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EFFECTIVENESS OF VITAMIN C ADMINISTRATION ON OUTCOME IN COVID-19 PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

INTRODUCTION

Coronavirus disease 2019 (Covid-19) is a disease characterized by severe acute respiratory syndrome.[1] It spread rapidly around the world and led to an increase in confirmed cases of Covid-19. Hence, the World Health Organization (WHO) declared a pandemic in 2020 due to this disease. The prevalence of Covid-19 in the world as of March 18, 2022, reached 480,170,572 confirmed cases, with a death toll of 6,124,396. In Indonesia, the incidence of Covid-19 was 6,001,751 confirmed cases, with a death toll of 154,774.[2]

Since its first appearance, the high rate of confirmed Covid-19 by reverse transcription-quantitative polymerase chain protein (RT-qPCR) and the death rate in Covid-19 patients has led to continued research on this subject, one of which is research on supplements for Covid-19 patients. [3] Additional supplementation in Covid-19 patients is necessary because the pathophysiological involvement is very complex and involves a decrease in the immune system. This additional supplement can act as an immunomodulator, antioxidant, and anti-inflammatory. [4]

The supplement for Covid-19 that has been widely studied is vitamin C. [5] Ascorbic acid, or vitamin C, is an antioxidant that can fight reactive oxygen species (ROS). In Covid-19 patients, there is excessive ROS production due to an impaired body defense system resulting in an increase in oxidative stress that contributes to tissue damage. [6] Apart from being an antioxidant, vitamin C also acts as an immunomodulator.[7,8] In the case of influenza, the administration of vitamin C has a symptom-ameliorating effect, reduces hospitalization duration, and significantly reduces the risk of death.[9]

Several studies on the effectiveness of vitamin C in Covid-19 patients have been conducted, both in RCT and cohort studies. The results show differences in the effectiveness of therapy and variations in the dose used. Therefore, further research studies are required to provide up-to-date information on the effectiveness, therapeutic dose, and side effects of vitamin C administration on outcomes in Covid-19 patients.

METHODS

We collected the data from articles published in Google Scholar, Pubmed, and Science Direct until April 25, 2022, using Coronavirus Disease, Covid-19, SARS-CoV-2, vitamin C, and ascorbic acid as the keywords. Critical analysis of the selected studies was performed using The Joanna Briggs Institute (JBI) Critical Appraisal Tools for risk assessment of bias by the researcher and three reviewers. The meta-analysis was generated in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The inclusion criteria used: (1) randomized control trial (RCT) and cohort studies, from 2019 to 2022; (2) studies related to the administration of vitamin C to Covid-19 patients (primary or reinfection Covid-19 patients); The exclusion criteria: (1) treatment of Covid-19 in the pregnant female population; (2) samples under 50 participants; (3) incomplete information or full texts unavailable.

We used Review Manager Software version 5.3 to perform our meta-analysis to estimate the pooled odds ratio (OR), mean difference (MD), and 95% confidence interval (95%CI). A p-value of less than

0.05 was considered to be statistically significant. The statistical heterogeneity was evaluated using the I^2 statistics. We performed a subgroup analysis among subjects who received vitamin C orally or intravenously, with mortality as the outcome of effectivity therapy, to diminish the impact of heterogeneity in the outcome of our results.

RESULTS

Based on the search of three databases, we found 1,222 studies. Subsequently, an eligibility assessment was conducted, and we excluded 1208 studies, resulting in fourteen studies for further review. The study selection process is laid out in Figure 1. From the 14 studies reviewed, ten articles discussed the administration of vitamin C as a single supplement[10–19], and four studies examined the administration of a combination of vitamin C[20–23]. We analyzed the articles by extracting and synthesizing data. Outcomes obtained from this study were grouped into three types: mortality, hospitalization, and symptoms (duration of illness, fever, and anosmia). The results of data extraction and synthesis are shown in Table 1.

The meta-analysis design was performed on eleven articles with oral or IV vitamin C administration based on mortality outcomes and six articles with hospitalization outcomes. Eight articles using an IV vitamin C intervention and three using an oral vitamin C intervention were depicted through forest plot analysis in Figures 2 and 4. When viewed from the articles obtained, the IV vitamin C intervention did not significantly affect the mortality of severe Covid-19 patients (OR 0.80, 95% CI 0.31–2.09, p= 0,66, I^2= 79%). Conversely, oral vitamin C significantly affected the mortality of asymptomatic Covid-19 patients and patients with mild to moderate symptoms of Covid-19 (OR 0.66, 95% CI 0.45–0.97, p= 0,04, I^2= 0%). In this case, oral vitamin C intervention can reduce the mortality rate in Covid-19 patients by 66% compared to the control group. The results of the second meta-analysis showed that the use of IV vitamin C had no effect (OR -0.21, 95% CI -2.70-2.28, p= 0,87, I^2= 94) on the duration of hospitalization for Covid-19 patients.

Based on the funnel plot analysis results obtained in Figures 3 and 5, the asymmetric distribution of the data indicates a high publication bias. These results can be caused by many factors, such as the small number of studies used and the lack of databases used. [24]

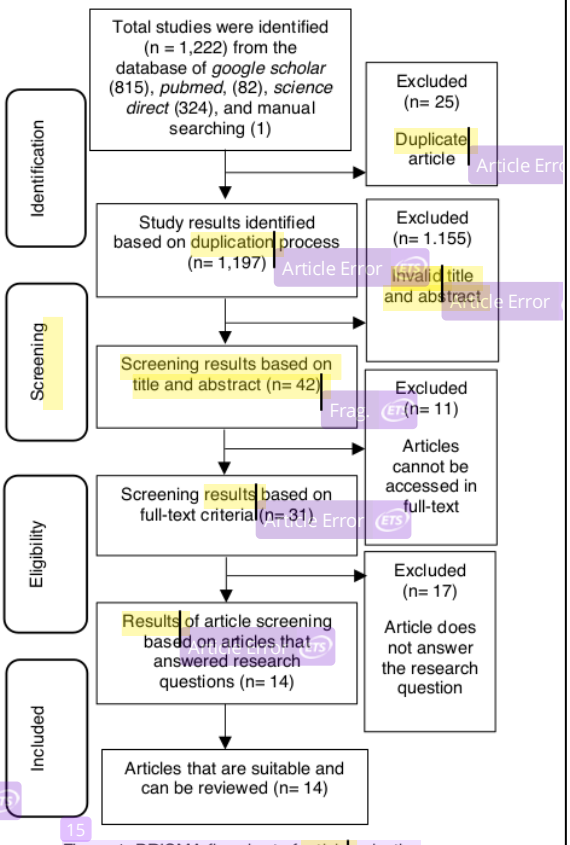

Figure 1. PRISMA flowchart of article selection

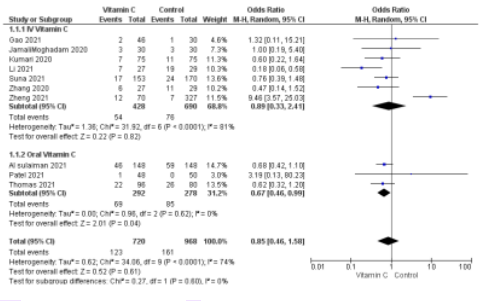

Figure 2. Forest plot analysis of IV and oral vitamin C on mortality outcomes

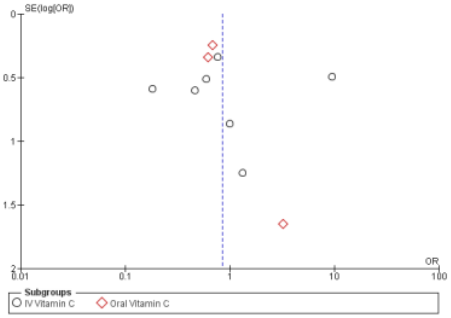

Figure 3. Results of funnel plot analysis of IV and oral vitamin C on mortality outcomes

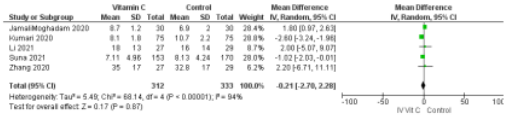

Figure 4. Forest plot analysis of vitamin C IV on inpatient outcomes

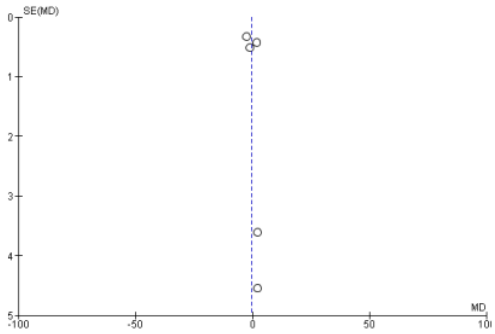

Figure 5. Results of the funnel plot analysis of vitamin C IV on inpatient outcomes

No	Author, Year of Publication, and Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
1	JamaliMoghadam, Saeidreza et al., 2020, Iran	RCT	Administration of vitamin C to 60 severe COVID-19 patients at Ziaeian Hospital, Iran from April - May 2020 was divided into two groups	Group I: vitamin C lovinapir/ritonavir and HCQ Group II: only lovinapir/ritonavir and HCQ	IV	6 grams vitamin C per day	5 days	Primary	There was an improvement in temperature in both groups, can reduce fever (p= 0,001)	Unknown
2	Kumari, Poona et al., 2020, Pakistan	RCT	Administration of vitamin C to 150 Covid-19 patients at Karachi Hospital from March – to July 2020 which was divided into two groups	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	50 mg/kg BW/day	4 weeks	Primary	Symptoms improved (fever, dry cough, anosmia, and diarrhea) more quickly (5-9 days) (p= 0,001) and hospitalization time (7-9 days) (p= 0,001) compared to the control group.	Unknown
3	Zhang, Jing et al., 2020, China	RCT	Administration of vitamin C to 56 patients with severe COVID-19 in the ICU of three hospitals in China from February to March 2020 which was divided into two groups	Group I: vitamin C Group II: bacteriostatic infusion	IV	12 grams 2 times a day	7 days	Primary	Did not affect the use of mechanical ventilation (p= 0,57)	Unknown
4	Li, Matthew et al., 2021, United States of America	*Cohort Retrospective*	Administration of vitamin C to 56 Covid-19 patients from April – to May 2020	Group I: vitamin C, hydrocortisone, and thiamine Group II: only standard therapy	IV	1.3 grams 4 times a day	4 days	Primary	Did not affect mortality (p= 0,05) and hospitalization duration (p= 0,71)	Unknown
5	Gao, Dengfeng et al., 2021, China	*Cohort Retrospective*	Administration of vitamin C to 76 Covid-19 patients in the ICU of the China Hospital	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	Loading dose of 6 grams of vitamin C IV twice a day on the first day	28 days	Primary	Reduced mortality (p= 0,03)	Unknown

			which was divided into two groups			followed by 6 grams a day the next day				
6	Hakamifard, Atousa et al., 2021, Iran	RCT	Administration of vitamin C and vitamin E to 72 Covid-19 patients with pneumonia in Iran	Group I: vitamin C, vitamin E, and standard therapy Group II: only standard therapy	Oral	Vitamin C: 1000 mg per day Vitamin E: 400 IU per day	7 days	Primary	Vitamin C and vitamin E did not have a significant effect on Covid-19 patients (p= 0,380)	Unknown
7	Suna, Kavurgaci et al., 2021, Turkey	*Cohort Retrospective*	Administration of vitamin C to 323 Covid-19 patients in Turkey in September 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 grams per day	30 days	Primary	Did not affect hospitalization duration (p= 0,05) and mortality (p= 0,52)	Unknown
8	Zheng, Shaoping et al., 2021, China	*Cohort Retrospective*	Administration of vitamins to 397 severe COVID-19 patients in China in February 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 – 4 grams per day	7 days	Primary	Did not affect mortality and symptom improvement (p= >0,05)	Unknown
9	Liu, Fang et al., 2020, China	RCT	IV administration of vitamin C to 308 patients in two ICUs in China	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	12 grams 2 times a day	7 days	Primary		Unknown
10	Majidi, Nazanin et al., 2021, Iran	RCT	Administration of vitamin C to 69 Covid-19 patients in Iran in May-June 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	Oral	500 mg per day	14 days	Primary	Reduced the average duration of hospitalization in Covid-19 patients four days faster than the control group (p = <0,01)	Unknown
11	Al Sulaiman, Khalid et al., 2021, Saudi Arabia	*Cohort Retrospective*	Administration of vitamin C to 739 severe COVID-19 patients in Saudi Arabia from March – to December 2020	Group I: were given vitamin C Group II: were not given vitamin C	Oral	1000 mg per day	30 days	Primary	Did not affect mortality (p= 0,11)	Unknown

12	Thomas, Suma et al., 2021, United States of America	RCT	214 Covid-19 patients were divided into four groups	Group I: Standard therapy (anti-viral) Group II: Vitamin C Group III: Zinc gluconate Group IV: Vitamin C and Zinc gluconate	Oral	50 mg zinc per day 8000 mg vitamin C (2-3 times a day)	10 days	Primary	There was no significant difference (p = 0.45) in the treated group (reduction of symptoms such as fever, shortness of breath, or fatigue)	Nausea, diarrhea, and stomach cramps in the vitamin C group
13	Ried, Karin et al., 2021, Australia and Turkey	RCT	237 Covid-19 patients were divided into two groups	Group I: HCQ, AZM, zinc Group II: HCQ, AZM, zinc, and IV C + all groups were given vitamin D3	Oral zinc IV vitamin C	Zinc citrate: 30 mg Vitamin D: 5000 IU Vitamin C: 50 mg/kg (divided by 4 times on the first day); 100 mg/kg (divided 4 times per day on the next 6 days)	14 days	Primary	Significantly faster recovery in the group with IV vitamin C (p= 0,0069)	Diarrhea, nausea, and vomiting in both groups
14	Margolin, Leon et al., 2021, United States of America	*Cohort*	113 individuals were given over the counter (OTC) products as treatment and prophylaxis	Group I: were given OTC (zinc, vitamin C, vitamin D, vitamin E, quinacl-lysine, azithromycin, and doxycycline) Group II: were not given OTC drugs	Oral	Zinc: 25 mg Vitamin C: 1000 mg Vitamin D: 1000 IU	5 days	Primary	Effective in treating mild to moderate symptoms (p = 0.04) at 2 doses/day, with no or only minimal addition to prescription (other standard antibiotics)	Unknown

DISCUSSION

This systematic review assessed studies related to the effectiveness, dosage, and side effects of vitamin C administration either alone or in combination up to April 25, 2022. Based on these results, eight of the 14 studies showed notable results according to the significant values obtained from the statistical test.

The effectiveness of vitamin C on outcomes in Covid-19 patients

The first outcome was the duration of hospitalization, and five studies assessed the variable duration of hospitalization as an outcome of the effectiveness of the therapy given. The meta-analysis results showed that the results were insignificant (p= 0.87). One of the studies[11] found that giving IV vitamin C at a dose of 50 mg/kg BW/day significantly (p= 0.0001) could reduce the duration of hospitalization by six to ten days faster than in the control group. A prior study[22] supported this finding and revealed that administering a combination of oral vitamin C at a dose of 100 mg per day, vitamin D, and zinc showed a significant (p = 0.00069) reduction in the duration of hospitalization compared to the control group. However, not all measurements of normal levels in the blood are carried out either before or after supplementation. Consequently, it cannot determine whether the levels in the blood are within normal limits.

The second outcome was symptoms, and five studies assessed this variable as an outcome of the effectiveness of the therapy given. The results of the study[10] explained that giving IV vitamin C significantly (p= 0.001) could reduce symptoms in the form of fever. This statement is in line with other studies[11,22,23], which found that giving IV vitamin C significantly (p<0.05) could reduce symptoms in the form of fever and the duration of pain was shorter than in the control group.

The third outcome was mortality, and two studies showed a decrease in mortality rates[12,18]. These studies showed significantly reduced mortality (p= 0.03 and p= 0.05) in the treatment group. The meta-analysis results for mortality outcomes showed significant results (p = 0.04) in the sub-group using oral vitamin C in asymptomatic to moderately symptomatic Covid-19 patients. Compared with the previous meta-analysis[25,26], it was explained that the administration of vitamin C did not affect Covid-19 patients. The distinction between the findings of previous studies and our study could be due to differences in research design. The prior study only used one study design, RCT. Other causes were found in the outcomes assessed[27,28]. Both studies used the outcome of using mechanical ventilation and duration of stay in the ICU. The patient's condition was already severe, making the effectiveness of a supplement decrease, therefore could give insignificant results. [27] Another reason for the difference in results could be due to many factors such as clinical classification of patients, advanced age, and comorbidities which are groups prone to worsening symptoms and even death. Comorbidities that aggravate the patient's condition include metabolic diseases, for instance, diabetes mellitus and hypertension, a history of smoking, and chronic lung disease (asthma, COPD, and chronic bronchitis).[26]

Therapeutic dose, method of administration, and duration of administration of vitamin C on outcomes for Covid-19 patients

Oral administration of vitamin C has been described by prior studies[14,19–21,23] using vitamin C at a dose of 500-1000 mg and 8000 mg per day. IV administration of vitamin C was used in other studies[10,12,16–18,22,23] using doses of 1.3 grams per day, 2-12 grams per day, 50 mg/kg BW/day, and 100 mg/kg BW/day. Oral vitamin C available in 100 mg, 250 mg, 500 mg, and 1000 mg, while for IV solutions are available in 100 mg/ml and 200 mg/ml.[16]

In general, dosing to get maximum results with minimal side effects needs to be considered based on the history of the disease, individual needs, over-the-counter drugs, and the costs involved. Based on cost-effective considerations, oral administration of vitamin C with a dose range of 500-1000 mg was significantly (p= 0.04) effective for

reducing mortality in asymptomatic Covid-19 patients to Covid-19 patients with moderate symptoms.

Side effects of vitamin C on outcomes for Covid-19 patients

Three of the 14 studies stated that there were side effects. These studies [12,21,22] conveyed similar side effects of vitamin C both orally and IV. Side effects manifested in digestive disorders include nausea, diarrhea, stomach cramps, and vomiting. IV administration of vitamin C still causes indigestion even though it is not as common as oral administration. [30] Digestive disorders in Covid-19 patients often occur because the ACE2 receptor is expressed in numerous body tissues. The digestive organs are receptors for the SARS-CoV-2 virus, which will activate ACE2 receptors in the digestive tract in the early stages of infection and cause digestive disorders. However, in the next phase, the symptoms of indigestion will decrease. On the condition that side effects arise, it is recommended to discontinue vitamin C since gastrointestinal disturbances might induce changes in gut microbes and increase pro-inflammatory cytokines.[31] Other side effects are lymphopenia, leukopenia, ARDS, shock, and sepsis. However, it has been confirmed that these side effects are not related to the administration of vitamin C.[12]

Apart from determining the dose and method of administering the drug, it is essential to consider the side effects due to supplementation. Multiple factors can induce side effects when consuming supplements, including the patient's medical history, such as gastritis, the degree of disease, reactions that may arise from each component, and the synergistic effect of the drug. The physician and other health professionals must ascertain this point to determine which factor these side effects emerge. Whether it is purely due to supplementation in the absence of other factors, the supplementation administration should be reconsidered. [32]

This systematic review is not without limitations, such as the limited number of similar study designs, thus using a combination of RCT and cohort study designs. Furthermore, not all studies include complete data, such as data on expected levels of vitamin C in human blood samples, follow-up data for patients after treatment, and strategies for dealing with lost follow-up patients. Lastly, there is heterogeneity in the meta-analytical assessment of IV vitamin C due to the heterogeneous population. Despite these limitations, our study engaged a plentiful entry consisting of 2,870 participants from fourteen studies with a low risk of bias from all articles.

CONCLUSION

Based on the meta-analysis conducted in this study, we found that oral administration of vitamin C has a significant effect ($p = 0.04$) on the mortality rate of Covid-19 patients, and the use of IV vitamin C showed no significant effect ($p = 0.87$) on the duration of hospitalization for Covid-19 patients. Other outcomes, in particular symptoms, can not measure the effectiveness of therapy due to the limitations of the participants involved in the study. In consideration of cost-effectiveness, oral administration of vitamin C with a dosage range of 500-1000 mg demonstrated efficacy in reducing mortality rates in Covid-19 patients. Side effects due to supplementation consumption include digestive disorders such as nausea, diarrhea, stomach cramps, and vomiting.

ACKNOWLEDGEMENT

We would like to thank Achmad Ilham Tohari for the technical assistance in the meta-analysis table.

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ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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7 Corrado Cordova, Francesco Violi, Cesare Alessandri, Stefania Basili, Roberto Barsi, Mirella Saliola, Michele Paradiso. "Improvement of blood gas levels after calcium-heparin treatment in patients with chronic obstructive pulmonary disease", Thrombosis Research, 1992 — 1%
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