CASE REPORT

EFFECTIVITY OF HIGH DOSE VITAMIN C AS ADJUVANT THERAPY IN HOSPITALIZED COVID-19 PATIENT

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ABSTRACT

Background: COVID-19 is an infectious disease caused by SARS-CoV-2 virus, which has become the main health issue worldwide. COVID-19 has a wide spectrum of clinical manifestations, ranged from asymptomatic to critical disease, which further can lead to death. In the advanced stage, COVID-19 can cause ARDS (Acute Respiratory Distress Syndrome), sepsis shock, and multiorgan failure that increase the hospitalization and mortality rate. Presently, the administration of high dose vitamin C (> 5 gram/day) is being considered as the adjuvant therapy in hospitalized COVID-19 patient. Objective: To explore the effect of high dose vitamin C in hospitalized COVID-19 patients.
Methods: Literature searching was done in five different databases (PubMed, Cochrane Library, SpringerLink, Semantic Scholar, and EBSCOhost) with „vitamin C", „high dose", „COVID-19", and „outcome" as the keywords.. The subsequent critical appraisal was performed in four relevant studies to assess the validity, importance, and applicability using Oxford Centre for Evidence-Based Medicine checklist. Result: Three studies showed that administration of high dose intravenous vitamin C in hospitalized COVID-19 patient could reduce COVID-19 symptoms, improve laboratory result, and prevent the aggravation of COVID-19 disease, yet its effect in reducing mortality rate was not seen yet. Meanwhile, one study didn"t show any good effect from the administration of high dose oral vitamin C in COVID-19 patient. **Conclusion:** The administration of high dose intravenous vitamin C can be considered as the adjuvant therapy in hospitalized COVID-19 patients.
Keywords: high dose vitamin C, COVID-19, clinical symptom improvement, laboratory value improvement, mortality rate reduction

ABSTRAK

Latar Belakang: COVID-19 merupakan suatu penyakit akibat infeksi virus SARS-CoV-2 yang saat ini sedang menjadi masalah kesehatan nomor satu di seluruh dunia. Penyakit ini memiliki berbagai manifestasi klinis, mulai dari asimptomatik, sakit ringan, sakit sedang, sakit berat, kritis, hingga menyebabkan kematian. Pada tahap lanjut, COVID-19 dapat menyebabkan ARDS, syok sepsis dan kegagalan multiorgan yang sering menyebabkan peningkatan tingkat hospitalisasi dan mortalitas pasien. Saat ini, pemberian vitamin C dosis tinggi (> 5 gram/hari) sedang dipertimbangkan untuk diberikan sebagai tambahan terapi standar pasien COVID-19. **Tujuan:** Mengetahui efektivitas pemberian vitamin C dosis tinggi pada pasien COVID-19 yang dirawat di rumah sakit. **Metode:** Pencarian studi dilakukan pada database seperti PubMed, Cochrane Library, SpringerLink, Semantic Scholar, dan EBSCOhost, serta dengan metode hand searching dengan kata kunci yaitu: vitamin C, high dose, COVID-19, dan outcome, menghasilkan 4 studi relevan yang dilakukan telaah kritis dengan menggunakan panduan dari Oxford Centre for Evidence-Based Medicine.
Hasil: Tiga studi menunjukkan hasil positif bahwa pemberian vitamin C intravena dosis tinggi pada pasien COVID-19 yang dirawat di rumah sakit dapat memperbaiki keadaan klinis, laboratorium, dan mencegah perburukan keadaan pasien COVID-19. Namun, efektivitasnya dalam penurunan angka mortalitas belum terlihat. Sedangkan, satu studi lain tidak menunjukkan efektivitas pemberian vitamin C oral dosis tinggi pada pasien COVID-19 yang dirawat. Kesimpulan: Pemberian vitamin C intravena dosis tinggi dapat dipertimbangkan sebagai tambahan terapi standar pada pasien COVID-19 yang dirawat.
Kata Kunci: vitamin C dosis tinggi, COVID-19, perbaikan keadaan klinis, perbaikan nilai laboratorium, penurunan tingkat mortalitas

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INTRODUCTION

Background

Coronavirus disease 2019 (COVID-19) is a disease with a high infection rate caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spread of this disease took place very quickly as the pandemic status was declared by WHO on March 11, 2020.[1,2] Indonesia is currently experiencing a second wave of spikes in the number of new cases of COVID-19. The total number of confirmed cases in Indonesia down to September 7, 2021 has reached 4.140.634 people with the number of death cases, 137.156 people (3,31% of total cases) which indicates the high level of seriousness of this disease. [3]

The spread of COVID-19 mainly spreads through droplet, airborne, or via surfaces of objects. Viruses that enter the human's body will bind to the angiotensin converting enzyme-2 (ACE-2) receptor, fuse with the cell membrane, and further enter the host cell. ACE-2 receptors can be found in airway epithelial cells, upper esophagus, ileal enterocytes, myocardial cells, renal proximal tubular cells, and bladder urothelial cells. In host cells, virus triggers an immune response that cause the production of proinflammatory cytokines and triggers inflammation in body tissues. As the result, tissue damage will occur and trigger a wide spectrum of clinical manifestations. Excessive production of cytokines can also lead to cytokine storm which causes acute respiratory distress syndrome (ARDS), multiorgan failure, or even death. [1-3]

COVID-19 can be diagnosed by its clinical manifestations and confirmed by laboratory tests, such as RT-PCR (definitive examination), antigen swab, or radiological examination (chest x-ray or CT-scan). The confirmed positive COVID-19 patients can have various manifestations ranging from asymptomatic, mild, moderate, severe, to critical conditions.[1] COVID-19 management includes the antiviral therapy (remdesivir, lapinavir, ritonavir), anti-SARS-CoV-2 neutralizing antibody products (convalescent plasma, casirivimab, imdevinab), immunomodulatory agents (corticosteroids, IL-1 antagonists, tocilizumab), healthy diet and supplement with high amount of micronutrients (vitamins, especially vitamin D and vitamin C; zinc, N-acetyl cysteine, and other micronutrients), and the usage of ventilation aids. [1,5]

Vitamin C is one of the recommended micronutrients for prevention and management of COVID-19. Vitamin C has antioxidant activity, immunomodulatory activity (stimulates IFN formation, lymphocyte proliferation, and neutrophil phagocytosis ability) and innate immune system enhancer activity. Latest study has shown that administration of high doses of vitamin C (at least 5 grams/day) can reduce of the length of hospitalization and mortality rates of hospitalized patients. High doses of intravenous vitamin C can also act as antioxidants in epithelial cells in the lungs so that high dose intravenous vitamin C are considered as the treatment for lower respiratory tract infections which are the main pathogenesis of COVID-19 disease.

Case Illustration

Mr. AW, 52 years old, was brought to the Emergency Room with the chief complaint of shortness of breath which had been worsened 1 day before hospital admission. *Primary* survey was assessed and patient was given nasal cannula. The shortness of breath was improved and patient was in stable condition. In history taking, patient was confirmed positive for COVID-19 3 days ago. From the physical examination, patient appeared to be fully conscious, moderately sick, tachypnea, subfebrile temperature. with oxygen saturation 95%. Bilateral coarse crackles were found on auscultation, while other examinations were normal. The patient was planned to perform some laboratories test and given the standard therapy of COVID-19. His wife asked about administration of high dose vitamin C for him.

Clinical Question

The clinical question in this report is "How is the effectivity of high-dose vitamin C

therapy in the improvement of clinical symptoms and reduction in mortality rates compared to hospitalized COVID-19 who do not receive high-dose vitamin C therapy?"

STUDY METHOD

Searching Strategy

The literature searching was done for two day (11-12 August 2021) using five databases. The literature searching strategy formulations and databases can be seen in Table 1. In addition, hand searching was also done to find more literature sources.

Table 1. Literature Searching Strategy

Database	Searching Strategy	Finding
Pubmed	((("Ascorbic Acid"[Mesh]) OR (Ascorbic Acid[Title/Abstract]) OR ("Ascorbic Acid") OR (Vitamin C[Title/Abstract]) OR ("Vitamin C") OR ("Vitamin-C") OR "(Vit C")) AND ("High Dose") AND (("COVID-19"[Mesh]) OR ("SARS-CoV-2"[Mesh]) OR ("SARS-CoV-2 variants" [Supplementary Concept]) OR (COVID-19[Title/Abstract]) OR (SARS-CoV-2[Title/Abstract) OR ("Coronavirus") OR ("Corona Virus") OR ("COVID") OR ("COVID19") OR ("COVID 19")) AND (("Outcome") OR (Outcome[Title/Abstract]) OR ("Symptom") OR (Symptom[Title/Abstract]))))	9
Cochrane Library	((Ascorbic Acid[Mesh]) AND (COVID-19[Mesh]) AND (Sign and Symptom[Mesh]))	1
SpringerLink	(("high dose") AND ("vitamin C") AND ("COVID-19") AND ("outcome"))	11
Semantic Scholar	(("high dose") AND (("vitamin C") NOT ("Vitamin D")) AND ("COVID-19") AND ("outcome"))	16
EBSCOhost	(("high dose") AND (("vitamin C") NOT ("Vitamin D")) AND (("COVID-19") OR ("COVID") OR ("SARS-CoV-2")) AND (("outcome") OR ("symptom")))	50
Hand search		3

Eligibility Criteria

The inclusion criteria of this report is the studies that meet the following criterias: 1) Patient (P) is an adult (18 years old or above) that is PCR positive confirmed COVID-19 patient with moderate to critical illness manifestation; 2) patient (P) has no history of vitamin C allergy, survival rate not less than 24 hours, not in pregnant or breastfeeding period, and no diseases or comorbidities; 3) Therapy given to intervention group (I) is high-doses of vitamin C (doses greater than 5 g/day or greater than 100 mg/kg/day) together with standard therapy for COVID-19; 4) Therapy given to the control group (C) is placebo or only standard therapy for COVID-19 patient; and 5) Study outcomes (O) are improvements in clinical symptoms and laboratory finding, as well as patient mortality. Study with designs other than systematic review RCTs, meta-analyses of

RCTs, RCTs, and cohorts, as well as study that are closed access and not available in English will be excluded from this report.

Article Selection

The literature searching on the five databases and hand searching mentioned before resulted in 95 literatures that will be selected based on the title and abstract, article duplication, PICO, as well as the inclusion and exclusion criteria described before. The full process of article selection can be seen in Figure 1.

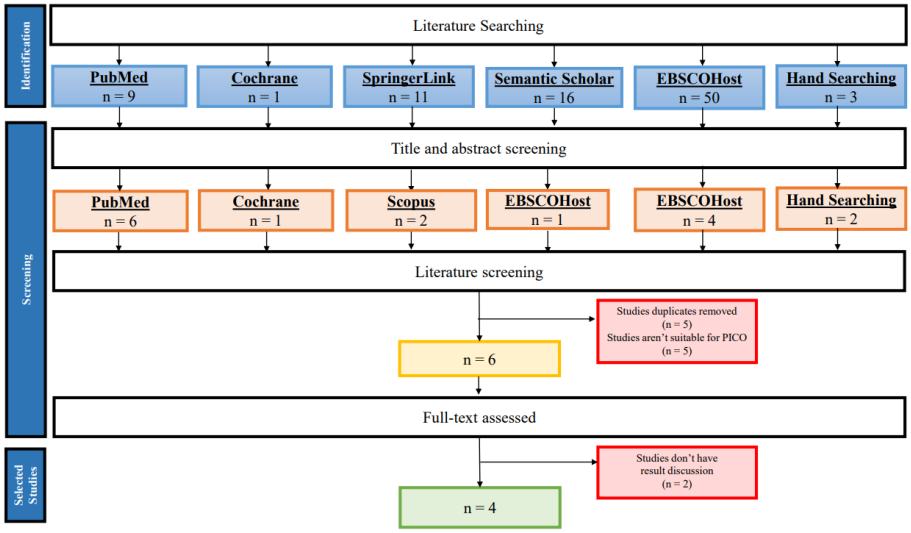

Figure 1. Searching Strategy Flowchart

Critical Appraisal

There are four studies (3 RCTs and 1 cohort study) that are included in this report. In this evidence-based case report, critical appraisal was done based on guidelines issued by the Oxford Center for Evidence-Based Medicine. Critical appraisal is aimed to assesses the validity, importance, and applicability aspects of each study. The result of critical appraisal can be seen in Table 2.

Tabel 2. Critical Appraisal Result

Author (Study design), Year	*Validity*					*Importance*	*Applicability*		
	Randomization	*Baseline*	*Allocation*	*Maintenance*	*Blinding*	*Effect size*	*Difference*	*Feasible*	*Benefits*
Zhang et al. (RCT), 2021 [6]	✓	✓	✓	✓	✓	IMVFD28 successful rate: 26/27 vs 22/29 (95% CI = -4,7–7,2; p=0,57) PaO2/FiO2 within 7 days: 20,0±96,68 mmHg vs -51,88±150,72 mmHg (95% CI = 5,92-172,45; p=0,04) IL-6 level within 7 days: 19.4 vs 158.0 (95% CI = -301,7 - (-29,8); p=0,04)	✗	✓	✓
Siahkali et al. (RCT), 2021 [7]	✓	✓	✓	✓	✗	Body temperature within 3 days: 36,75^0 C vs 37,25^0 C (p=0,001) Peripheral capillary oxygen saturation: 90,5% vs 88,0% (p=0,014)	✗	✓	✗
Thomas et al. (RCT), 2021 [8]	✓	✗	✓	✓	✗	Duration required to reduce 50% of symptoms severity scores: 5,5±3,7 days vs 6,7±4,4 days, p = 0,38 Hospitalization rate: 2±4,2% vs 3±6,0%; p = 0,50 Mortality rate: 1±2,1% vs 0; p = 0,40	✗	✓	✗
Zhao et al. retrospective cohort), 2021 [9]	✗	✓	✓	✓	✗	Disease worsening rate: 4/55 patients vs 12/55 patients (RR = 0,28; 95% CI = 0,08-0,93; p = 0,03) SIRS incidence within 7 days: 2/21 patients vs 10/22 patients (RR = 0.13; 95% CI = 0,02-0,68; p = 0,0086) SIRS duration: 2 days vs 6 days (p = 0,0004) CRP level: 0,5 mg/dL; 95% CI = 0,5-0,6 mg/dL vs 0,5 mg/dL; 95% CI = 0,5- 7,7 mg/dL; p = 0,005	✗	✓	✓

						CD4+ T cell lymphocytes count: 334 cells; 95% CI = 191,9-409,3 cells vs 151 cells; 95% CI = 43,5-240 cells; p = 0,04 D-dimer level: 0,3 µg/mL; 95% CI = 0,2-0,4 µg/mL vs 0,4 µg/mL; 95% CI = 0,2-0,7 µg/mL; p = 0,05, APTT within three days from admission: 37,7 s; 95% CI = 15,2-39,3 s vs 40,1 s; 36,8-44,2 s, p = 0,02 APTT within seven days from admission 36,9 s; 95% CI = 34,9-38,9 s vs 40,8 s; 95% CI = 36,5-43,5 s; p = 0,02			

DISCUSSION

In literature searching conducted, there were not many studies that directly evaluate the effectivity of high doses of vitamin C in hospitalized COVID-19 patients. Zhang et al. conducted a study regarding the use of high-dose intravenous vitamin C in hospitalized COVID-19 patients with critical symptoms and its relationship with invasive mechanical ventilation-free day in 28 days (IMVFD28) as the primary outcome, as well as mortality rate within 28 days, damage organs based on SOFA score, and the level of inflammation (serum IL-6) as the secondary outcomes. From 28 critical ill COVID-19 patients who received high doses of intravenous vitamin C, as many as 26 patients (96,3%) were successful in IMVFD28, while only 22 patients (75,9%) of 28 control patients were successful. However, the difference was not statistically significant (p=0,57). Then, this study showed the statistically significant results in terms of increasing PaO2/FiO2 values and decreasing IL-6 level within seven days. An increase in the value of PaO2/FiO2 indicates the increase in oxygenation capacity of the lungs. IL-6 is one of the cytokines that plays important role in SIRS and tissue damage so the decrease in IL-6 level is a predictive biomarker of severity improvement in COVID-19.[6]

An RCT study conducted by Siahkali et al. evaluated the effect of using high-dose intravenous vitamin C on 60 hospitalized COVID-19 patients who were divided into two groups. Assessment of mortality rate, duration of hospitalization, and need for ICU admission was done as primary outcome, while assessment of SpO_2 values and vital signs was done as the secondary outcome. As the result, there was no significant difference in the main outcome components between two groups. Besides, statistically significant results were found in the decrease of body temperature and the increase of peripheral capillary oxygen saturation in three days since hospital admission in intervention group compared to control group.[7]

Thomas et al. evaluated the effect of giving high dose of oral vitamin C on COVID-19 patients that received outpatient care. Primary outcome (time required to reduce symptom severity scores by 50%) and secondary outcomes (time required to completely reduce the symptom severity scores to 0, hospitalization rate, mortality rate, and side effect of supplementation) were assessed in this study. There were no statistically significant differences between two groups in the primary and secondary outcomes of this study. However, there are about 105 of subjects who experience side effects of vitamin C supplementation, such as GI intolerance, nausea, diarrhea, and stomach cramps. Limitations of this study that may influenced the result of this study include: the absence of placebo in the control group, the open-label study design, patients knowing what therapy they received, and not stratifying symptoms by age, sex, and race.[8]

A retrospective cohort study conducted by Zhao et al. assessed the effect of high-dose intravenous vitamin C on adult COVID-19 patient with moderate illness clinical symptoms by observing disease progression to severe or critical illness as the primary outcome and inflammatory response, immune function, organ function, and time to reach negative viral load. From 55 patients with moderate symptoms of COVID-19 who were given high doses of vitamin C, only 4 patients (7,27%) progressed to severe or critical illness; while in the control group, there were 12 out of 55 patients (21,81%) who progressed to the more serious condition (p=0,03). The calculated NNT (*number needed to treat*) value is 6,975, which means that administration of high doses of intravenous vitamin C in seven moderate illness COVID-19 patients can prevent one additional case of COVID-19 disease progression on to the more serious

condition. In addition, significant differences were also found in decreasing incidence and duration of SIRS, CRP values, d-dimer levels, APTT on the third and seventh day of admission; and increasing CD4+ T lymphocytes. However, the mechanism of action of vitamin C in reducing the incidence and duration of SIRS is not yet known. The decrease in lymphocytes is caused by infection of SARS-CoV-2 which kills the lymphocytes, as well as induces the release of antibodies and cytokines that inhibits the growth and induces apoptosis of hematopoietic cells. Previous in vitro and in vivo studies have shown that vitamin C plays an important role in the development, maturation, and proliferation of T lymphocytes. Last, coagulopathy is one of the clinical manifestations in COVID-19 characterized by the increase in the d-dimer level. Vitamin C has an effect in repairing endothelial damage that reduces the clot formation and incidence of angiopathy in COVID-19 patients.[9]

The discussion of four literatures above shows that administration of high dose intravenous C can prevent the disease worsening, increase the clinical condition, and improve the laboratory finding. However, the effect in reducing mortality rate and increasing successful rate of IMVFD28 is not yet seen. On the other side, side effect was reported in the administration of high-dose oral vitamin C such as gastrointestinal intolerance, although oral administration of high-dose vitamin C has not shown any effectiveness in hospitalized COVID-19 patients.[6-9]

CONCLUSION

Administration of high-dose intravenous vitamin C (above 5 g/day) has shown effectiveness in improving clinical symptoms, improving laboratory finding, and preventing the worsening of COVID-19 in hospitalized COVID-19 patients; but the effect in reducing mortality rate is not yet seen. Meanwhile, the administration of high-dose of oral vitamin C has not shown any effectiveness in hospitalize COVID-19 patients, and instead causes side effects such as gastrointestinal intolerance, nausea, diarrhea, and stomach cramping so it is still not recommended to be used.

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