REVIEW DERLEME

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The Story of Vitamin C and its Versions in Sepsis and COVID-19: Traditional Review

C Vitamininin Hikâyesi ve Sepsis ve COVID-19'daki Versiyonları: Geleneksel Derleme

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ABSTRACT The multifaceted role of vitamin C, also known as ascorbic acid, in cellular homeostasis has been underscored, with particular emphasis on its involvement as a co-factor in crucial hydroxylation reactions, facilitation of collagen formation, and participation in enzymatic reactions crucial for maintaining cellular and tissue functions. Moreover, its attributed capacity to neutralize free radicals, protect cells against oxidative stress, and mitigate inflammatory responses accentuates its potential therapeutic significance. This review aims to comprehensively explore the contemporary understanding of vitamin C's therapeutic implications in sepsis and coronavirus disease-2019 (COVID-19) based on the relevant publications from the past years. While previous investigations have encompassed a range of study designs, including epidemiological research, this presented paper deliberately narrows its focus to recent randomized clinical trials (RCTs) and the latest systematic meta-analysis involving only RCTs, providing a higher level of evidence than observational studies. An exception is made for a meta-analysis examining vitamin C's role in COVID-19 patients, including previous RCTs and retrospective studies. The question in the present paper is whether vitamin C is efficacious in preventing and treating critical illnesses, particularly sepsis and COVID-19. The current evidence is still insufficient based on available publications from the last years and recent meta-analyses on this topic. Accordingly, larger high-quality randomized clinical trial studies are needed to provide more definitive insights into the efficacy of vitamin C in addressing critical illnesses.

Keywords: Ascorbate; ascorbic acid; COVID-19; intensive care unit; sepsis; vitamin C

ÖZET Askorbik asit olarak da bilinen C vitamininin hücresel homeostazdaki çok yönlü rolü, özellikle önemli hidroksilasyon reaksiyonlarında yardımcı bir faktör olarak rol oynaması, kolajen oluşumunu kolaylaştırması ve hücresel ve doku fonksiyonlarını sürdürmek için çok önemli enzimatik reaksiyonlara katılımı ile vurgulanmaktadır. Ayrıca potansiyel terapötik önemi serbest radikalleri nötralize etme, hücreleri oksidatif strese karşı koruma ve inflamatuar yanıtları azaltma kapasitesine dayandırılmaktadır. Bu derlemede, geçmiş yıllardaki ilgili yayınlar temel alınarak C vitamininin sepsis ve koronavirüs hastalığı-2019'daki (COVID-19) terapötik etkilerinin kapsamlı ve güncel bir şekilde araştırmayı amaçlamaktadır. Önceki araştırmalar, epidemiyolojik araştırmalar da dâhil olmak üzere bir dizi çalışma tasarımını kapsarken, sunulan bu makale bilinçli olarak randomize klinik çalışmalara ve yalnızca gözlemsel çalışmalara kıyasla daha yüksek düzeyde kanıt sağlayan randomize klinik çalışmaları içeren en son sistematik metaanalizlere odaklanmaktadır. COVID-19 hastalarında C vitamininin rolünü inceleyen hem önceki randomize klinik çalışmaları hem de retrospektif çalışmaları içeren bir metaanaliz için bir istisna yapılmıştır. Sunulan bu makaledeki soru, başta sepsis ve COVID-19 olmak üzere kritik hastalıkların önlenmesinde ve tedavisinde C vitamininin etkili olup olmadığıdır. Son yıllardaki mevcut yayınlara ve bu konudaki son metaanalizlere dayalı mevcut kanıtlar hâlen yetersizdir. Buna göre C vitamininin kritik hastalıklarda etkinliği hakkında daha kesin bilgiler sağlamak için daha büyük yüksek kaliteli randomize klinik çalışmalara gereksinim vardır.

Anahtar Kelimeler: Askorbat; askorbik asit; COVID-19; yoğun bakım ünitesi; sepsis; vitamin C

Vitamin C, also known as ascorbic acid (ascorbate), is a water-soluble micronutrient that plays an important role in various biological processes, including wound healing, synthesis of connective tissue, and the absorption and storage of iron in the human body.[1,2] Humans cannot synthesize vitamin C in their bodies because of

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the absence of the L-gluconolactone oxidase enzyme, which is necessary for the final step of the ascorbic biosynthesis pathway from glucose through various oxidation steps.[1] Severe vitamin C deficiency can result in adverse symptoms such as bleeding and clinical syndromes like scurvy. It becomes imperative for humans to get vitamin C with sufficient daily consumption through an even dietary intake or supplementation.[3] A relationship exists between dose and plasma/tissue concentrations, bioavailability, excretion by the renal system, and potential toxic effects.[4] The recommended dietary allowance (RDA) for vitamin C varies among global health authorities, with criteria ranging from approximately 45 mg/day for basic needs to around 200 mg/day to optimize overall health.[3] Most authorities have considered the enhanced needs of adults, pregnant or lactating women, and smokers, as shown in Table 1.[3,5,6]

As shown in Table 2, the dietary reference values of vitamin C are recommended by the nutrition societies of Germany, Austria, and Switzerland and the European Food Safety Authority panel.[5,6] On the other hand, some individuals misuse vitamin C supplements to treat or prevent certain diseases, particularly common colds.[7,8] It's important to note that vitamin C has potential benefits due to its anti-inflammatory and antioxidant properties and ability to enhance immune function. However, unconsciously, excessive intake of supplements can lead to serious side effects such as gastrointestinal problems, oxalate kidney stones, and nephropathy.[9]

TABLE 1: RDAs of vitamin C vary depending on gender, physiologic status, and smoking habits.

	RDA (mg/day)		
Situation	**NIH**	**EFSA**	**DGE**
Females	75	95	95
Males	90	110	110
Pregnants	85	105	105
Nursing mothers	120	155	125
Smokers	add, +35		add, +45

RDAs: Recommended dietary allowances; NIH: U.S. National Institutes of Health; EFSA: European Food Safety Authority; DGE: German Nutrition Society.

TABLE 2: RDAs of vitamin C intake in infants, children, and adolescents.

	RDA (mg/day)	
Age	**EFSA, 2013**	**DACH, 2015**
7-11 months		20
1-3 years	20	20
4-6 years	30	30
7-10 years	45	45
11-12 years	70	65
13-14 years	70	85
15-17 years	100 (M)-90 (F)	105 (M)-90 (F)
≥18 years	110 (M)-95 (F)	110 (M)-95 (F)

RDAs: Recommended dietary allowances; EFSA: European Food Safety Authority; DACH: The Nutrition Societies of Germany, Austria, and Switzerland; M: Male; F: Female.

SEARCH STRATEGY

In this review, literature was identified using the following scientific platforms: ("Ascorbic acid" OR "Vitamin C" OR "Sodium ascorbate" OR "L-ascorbic") and ("Coronavirus" OR "COVID-19 19" OR "COVID-19" OR "Corona" OR "COVID" OR "SARS-CoV2"), AND ("Sepsis" OR Septic shock") in PubMed (NLM, US), Scopus (Elsevier), and Web of Science (WoS, Clarivate Analytics, US) databases. All the randomized controlled trials and clinical trials (RCTs) included in the coronavirus disease-2019 (COVID-19) part of the conventional review were conducted between 2019 and 2021. Moreover, most background knowledge was derived from studies published during the past two decades, supplemented by a few older works. All English research included human patients, both children, and adults, and utilized vitamin C as a therapeutic or preventative intervention. Relevant literature was carefully examined to ensure its suitability for this review. Papers connected to the issue were included in the study as evidence to support the needed sections of this review.

SOURCES OF VITAMIN C

Vitamin C is derived from two primary sources: natural food and supplements. Citrus fruits and leafy greens are abundant in natural vitamin C. Incorporating these fruits and vegetables into a well-balanced diet is the primary and most effective way to fulfill vitamin C requirements naturally.[1,10] Additionally, breast milk is a natural source of ascorbic acid for newborns and infants, with vitamin C content influenced by the mother's dietary intake.[5] In cases of dietary restrictions or specific health conditions,

vitamin C supplements may be necessary to maintain the required levels. These supplements are available over the counter in various forms, including chewable tablets, capsules, powders, and intravenous (i.v.) formulations.[11] Factors such as heat, light, air exposure, cooking duration, and the processing of frozen foods can lead to vitamin C degradation. Therefore, prioritizing the consumption of fresh fruits and vegetables is the key to maximizing vitamin C intake and minimizing nutrient loss.[12,13]

KINETICS OF VITAMIN C

Absorption and bioavailability: The minority of ascorbic acid is relatively absorbed in the buccal mucosa mediated by passive diffusion, and the majority of ascorbic acid is readily absorbed in the small intestine through an energy-dependent active transport process across cell membranes.[1] The two primary transporters are sodium-dependent vitamin C transporters (SVCTs), primarily SVCT 1&2, and glucose transporters (GLUTs), which help the body to absorb and maintain its levels constant in various tissues and cells; any dysregulation of these transporters can lead to an imbalance in vitamin C homeostasis.[14] Active transport mechanisms in intestinal absorption and renal excretion regulate blood level and bioavailability, resulting in nonlinear, dose-dependent pharmacokinetics.[6] Once vitamin C levels drop below the subthreshold (1.4 mg/dL), it is reabsorbed from the renal tubule rather than excreted into urine, whereas at elevated vitamin C plasma levels, ascorbic acid is excreted in urine. The bioavailability of i.v. vitamin C is significantly higher than oral vitamin C when both are administered at the same dose.[14-17] The maximum bioavailability, reaching 70-80 µM, is achieved with a modest 200 mg dose.[6,16] However, increased vitamin C doses decrease bioavailability by half.[16,17]

Distribution: Once vitamin C is absorbed primarily in the small intestine, it enters the bloodstream in the ionized form of ascorbate. It is distributed via blood circulation in various tissues and organs, including the brain, kidney, liver, skin, adrenal glands, immune system, and other organs.[14,18] The distribution of vitamin C in tissues is indeed mediated by various mechanisms, primarily through facilitated diffusion and active transport. These processes are influenced by the concentration gradient of vitamin C. SVCTs, and GLUTs are crucial in transporting vitamin C from the bloodstream into cells and its distribution to various tissues in the body.[14,19,20] SVCTs are widely expressed in all organs and play an important role in the distribution of vitamin C throughout the body; they are responsible for the uptake by intestinal absorption and re-uptake by renal reabsorption of ascorbate from the blood to the different tissues.[14,20] After ingestion of vitamin C, it is absorbed primarily in the small intestine as ascorbate by SVCT1. After that, inside the intestinal cell, ascorbate is oxidized to dehydroascorbic acid (DHA) and is transported to the bloodstream by GLUT 1&2, which is then recycled to ascorbate is a continuous process that plays a vital function in maintaining the homeostasis of vitamin C in the body to support the diverse physiological functions of vitamin C throughout the body.[14,21] Vitamin C enters the blood only as an ascorbate ion that is easily oxidized to DHA and then is reduced back to ascorbate to maintain an intracellular vitamin C concentration similar to that of plasma.[22] Hence, in the bloodstream of healthy individuals, the prevailing form of ascorbate is in its reduced state, while DHA is present at minimal levels.[6,22] In the context of the brain, which is recognized as the organ with the highest concentration of vitamin C in the body, it is noteworthy that DHA can readily pass the blood-brain barrier (BBB). In contrast, ascorbate cannot directly cross the BBB but can enter the brain's cerebrospinal fluid via the SVCT2.[23]

Metabolism: The metabolic processes of ascorbate are closely linked to its function as an antioxidant.[15] It is a proficient electron donor, supplying electrons effectively in various biological processes, whether acting as a coenzyme or a free radicals scavenger.[1] The metabolism of ascorbate involves different aspects:

Antioxidant role: Ascorbate contains an oxygen atom with two electrons and readily provides an electron to neutralize free radicals, such as hydrogen superoxide or reactive oxygen species (ROS) through the capacity of ascorbate peroxidase (APX) enzyme.[24,25] This action contributes to alleviating oxidative stress on cells and tissues, thereby helping to maintain redox homeostasis. Ascorbate demonstrates

its inherent reducing capabilities through the capacity of APX to catalyse the reduction of hydrogen peroxide (H_2O_2) to water.[26]

Enzymatic cycling: In another scenario, the metabolism of ascorbate involves a pivotal role played by the APX enzyme accepting an electron from ascorbate and resulting in the generation of an ascorbyl radical, also referred to as monohydroascorbate (MHDA). MHDA is then reversibly transformed into DHA through the same enzyme system.[27]

Recycling DHA: The crucial enzyme DHA reductase catalyses the glutathione (GSH)-dependent reduction of oxidized ascorbate in ascorbate recycling. In this ascorbate-GSH cycle, GSH is oxidized from GSH disulfide to GSH by using nicotinamide adenine dinucleotide phosphate [$NAD(P)^+$], which acquires an electron from GSH; it results in the generation of H_2O_2 and the formation of the ascorbate radical within cells, which may contribute to oxidative damage to DNA.[24,27] This reduction process requires the utilization of cellular molecules, including GSH and NADPH, that lead to the generation of H_2O_2 with the ascorbate radical within the cells. Hydrogen peroxide is a type of ROS that can lead to oxidative damage to DNA within the cells.[27]

Electron transport: The ascorbate electron chain involves a complex series of reactions and interactions in the metabolism of vitamin C. When two molecules of ascorbyl radicals are nearby for an extended period, they may undergo a spontaneous disproportionation reaction.[28] During this reaction, one of the ascorbyl radicals donates an electron to the other, leading to the regeneration of both ascorbate and DHA.[27,28]

Further metabolism: During vitamin C hepatic metabolism, DHA undergoes subsequent transformations, resulting in the production of diverse byproducts, such as 2,3-diketogulonic acid and oxalic acid (and oxalates), primarily eliminated through urine.[29-31] Notably, oxalic acid or oxalates can combine with calcium, giving rise to calcium oxalate compounds that tend to crystallize and accumulate in kidneys, ultimately contributing to the formation of kidney stones.[31]

***Excretion*:** Vitamin C is metabolized in the liver into various intermediate molecules. In the end, vitamin C and its metabolites accumulate in the kidney and are excreted in urine, depending on the amount of intake.[30,31] Vitamin C is initially excreted from the body through glomerular filtration in the kidney, where substances in the blood are filtered into the renal tubules.[14] The renal tubules are responsible for further processing and reabsorption of essential substances that the body needs to retain through the action of SVCTs.[20] The amount of vitamin C excreted in urine is directly linked to its concentration in the bloodstream.[21] When the rate at which vitamin C is introduced to the renal tubules through glomerular filtration exceeds a certain maximum threshold, the excess is eliminated in the urine.[6] However, when vitamin C levels in the blood are below a subthreshold level (approximately 1.4 mg/dL or 0.8 mM), the kidneys reabsorb it instead of excreting it in the urine.[14] The reabsorption process is paramount as it prevents unnecessary vitamin C loss in the urine and ensures that adequate levels of ascorbic acid are maintained in the bloodstream.[32]

In contrast, most vitamin C metabolites are eliminated through urine, and only a minor proportion of ascorbate is excreted in the urine.[15,33] This is because most ascorbate, which undergoes glomerular filtration in the kidneys, is efficiently reabsorbed into renal tubular cells and then returned to the bloodstream to maintain vitamin C balance. Free DHA in urine is relatively uncommon, as it can undergo recycling processes to be converted back into ascorbate within the body.[15] The elimination of vitamin C byproducts, including oxalate and urate, is linked to the dosage of vitamin C, influenced by both its metabolism and reabsorption. Higher doses of vitamin C, exceeding 1,000 mg, result in reduced bioavailability and increased urinary excretion.[14]

KNOWN FUNCTIONS OF VITAMIN C

Vitamin C affects many enzyme activities and physiological processes due to its anti-inflammatory and antioxidant properties. The primary function of ascorbate may be its role as a reducing agent, which, along with other agents that reduce, serves as an antioxidant and co-factor for various enzymes, hormones, and amino acids.[1]

As an antioxidant, vitamin C scavenges "toxic" free radicals and diminishes the generation of ROS, potentially influencing conditions such as sepsis, can-

cer, and various diseases.[34] Moreover, vitamin C can restore vitamin E to its active antioxidant state, ensuring continuous cellular protection against oxidative damage.[1] Vitamin C is a co-factor in collagen production and connective tissue synthesis, synthesis of carnitine for cardiac function and energy production, and hydroxylation of dopamine, leading to neurohormones like norepinephrine. It also activates hormones such as vasopressin, oxytocin, steroids, and catecholamines, contributing to various physiological processes.[35]

An anti-inflammatory vitamin C contributes to inflammation control by reducing the synthesis of pro-inflammatory prostaglandins. It is a crucial pro-inflammatory signaling that impacts the nuclear factor kappa B (NF-κB)/tumour necrosis factor-alpha (TNF-α) pathway. Through downregulation of NF-κB, ascorbate exhibits anti-inflammatory properties, leading to the reduction of pro-inflammatory gene expression, including TNF-α, thereby mitigating inflammation associated with the NF-κB/TNF-α pathway.[36]

As an immune function enhancer utilizing its potent antioxidant properties, vitamin C effectively combats oxidative stress, improving immune modulation involving various immune cell types such as neutrophils, T cells, B cells, and natural killer cells.[37,38]

VITAMIN C IN SEPSIS VERSION

Sepsis is a critical medical disorder characterized by uncontrolled inflammation and unstable blood flow, resulting in shock, failure of many organs, and, ultimately, death. The fatality rate of sepsis remains elevated, with a generally unfavorable prognosis.[39] Vitamin C's potential to inhibit inflammation through its antioxidant properties is still uncertain due to insufficient clear evidence.[40,41] Notably, septic shock patients have baseline levels of vitamin C that are lower than the reference value. This state occurs suddenly in patients with sepsis and is caused by metabolic consumption, as intestinal absorption remains unaffected.[42]

Commonly evaluated outcomes for sepsis patients in clinical practice include mortality, the sequential organ failure assessment (SOFA) score, and the need for vasopressor medication. RCTs have examined the effectiveness of i.v. vitamin C treatment, either by itself or in conjunction with hydrocortisone/thiamine (HAT) therapy, in patients suffering from sepsis and/or septic shock. Several studies have indicated that vitamin C therapies are linked to decreased fatality rates and/or lower SOFA scores and/or reduced need for vasopressors and/or shorter durations of stay in the intensive care unit (ICU) as compared to the control group in cases of sepsis.[43-45] However, other studies reported no statistically significant differences between the groups.[46-48] The heterogeneous results are due to the lack of large RCTs focusing on vitamin C in sepsis and septic shock. Many clinical trials have involved small sample sizes; therefore, to establish conclusive evidence for decision-making, conducting larger RCTs with enhanced methodological quality, increased participant numbers, and an assessment of clinically relevant outcomes is imperative. The LOVIT Trial, published in June 2022, highlighted the role of i.v. high-dose vitamin C in septic shock patients and, notably, was the first study to include a large sample size. Involving 872 patients in randomization over the initial 11 days demonstrated no difference in mortality between the groups; however, at 28 days, individuals who received i.v. vitamin C showed an increased likelihood of death and dysfunctions in organs compared to placebo controls.[49]

Vitamin C As A Monotherapy Agent in Sepsis

The most recent meta-analysis, which included randomized controlled trials with 1,394 patients, investigated the impact of i.v. vitamin C is high-dose in individuals with sepsis and septic shock. The pooled analysis indicated statistically significant improvements in outcomes, such as diminished short-term mortality and decreased duration of vasoactive drug use in sepsis patients. Nevertheless, patients with septic shock did not show significant benefits in either short-term or long-term mortality. In addition, there were no significant differences in SOFA scores and the length of ICU stay with sepsis and septic shock.[50] The subsequent RCTs following this meta-analysis have shown contrasting results. For example, a recent post-hoc Bayesian reanalysis of the LOVIT trial involving 35 ICU sepsis patients revealed contrasting results. In that study, i.v. vitamin C (administered at 50 mg/kg over 30-60 minutes every 6 hours for 96

hours) was associated with a higher risk of death or persistent organ dysfunction at 28 days compared to the placebo group.[51] Furthermore, a recent RCT involving a single mega-dose of sodium ascorbate (30 g over 1 hour followed by 30 g over 5 hours) in septic shock patients indicated a significant reduction in vasopressor dose and SOFA score over time, with no differences in other clinical outcomes.[52] Another recent RCT in patients with septic shock suggested that oral vitamin C administered for 5 days reduced SOFA score and invasive mechanical ventilation; however, the groups showed no significant difference in mortality or hospital stay length.[53]

Combination Therapy With Vitamin C in Sepsis

In a recent systematic review and meta-analysis, which considered data up to October 31, 2022, that encompassed eight randomized clinical trials, it was determined that HAT therapy did not result in reductions in mortality rates, SOFA score, length of stay in the ICU or hospital, or the duration of vasopressor use when comparing HAT patients and control subjects.[54] Furthermore, subsequent RCTs conducted after this meta-analysis showed no significant advance in outcomes for sepsis patients compared to those who received a placebo.[55-57]

Generally, research on the impact of vitamin C in sepsis remains highly controversial, with varying results and implications depending on the specific patient population and conditions. Further large randomized clinical trials are required to estimate the safety and efficacy of vitamin C in sepsis patients.

VITAMIN C IN COVID-19 VERSION

Since the outbreak of the COVID-19 pandemic in 2019, millions of people have turned to vitamin C supplementation, considering its role as a crucial antioxidant and immune system enhancer for preventing viral infections.[58,59] The efficacy of vitamin C in preventing or shortening the duration of respiratory tract infections and the common cold has been controversial for many years, yielding inconsistent findings across various research.[60] Most randomized clinical trials investigating the high-dose i.v. administration of vitamin C in COVID-19 patients have yielded mixed results concerning laboratory and clinical outcomes. Some trials suggested that high-dose i.v. vitamin C may benefit severe COVID-19 cases.[61,62] For instance, one trial involving 18 patients treated with 2 g of i.v. vitamin C every 6 hours for 5 days, in addition to standard treatment, demonstrated improved respiratory function and lung conditions in the vitamin C group.[63]

On the other hand, another randomized clinical trial with 30 patients suffering from severe COVID-19 administered 1.5 g of i.v. vitamin C every 6 hours for 5 days. However, the outcomes result did not show significant differences in oxygen saturation, length of ICU stay, and mortality between the vitamin C and control groups.[64] Studies conducted by Kumari et al. and Zhang et al. focus on patients with severe COVID-19 infection who received i.v. vitamin C, compared to a control group, reported no significant differences in the need for mechanical ventilation and mortality between the two groups.[65,66]

A meta-analysis of six RCTs with 572 COVID-19 patients found no reduction in mortality, hospital stay, or symptom severity with oral or i.v. vitamin C treatment.[67] In contrast, the updated meta-analysis in October 2022, incorporating a sub-analysis, demonstrated a significant decrease in hospital mortality associated with oral and i.v. vitamin C use in nine randomized trials compared to the control group (23.9% versus 35.8%, respectively; p=0.003). Additionally, a pooled analysis was conducted on RCTs and retrospective studies concerning the route of vitamin C administration. Intravenous vitamin C administration showed a non-significant reduction in-hospital mortality [odds raito (OR)=0.69; 95% confidence interval (CI): 0.36 to 1.33; p=0.270], while orally administered vitamin C exhibited a significant reduction in hospital mortality (OR=0.38; 95% CI: 0.17 to 0.89; p=0.030). It is notable that in some studies, vitamin C was administered in combination with other substances (such as vitamins C and E, or a combination of vitamins A, B, C, D, and E, or vitamin C, melatonin, and zinc), resulting in controversial outcomes. However, the sub-analysis demonstrated a significant reduction in hospital mortality when vitamin C was administered alone (OR=0.50; 95% CI: 0.39 to 0.66; p<0.001) but yielded insignificant results when combined with other substances

(OR=1.39; 95% CI: 0.25 to 7.77; p=0.710).[68] Moreover, a recent meta-analysis including data collected to January 15, 2023, involving seven RCTs (574 COVID-19 patients) found a significant difference in mortality between vitamin C monotherapy and controls (p=0.030; relative risk 0.84, 95% CI 0.72 to 0.98, I2=0%). However, the sequence trial analysis exposed an erroneous indication of effectiveness, highlighting the necessity for further trials to validate the findings.[69] Furthermore, the most extensive study released up until now demonstrated the possibility of both harmful effects and effectiveness of vitamin C in the overall outcome of patient recuperation.[70] While i.v. vitamin C may exhibit more efficacy than oral formulations; the results of some randomized controlled trials and meta-analyses suggested that i.v. vitamin C may not be able to decrease the death rate or the severity of COVID-19. The clinical significance of vitamin C in preventing and treating infections, particularly in patients with COVID-19, remains uncertain, thus necessitating further clinical trials to assess its safety and efficacy.

CONCLUSION

It's crucial to consult with healthcare professionals about the most appropriate and safe doses that meet individual vitamin C needs and maintain the desired levels. Therefore, the dosage of vitamin C should be carefully and individually determined under the supervision of healthcare providers, especially for those with significant medical conditions or potential interactions with other medications. Despite the importance of vitamin C in various biological functions and the prevention and treatment of many medical conditions due to its anti-inflammatory and antioxidant properties, the efficiency of ascorbic acid in some diseases, including sepsis and COVID-19, is still blurred. Recent RCTs have shown that i.v. vitamin C does not significantly impact progression-free survival or the duration of hospitalization. Despite the anticipated benefits of vitamin C's anti-inflammatory and antioxidant activities in enhancing clinical outcomes for sepsis patients, including overall survival, reduction in SOFA score, decreased vasopressor requirement, and shorter ICU stays, existing studies do not yield conclusive evidence of its effectiveness in cases with sepsis or septic shock. A limitation of these studies included a small number of RCTs, leading to high heterogeneity levels and the utilization of the random effects model. A panel of 21 experts from 16 countries updated a meta-analysis and systematic review, including 38 RCTs in patients with sepsis. The panel advised against the utilization of i.v. vitamin C treatment in the clinical management of sepsis or septic shock in older individuals. This advice is supported by limited and uncertain evidence, as there is a significant variation in the findings of multiple research and a substantial fraction of these studies have a higher risk of bias. The findings from several investigations, including recent rigorous trials, failed to validate the advantages of vitamin C.

The findings indicate low evidence for the effects of vitamin C on reducing short-term mortality and the duration of vasopressor support. Moreover, the evidence regarding the impact of vitamin C on the duration of mechanical ventilation, length of stay in the ICU, and length of hospital stay is very low. Additionally, i.v. vitamin C has no significant impact in the long term. Similar to the outcomes observed in sepsis, the therapeutic impact of vitamin C treatment in COVID-19 patients remains controversial. The results of randomized clinical trials investigating the high-dose i.v. administration of vitamin C in COVID-19 patients is contradicted. Moreover, meta-analyses emphasize the absence of evidence substantiating the effectiveness of vitamin C in relieving symptoms related to COVID-19. The interpretation of results is challenging due to variations in populations, doses, administration routes, and the limited sample size. Vitamin C has a generally acceptable safety profile with minor adverse effects, even at high intakes. Critically ill patients, especially those with conditions like sepsis and COVID-19, may have a deficiency in circulating vitamin C associated with severity and poor outcomes. Whether vitamin C is beneficial in treating patients with/or without this deficiency remains.

Presently, there is inadequate evidence to substantiate the efficacy of vitamin C in preventing or treating COVID-19 and sepsis. Further, extensive, RCTs of significant scale are required to examine the precise impact of vitamin C on different medical problems and unravel this enigma.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Terken Baydar;* ***Design:*** *Omnia Abdo Mahmoud Hemdan;* ***Control/Supervision:*** *Terken Baydar;* ***Analysis and/or Interpretation:*** *Omnia Abdo Mahmoud Hemdan, Sonia Sanajou;* ***Literature Review:*** *Omnia Abdo Mahmoud Hemdan;* ***Writing the Article:*** *Omnia Abdo Mahmoud Hemdan;* ***Critical Review:*** *Sonia Sanajou, Terken Baydar;* ***References and Fundings:*** *Terken Baydar.*

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