent due to its rapid onset of action, safe hemodynamic profile, minimal histamine production, and little influence on respiratory depression (Meyancı et al, 2015).

However, the use of this drug has been limited, as it induces adrenal suppression, even in a single dose (Hildreth et al, 2008), for up to 24 hours. This occurs because etomidate, mediated by the imidazole radical, reduces cortisol biosynthesis by blocking the enzyme 11-beta-hydroxylase, responsible for the conversion of 11-deoxycortisol to cortisol, resulting in a reduction in serum cortisol levels (Soleimanpour, 2023).

Cortisol is known to be the most abundant endogenous glucocorticoid and to increase the vasopressor response to catecholamines by blocking beta-adrenergic receptors (Carr et al, 2015), playing a fundamental role in maintaining hemodynamic stability in hospitalized patients. Therefore, studies correlate etomidate-induced adrenal suppression with worse outcomes, such as nosocomial pneumonia, acute respiratory distress syndrome, sepsis, multiple organ failure, increased need for vasoactive drugs, increased length of hospital stay, and mortality (Kotani et al, 2023).

Vitamin C (ascorbic acid) plays an important role in the synthesis of cortisol, specifically in the terminal stage of the conversion of 11-deoxycortisol to cortisol. It also contributes to the synthesis of catecholamines by acting as a cofactor in the synthesis of norepinephrine (Boidin et al, 1986).

In this sense, Boidin et al, in 1986, initiated the discussion on vitamin C as a treatment option for etomidate-induced adrenal insufficiency. Administration of vitamin C in septic shock could maintain endogenous catecholamine synthesis and consequently reduce the need for administration of exogenous vasopressor drugs (Carr et al, 2015).

However, many studies report a controversial result on whether vitamin C can promote cortisol formation in patients with etomidate-induced adrenal suppression (Nooraei et al, 2016). There is a lack of evidence that keeps this discussion under investigation.

This study aims to summarize the outcomes of clinical trials conducted to date to evaluate the influence of vitamin C administration on etomidate-induced adrenal suppression, in order to add to the literature and encourage the production of new research that contributes scientific evidence for safe and effective care.

METHODOLOGY

This is a descriptive bibliographic research, based on a free literature review. The articles and texts used for analysis were published in the last 10 years; the time period chosen was due to the large gap between literary productions, and their consequent scarcity.

The collection of articles and data for review took place between January 2024 and April 2024. The data were obtained through research in books, multidisciplinary articles, journals and texts published electronically. Three databases were used to search for material according to the study criteria: National Library of Medicine (MEDLINE - PubMED), Cochrane Library, Embase and Scientific Electronic Library Online (Scielo). The search strategies used were determined by the descriptors: "Etomidate", "Adrenal suppression", "Vitamin C", with the Boolean operator "AND" and "OR" and 13 works were selected.

As a criterion for selecting articles, it was necessary that they were correlated with the objective proposed in this article, that is, they were clinical trials, as well as meta-analyses, literature reviews and book chapters that evaluated the influence of ascorbic acid administration on adrenal suppression induced by etomidate.

RESULTS AND DISCUSSION

In 1986, Boidin et al., initiated the discussion that supplementation with vitamin C, an important source of nicotinamide adenine dinucleotide phosphate, inhibits adrenal suppression by etomidate by promoting the turnover rate of 11-β-hydroxylase, thus increasing cortisol formation. The blockade of 11 β-hydroxylase appears to be related to the imidazole free radical of etomidate, which is related to cytochrome P-450.

Later, in 2005, Malerba et al., 2005, added that this resulted in the inhibition of the resynthesis of vitamin C, which is necessary for the production of steroids in humans. Blockade of the cytochrome P-450-dependent enzyme 11 β-hydroxylase results in decreased production of mineralocorticoids in critically ill patients.

After these findings, there was a gap in scientific production on the subject. In the last 10 years, new studies, including some randomized clinical trials, have raised the discussion again, bringing pertinent results and contributing to the verification of the influence of Vitamin C on the adrenocortical axis after inhibition by etomidate.

With regard to organic disorders, according to Marick et al, 2017, vitamin C levels are depleted in sepsis. Based on this thought, Carr et al, 2017, state that it is conceivable that the administration of vitamin C to septic patients with hypovitaminosis C may improve the endogenous synthesis of vasopressors, and thus alleviate the need for exogenous

administration of vasopressors. They also add that ascorbate-dependent vasopressor synthesis represents a little-explored biochemical mechanism by which ascorbate could act as an adjuvant therapy for severe sepsis and septic shock.

Nooraei et al, 2016, conducted a randomized study with 40 ASA 1 and 2 patients undergoing elective laparotomy surgery. They compared an intervention group (IG), which would receive 1g of intravenous vitamin C 1 hour before induction with etomidate, and a control group (CG), which would receive 1g of saline solution in the same color, in order to ensure blinded evaluation of the results. Some of the preoperative and postoperative outcomes were: blood pressure (BP), serum cortisol and C-reactive protein (CRP). There was no significant difference in BP values ($p>0.05$) between groups, but serum cortisol levels fell significantly in the CG (from 16.2±6.3 to 8.5±4.2, $p=0.0005$), while the IG did not show a statistically significant reduction (from 17.5±5.6 to 16.8±6.4, $p=0.75$). CRP also increased significantly in the CG (from 0.97±0.8 to 2.32±1.25, $p=0.0015$), while in the IG there was no significant increase (from 0.92±0.75 to 1.1±0.80, $p=0.52$). These results contribute to the idea that vitamin C can preserve serum cortisol levels, as well as providing information that it appears to reduce CRP levels, an important inflammatory marker. On the other hand, the BP outcome did not show any influence on the hemodynamics of this group of patients.

In contrast, Sarda et al, 2022, conducted a study that compared etomidate to propofol, and the outcomes systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were more stable in the etomidate group compared to the propofol group. Serum cortisol levels before surgery in both groups were within normal limits and comparable, followed by a significant decline in the etomidate group and an increase in the propofol group in the immediate postoperative period.

It is well known that even a single dose of etomidate can suppress adrenal function, as stated by Charuvi et al, 2020, when identifying that a single dose of etomidate in patients undergoing laparoscopic cholecystectomy suppressed serum cortisol levels. They argue that its use could probably be restricted to situations where it offers a clinical advantage over other available drugs, until the clinical relevance of the adrenal suppression effects of etomidate is fully known. In the study carried out by Das D et al, 2016, 70 patients who were to undergo cardiopulmonary bypass for cardiac surgery were randomized. Group I (GI) received 500 mg, twice a day, of vitamin C for one week before surgery, while group II (GII), a control group, received a placebo. Both were induced with etomidate. Serum cortisol was assessed at several time points, up to 24 hours after induction. In the first hour, GI had significantly higher cortisol values than GII (GI 69.51 ± 7.65, GII 27.74 ± 4.72, $P < 0.05$). The need for epinephrine was significantly higher in GII (3.4 ± 1.09) than in GI (2.83 ± 1.27), $P = 0.047$. The outcomes length of ICU stays, time to extubation, and arrhythmias were similar in both groups. The results of this study suggest that etomidate can be used safely in this group of patients undergoing extracorporeal circulation during cardiac surgery, as long as it is associated with the use of vitamin C.

Unlike the study above, still in the context of this group of patients undergoing cardiac surgeries, Brito H. K. M. et al, 2021, in their systematic review, found a positive influence on the arrhythmia outcome. They report that patients undergoing anesthetic induction with vitamin C supplementation obtained benefits after cardiac surgeries, such as the prevention of atrial fibrillation. Vitamin C can lead to a

decrease in the toxicity of anesthetics, and this appears to favor the differentiation of stem cells into cardiomyocytes.

Panahi et al, 2023, conducted a study with 51 trauma patients, undergoing rapid sequence intubation with etomidate. Group 1 (G1), control, received a placebo, while group 2, intervention (G2), received 1g of vitamin C before induction. A statistically significant difference was observed in the mean serum cortisol level of groups G1 and G2 before induction (P=0.002). Three hours after induction, the mean serum cortisol level was significantly higher in G2 compared to G1 ($P < 0.001$). These findings are consistent with those of other studies, which corroborate the idea that vitamin C can decrease adrenal suppression induced by etomidate, maintaining serum cortisol levels similar to those before induction.

A study carried out in animals by Sun Y et al, 2017, showed that the administration of intravenous vitamin C twenty minutes before etomidate in rabbits significantly increased the serum cortisol level ($p < 0.05$) and discussed in its results that there is an influence of vitamin C on the inhibitory effect of etomidate on the adrenocortical axis.

In addition, a recent meta-analysis (Kotani et al, 2023) evaluated the effects of etomidate on the primary outcome of mortality (at the time determined by the author of the included article) and on the secondary outcome of adrenal insufficiency. Eleven studies published between 1999 and 2022 were included. Among the 2,704 patients evaluated, the groups of patients in which etomidate was used had higher mortality when compared to patients who did not use it. The authors also found a higher incidence of adrenal insufficiency in the group of patients who used etomidate, which leads to the hypothesis that this is the justification for the higher mortality in this group. In view of this, the authors suggest that other anesthetic inducers be considered instead of etomidate.

Besides, in this sense, Soleimanpur, 2023, argues that the effects of vitamin C on cortisol levels begin to decrease over time, and that, in addition, adrenal suppression induced by etomidate decreases over time, and that, therefore, these factors require further investigation.

Once the association between adrenal suppression and mortality is confirmed, the need for further studies that demonstrate strategies that appear to circumvent this outcome is justified.

CONCLUSION

Induction of anesthesia with a single dose of etomidate, although cardiostable, can promote adrenal suppression and decrease serum cortisol levels, and is associated with higher mortality rates. Vitamin C plays an important role in the adrenocortical axis, preserving serum cortisol levels. According to the evidence presented here, administration of vitamin C before induction of anesthesia with etomidate appears to be safe and effective in maintaining serum cortisol levels. However, some limitations, such as the low number of randomized clinical trials and the lack of pediatric populations evaluated, make it difficult to consolidate the findings. The present study suggests that new clinical trials must be conducted for elucidation purposes.

REFERENCES

1. Boidin MP. **Steroid response to ACTH and to ascorbinic acid during infusion of etomidate for general surgery.** Acta Anaesthesiol Belg. 1985 Mar;36(1):15-22. PMID: 2990136.

2. BrITO, H. K. M.; MENDES, N. B.; FERREIRA, D. B.; OLIVEIRA, A. L. de S.; TOSTA, A. L. F.; ANDRADE, A. F. B.; MARQUES, H. M. M.; FIGUEREDO, M. R. **Os benefícios da utilização de vitamina C no perioperatório de cirurgias cardíacas/ The benefits of the use of vitamin C in the perioperatory of cardiac surgeries.** Brazilian Journal of Health Review, *[S. l.]*, v. 4, n. 4, p. 18267–18275, 2021. DOI: 10.34119/bjhrv4n4-299.

3. Carr AC, Shaw GM, Fowler AA, Natarajan R. **Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock?** Crit Care. 2015;19:418. doi: 10.1186/s13054-015-1131-2.

4. Charuvi S, Sahajananda H, Dwajani S. **Suppression of Cortisol Levels by a Bolus Dose of Etomidate in Patients Undergoing Laparoscopic Cholecystectomy.** *J Med Sci.* 2020; **6** (3):41–6

5. Das D, Sen C, Goswami A. **Effect of Vitamin C on adrenal suppression by etomidate induction in patients undergoing cardiac surgery: A randomized controlled trial.** Ann Card Anaesth. 2016 Jul-Sep;19(3):410-7. doi: 10.4103/0971-9784.185522. PMID: 27397444; PMCID: PMC4971968.

6. 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 Sep;65(3):573-9. doi: 10.1097/ TA.0b013e31818255e8. PMID: 18784570.

7. Kotani Y, Piersanti G, Maiucci G, Fresilli S, Turi S, Montanaro G, Zangrillo A, Lee TC, Landoni G. **Etomidate as an induction agent for endotracheal intubation in critically ill patients: A meta-analysis of randomized trials.** J Crit Care. 2023 Oct;77:154317. doi: 10.1016/ j.jcrc.2023.154317. Epub 2023 Apr 29. PMID: 37127020.

8. Malerba G, Romano-Girard F, Cravoisy A, Dousset B, Nace L, Lévy B, *et al.* **Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation.** Intensive Care Med 2005;31:388-92.

9. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. **Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before- after study.** Chest. 2017;151(6):1229-38. doi: 10.1016/j. chest.2016.11.036.

10. Meyancı Köksal G, Erbabacan E, Tunalı Y, Karaören G, Vehid S, Öz H. **The effect of single dose etomidate during emergency intubation on hemodynamics and adrenal cortex.** Ulus Travma Acil Cerrahi Derg. 2015 Sep;21(5):358-65. doi: 10.5505/tjtes.2015.06325. PMID: 26388272.

11. Nooraee 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 [Internet]. 2015 Dec. 22 [cited 2024 Feb. 25];1(1):28-33. Available from: **https://journals.sbmu.ac.ir/jcma/article/ view/10149**

12. Sarda BG, Raipure AM, Ruparel DH. **Serum Cortisol Levels with Etomidate Induction: A Speculation That Needs To Be Reviewed.** Anesth Essays Res. 2021 Jul-Sep;15(3):312-315. doi: 10.4103/aer.aer_118_21. Epub 2022 Feb 14. PMID: 35320963; PMCID: PMC8936860.

13. Soleimanpour H. **The magical role of vitamin C on adrenal insufficiency subsequent to etomidate administration: ongoing challenges in the management of trauma patients.** *Int J Drug Res Clin.* 2023;1:e1. doi: 10.34172/ijdrc.2023.e1.

14. Panahi JR, Paknezhad SP, Vahedi A, Shahsavarinia K, Laleh MR, Soleimanpour H. **Effect of vitamin C on adrenal suppression following etomidate for rapid sequence induction in trauma patients: a randomized clinical trial.** BMC Anesthesiol. 2023 Apr 1;23(1):104. doi: 10.1186/ s12871-023-02065-5. Erratum in: BMC Anesthesiol. 2023 May 11;23(1):162. PMID: 37005585; PMCID: PMC10067157.

15. Sun Y, Feng S, Li L, Huang K. **Effects of ascorbic acid on etomidate-induced inhibition of adrenocortical function in rabbits**. Int J Clin Exp Med. 2017;10(8):12553-8.