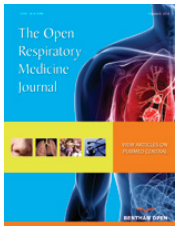

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EDITORIAL

Revisiting the Role of Vitamin C in Sepsis. Is it a Forlorn Hope or is there Still Dearth of data?

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This editorial intends to succinctly discuss the outcomes of a recent study by Fowler AA III *et al*. regarding the effects of intravenous (IV) vitamin C in patients with sepsis and Acute Respiratory Distress Syndrome (ARDS) [1]. Despite the advancement in diagnostic and therapeutic modalities, adoption of protocol-based management strategies and a better understanding of the pathophysiology of sepsis, the burden of mortality and morbidity from sepsis remains humongous [2 - 4]. In a relentless effort to add to the current repertoire of therapeutic options in sepsis, potential beneficial effects of Vitamin C have been tested in the study by Fowler AA III *et al*. [1]. The results of this study have garnered a huge deal of interest in the medical fraternity.

Fowler AA III *et al*., in a randomized, double-blind, placebo-controlled, multi-center trial, published the effects of intravenous (IV) vitamin C in patients with sepsis and ARDS [1]. The primary outcome of interest was to observe if there would be an improvement in organ failure assessed by modified sequential organ failure assessment (mSOFA) score with a continuous 96-hour infusion of IV vitamin C. Evidence of attenuation in inflammatory markers and vascular injury were also gauged utilizing C-reactive protein level and thrombodulin levels respectively. The study did not show any significant improvement in organ dysfunction or markers of inflammation and vascular injury [1]. Out of the 46 secondary outcomes that were evaluated, only 3 of them showed significant difference, *i.e*., improvement in 28-day all-cause mortality among the vitamin C group (29.8% *vs*. 46.3%, p=0.03), increased intensive care unit-free days among Vitamin C group (10.7 *vs*. 7.7, p-0.03) and increased hospital free days to day 60 (22.6 *vs*. 15.5, p=0.04) [1]. Regardless of the results of this study, there is still palpable exuberance about the role of vitamin C in sepsis among clinicians. Expert opinions are polarized, as they relate to merit and demerits of vitamin C.

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Pundits, who advocated in favor of its use, had their optimism fueled by abundant plausible data that indicated protective role of vitamin C due to its action against cell damage and organ dysfunction induced by oxidative stress [2] as well as mortality benefit as secondary outcome in Fowler study [1]. Even though the primary outcome, as well as the several secondary outcomes of the study by Fowler AA III *et al*. showed no benefit, improvement in mortality among vitamin C group raises even more questions as to its role in benefitting a patient with severe sepsis and ARDS patients, who have very high mortality [1].

Implementation of three and six-hours sepsis bundles, based on the surviving sepsis campaign, has led to a reduction in case fatality rates [2, 3]. Yet, mortality from sepsis is high, with more than 6 million deaths annually, estimated worldwide [4]. Current strategies for sepsis management are based on three basic features, *i.e*., source control, judicious and appropriate antibiotics use and use of fluid or vasopressor agents to maintain hemodynamic stability [2]. Recent evidence has focused on early resuscitation within 24-48 hours. Resuscitation encompasses crystalloid, vasopressor agents with norepinephrine as first-line agents followed by vasopressin, lung-protective ventilation with low tidal volume and appropriate positive end-expiratory pressure and intensive glucose control with target levels of 180 mg/dl or less [2]. This strategy fails to address the dysregulated inflammatory response due to the release of cytokines. With the high oxidative stress in sepsis, there is elevated vitamin C consumption. Thus, recent focus on sepsis management has shifted to the use of antioxidants such as vitamin C. A recent study by Marik *et al*. on the use of hydrocortisone, thiamine and vitamin C in sepsis challenged the status quo in the contemporary dogma of sepsis management by emphasizing on the need to add to the current armory [5].

Though vitamin C was first discovered in the 1920s, the only proven clinical benefit of its role is in the prevention of scurvy [2]. The utilization of vitamin C for conditions other

than scurvy prevention has been debated for many years. In this context, it has to be acknowledged that most of the investigators are fascinated by vitamin C in sepsis, due to its antioxidant effect. Moreover, the rationale for parenteral administration of vitamin C in severe sepsis and septic shock per se is to compensate for increased turnover of vitamin C in the increased inflammatory state [6]. Vitamin C also enhances the endogenous production of vasopressin and norepinephrine by acting as a co-factor for tyrosine hydroxylase and dopamine beta-hydroxylase [7]. Besides, it improves microvascular function, prevents apoptosis, mediates smooth muscle relaxation, maintains endothelial barrier function and imposes bacteriostatic action in septic patients [2].

Prior to the study by Flower AA III *et al*., several studies suggested the beneficial effects of vitamin C in decreasing multi-organ failure. In a study of 595 surgical patients with a critical illness, the administration of vitamin C and vitamin E showed a decreased incidence of multi-organ failure and Intensive Care Unit (ICU) length of stay [8]. In a double-blind randomized controlled trial, the administration of ascorbic acid was found to have a significantly lower requirement of vasopressor agents, earlier weaning of vasopressors and an overall decrease in 28-day mortality as compared to placebo [9]. Vitamin C has been found to decrease endothelial leakage, resulting in decreased fluid requirement and higher urine output in burned patients in a prospective randomized controlled trial [10]. Marik *et al*. showed a significant reduction in mortality among septic shock patients with the administration of 1500 mg of vitamin C IV every six hours along with thiamine and hydrocortisone for four days or until ICU discharge [5]. This study showed potential beneficial effects of vitamin C along with thiamine and hydrocortisone in sepsis. Evidence of the use of vitamin C among the burn patients suggests decreased endothelial damage and capillary leak, which is a significant pathophysiologic mechanism in septic patients.

The study by Fowler AA III and colleagues failed to show significant improvement in organ dysfunction or attenuate markers of inflammation with a 96-hour infusion of vitamin C at a dose of 50 mg /kg every six hours [1]. Though, mortality benefit with the secondary outcome raises more questions than providing answers, as mentioned by the investigators themselves, there are several limitations to this study, which could have its effect on the results. Patients were enrolled in the study only after they developed ARDS, which could have delayed the administration of vitamin C to achieve a significant improvement in mSOFA scores and markers of inflammation. This is more relevant since this study was designed on the premises of positive outcomes of vitamin C in the early stages of sepsis evident as obvious in the phase I safety trial which did not include ARDS patients [11]. Smaller sample size and heterogeneity of the population studied may have made the study underpowered to detect significant benefits. The authors also expressed a concern if the dose of vitamin C administered was sufficient for ARDS patient cohort in particular. Besides, the concern for internal selection bias was also a limiting factor [1].

Any healthy scientific debate always raises concerns regarding the adverse effects of vitamin C when used at a high dose. Acute impairment in renal function, glucose-6-phosphate deficiency, and calcium oxalate nephropathy due to metabolization into oxalic acid are potentially toxic adverse effects that have been of major concern [2, 12]. Besides, inaccuracy in point-of-care glucose measurement due to the structural similarity between glucose and vitamin C has also been reported [13]. Thus, any systematic studies performed in the future should make more emphatic efforts to address potential serious adverse events.

In the wake of evidence from this recent study [1], should we forfeit the notion of using antioxidants such as vitamin C as adjunctive therapy and think of it as forlorn hope? Given ample plausible data in favor of vitamin C mediated antioxidative effects in organ dysfunction as well as some mortality benefit as a secondary outcome in Fowler study [1], we opine that there should be a relentless pursuit of further data with the aid of larger trials. The unwavering enthusiasm determining the role of vitamin C in sepsis should not die yet.

REFERENCES

[1] Fowler AA III, Truwit JD, Hite RD, *et al.* Effect of Vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. JAMA 2019; 322(13): 1261-70. [http://dx.doi.org/10.1001/jama.2019.11825] [PMID: 31573637]

[2] Kuhn SO, Meissner K, Mayes LM, Bartels K. Vitamin C in sepsis. Curr Opin Anaesthesiol 2018; 31(1): 55-60. [http://dx.doi.org/10.1097/ACO.0000000000000549] [PMID: 29176375]

[3] Dellinger RP, Levy MM, Carlet JM, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36(1): 296-327. [http://dx.doi.org/10.1097/01.CCM.0000298158.12101.41] [PMID: 18158437]

[4] Fleischmann C, Scherag A, Adhikari NKJ, *et al.* International forum of acute care trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193(3): 259-72. [http://dx.doi.org/10.1164/rccm.201504-0781OC] [PMID: 26414292]

[5] 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. [http://dx.doi.org/10.1016/j.chest.2016.11.036] [PMID: 27940189]

[6] Borrelli E, Roux-Lombard P, Grau GE, *et al.* Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Crit Care Med 1996; 24(3): 392-7. [http://dx.doi.org/10.1097/00003246-199603000-00006] [PMID: 8625625]

[7] Carr AC, Shaw GM, Fowler AA, *et al.* Ascorbate-dependent vasopressor synthesis: A rationale for vitamin C administration in severe sepsis and septic shock? Crit Care 2015; 19: 418. [http://dx.doi.org/10.1186/s13054-015-1131-2]

[8] Nathens AB, Neff MJ, Jurkovich GJ, *et al.* Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 2002; 236(6): 814-22. [http://dx.doi.org/10.1097/00000658-200212000-00014] [PMID: 12454520]

[9] Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 2016; 5(2): 94-100. [http://dx.doi.org/10.4103/2279-042X.179569] [PMID: 27162802]

[10] Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg 2000; 135(3): 326-31. [http://dx.doi.org/10.1001/archsurg.135.3.326] [PMID: 10722036]

[11] Fowler AA 3rd, Syed AA, Knowlson S, *et al.* Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014; 12: 32.

[12] Levine M, Conry-Cantilena C, Wang Y, *et al.* Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996; 93(8): 3704-9. [http://dx.doi.org/10.1073/pnas.93.8.3704] [PMID: 8623000]

[13] Sartor Z, Kesey J, Dissanaike S. The effects of intravenous Vitamin C on point-of-care glucose monitoring. J Burn Care Res 2015; 36(1): 50-6. [http://dx.doi.org/10.1097/BCR.0000000000000142] [PMID: 25127026]