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What are the conclusions of the recent studies about administrating vitamin C in sepsis? The review

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Abstract

Introduction and purpose: Sepsis is defined by the Sepsis-3 definition as life-threatening organ dysfunction caused by a dysregulated host response to infection¹. Common manifestations of sepsis are fever, tachycardia, tachypnoea, confusion, hemodynamic dysfunction, and worsening of tissue perfusion. Sepsis may cause septic shock. The immune system produces reactive oxygen species which can also have an adverse influence on vasoconstriction⁵. There is a decrease in vitamin C levels in the plasma of patients with multiple organ failure⁶. Vitamin C plays a role in the synthesis of catecholamines and has antioxidant properties. The usage of vitamin C in sepsis patients has been arousing expectations for many years.

Brief description of the state of knowledge: The current state of knowledge indicates that there is no beneficent effect of ascorbic acid on the population which suffered from sepsis. What is more, there is some proof that administrating that vitamin can be noxious and factor into brain functions¹⁹. There are also suggestions that it could increase mortality⁸.

Conclusions: Recent studies do not recommend ascorbic acid as a treatment for sepsis. There is not out of the question that in some subpopulations due to pathogens or failed organs administrating vitamin C would benefit. Further research on this topic needs to be followed up.

Keywords: sepsis, ascorbic acid, vitamin C, sepsis medication, septic shock

1. Introduction

Sepsis is defined by the Sepsis-3 definition as *life-threatening organ dysfunction caused by a dysregulated host response to infection*¹. Common manifestations of sepsis are fever, tachycardia, tachypnoea, confusion, hemodynamic dysfunction, and worsening of tissue perfusion. That leads to a severe state of the patients which is a challenge to medical care. The seriousness of this problem is heightened by the fact that 26.7% of sepsis patients die² and 41.9% of patients who required ICU treatment die before discharge from the hospital². New methods of sepsis treatment are searched because of those reasons. Recently researchers have focused on the usage of vitamin C in sepsis treatment. Two main aspects that justify the application of vitamin C in sepsis patients are antioxidative qualities and input in the synthesis of catecholamines. Sepsis leads to perfusion worsening by vasodilatation which may cause septic shock. The recommended method of counteracting those changes is catecholamines administrating³. Vitamin C takes part in the production of endogenous catecholamines⁴ and may have a significant influence on patients' survival. The immune system produces reactive oxygen species (ROS) as a defense against pathogens. Unfortunately, ROS can also have an adverse influence on vasoconstriction⁵. ROS neutralization featuring vitamin C was considered as protection for sepsis patients and a cause of decreased death ratio⁵. What is more, there is a decrease in vitamin C levels in the plasma of patients with multiple organ failure⁶.

2. State of Knowledge

The usage of vitamin C in sepsis patients has been arousing expectations for many years. The theoretical base of vitamin C's effect on tissues has been given hope that it might be a remedy that decreases mortality. This particular vitamin plays a role in the synthesis of catecholamines and has antioxidant properties. Sepsis causes vasodilatation, which worsens perfusion and may result in septic shock. Catecholamine administration is advised as a remedy for those changes¹. Vitamin C is involved in the synthesis of endogenous catecholamines⁴, which may have a big impact on a patient's survival chances.

2.1 Recent scientific evidence

CITRIS-ALI Randomized Clinical Trial

A randomized double-blinded trial called CITRIS-ALI became to answer the question if vitamin C influences multi-organ failure, biomarkers of inflammation, and vascular injuries⁷. The dose of vitamin C used in the treatment group was 50 mg/kg actual body weight every 6 hours for 96 hrs. The study population was 167 people. Worth pointing out is that patients were randomized in 24h after ICU admission and ARDS was needed to include patients in the trial. Organ failure measured by the mSOFA scale after 96 hours did not show a significant difference between vitamin C and the placebo group⁷. Inflammation gauged by C-reactive protein and vascular injury measured by thrombomodulin levels after 168 hours did not indicate any difference among both groups⁷. What is more interesting 3 of the 46 secondary outcomes proved distinction. The number of ventilator-free days to day 28th was higher in the vitamin C group vs in the placebo group⁷. Also, the intervention group demonstrated more hospital-free days⁷. The biggest surprise was the fact that at day 28 mortality was about 16% lower in the vitamin C group⁷. Although the results were promising, the authors took them skeptically. Analyses did not count multiple comparisons⁷. Because of that researchers took the secondary outcomes only speculative. There is a need for further research.

LOVIT Randomized Clinical Trial

LOVIT clinical trial⁸ resolved doubts of CITRIS-ALI authors. It is a clinical double-blinded randomized trial with a placebo and vitamin C group. There are similarities to CITRIS-ALI as randomization in 24 hrs after ICU admission, dosage, and time of treatment of vitamin C (50 mg/kg body weight every 6 hours during 96 hrs)^{7 8}. Distinctions between the two trials answer the CITRIS-ALI authors' doubts because the primary outcome was death or persistent organ dysfunction on trial the 28th day. What is more, ARDS was not needed for randomization. That rejects the suggestion that lack of efficacy was induced by ARDS. The analyzed population was also larger (872 people). The results are clear. 44.5% of patients in the intervention group versus 38.5% of patients in the control group died or had persistent organ dysfunction at day 28⁸. Secondary outcomes: the number of days without organ dysfunction and mortality on the 28th day confirms the harmful action of vitamin C on sepsis patients⁸. It shows that vitamin C has a therapeutic influence on patients with sepsis but also can worsen their health state and even increase mortality.

The VITAMINS Randomized Clinical Trial

Another randomized trial conducted in Australia, New Zealand, and Brazil compares the positive action of vitamin C, thiamine, and hydrocortisone to hydrocortisone alone. The usage of thiamine in the control group was discretionary. The study included 211 patients primarily diagnosed with septic shock and randomized in 24 hours ICU administration. Vitamin C dosage was 1.5g every six hours which is lower than in other studies^{9 7 10}. Results follow the viewpoint of the worthlessness of administration of vitamin C in sepsis because there was no significant difference in time alive and free of vasopressors up to day 7⁹

The VICTAS Randomized Clinical Trial

501 sepsis patients in the US carried on another randomized trial researching vitamin C effectiveness. Time of enrolment was classically in 24 h after ICU administration. A dosage of 1.5g vitamin C combined with thiamine and steroid (administrated every 6 hrs in 96 hrs) was compared to a placebo¹¹. The clinical team can use open-label corticosteroids. Results do not prove clinical usefulness because there was a non-significant difference between ventilator- and vasopressor-free days within 30 days among the placebo and intervention group¹¹.

The ACTS Randomized Clinical Trial

200 sepsis patients were randomized to the placebo group or intervention group who received 1.5 g of vitamin C, hydrocortisone, and thiamine every 6 hrs for 4 days. There was not a statistically significant difference in SOFA score change over 72 hours among both groups¹². It means that it is more of the same randomized trial which proves vitamin C uselessness in sepsis treatment

2.2 Other studies

Other smaller studies also did not show a significant statistical difference between sepsis patients receiving vitamin C (alone or as part of an intervention) or a placebo. The spectrum of differences was: dose or duration of

total vasopressor administration^{10 13}; mortality^{13 14}; ventilation-free days^{13 14} and changes of SOFA score¹³. Despite the size of the study, the conclusion contained in it is compatible with other bigger studies shown above.

Studies that evidence the beneficial effect of vitamin C

The trial presenting the benefits of vitamin C have weaker evidence than the above research because it was conducted on small amount of patient- 40¹⁵. Another study showing vitamin C superiority was before-after, case-control research where data from the control group was stored in 2015-2017 and enrolment of the intervention group was in the years 2017-2019¹⁶. That time gap may have an impact on results and may resolve doubts about accuracy. The next research which demonstrated that vitamin C has therapeutic action has some crucial limitations. Researchers studied the impact on sepsis patients but the intervention group was split among many substations like vitamin C, E; N-acetylcysteine, and melatonin. It caused that in every group including the control group were about 20 patients¹⁷. That small population cannot show such real-life results as studies conducted on a larger population. After all even this trial did not show lower intrahospital mortality in the vitamin C group despite a decrease in SOFA score¹⁷. What is interesting there was a big study that included 72 654 patients (which is the biggest-sized research analyzed in this article) which shows the predominance of vitamin C over the controlled group¹⁸. Although it may be misleading because even authors believe that the difference between both groups is small¹⁸. What is more, it is a retrospective cohort study. That indicates that its results should be considered with larger suspicion than the results of randomized controlled trials.

Brain protective action of vitamin C

The newest investigation came up with a very interesting conclusion that vitamin C, thiamine, and steroids in venous intake worsen long-term cognitive, psychological, and functional outcomes in those who recover from sepsis¹⁹. Sepsis survivors were tested on psychological cognitive tests which showed worse results in those who had been treated with vitamin C thiamine and steroids versus the control group¹⁹. PTSD odds were more frequent in the investigation group¹⁹. There was no statistically efficient treatment influence of vitamin C, thiamine, and steroids on depression and bettering daily functioning¹⁹. This research is important because it shows that this treatment takes impacts the functioning of sepsis survivors in the long term. This research is crucial because sepsis induces cognitive function worsening and functional disability at itself in the elderly population for at least 8 years²⁰. Vitamins C with vitamin B1 and steroids have no treatment effects. What is more, they can even have a worsening impact. That conclusion is supported by other smaller retrospective research which indicates that vitamin C and B1 have no impact on delirium-free days in the sepsis population²¹.

3. Conclusions and Further Perspectives

Unfortunately, for the moment there is no incontrovertible evidence that shows the beneficent effect of ascorbic acid on the population which suffered from sepsis. What is more, there is some proof that administrating that vitamin can be noxious and factor into brain functions¹⁹. There are also suggestions that it could increase mortality⁸. It is necessary to mention that sepsis is a capacious diagnosis that can be divided into many categories due to pathogens and failed organs. It is not out of the question that in that subpopulations administrating vitamin C would benefit and researches need to be followed up.

Recent studies do not recommend ascorbic acid as a treatment for sepsis. It is compatible with the International Guidelines for Management of Sepsis and Septic Shock 2021. At this stage treatment of sepsis involves crystalloids, antibiotics, norepinephrine as a catecholamine by choice, and steroids³. There is not out of the question that in some subpopulations due to pathogens or failed organs administrating vitamin C would benefit. Further research on this topic needs to be followed up.

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