



INTRAVENOUS VITAMIN C FOR COVID-19

Based on available evidence up to 16 November 2020

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) which began in Wuhan, China in December 2019, has caused a total of more than 46 million confirmed SARS-CoV-2 infections, including more than 1.2 million deaths.¹ Infected patients presented predominantly with fever and cough as well as dyspnoea and myalgia.² Some proportion of confirmed cases developed severe disease which involves acute lung injury and acute respiratory distress syndrome (ARDS) which can precipitated into multiple organ failure and death.² It has been reported that this is a result of host immune response dysfunction - a 'cytokine storm', most often denotes an injurious and hyperactive immune responses. These are characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators which often contributes to sepsis and septic shock in critically-ill COVID-19 patients.³

In the absence of an approved vaccine, a number of empirical therapeutic approaches have emerged including intravenous (IV) vitamin C administration in critically-ill patients with COVID-19. Vitamin C, or ascorbic acid, is essential for a normal and well-functional host defense mechanism.⁴ It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity as well as attenuating oxidative stress or inflammation, enhancing immune cell function and improving vasopressor synthesis.⁴

EVIDENCE on EFFECTIVENESS and SAFETY

There were two articles retrieved from the scientific databases (Medline, EMBASE, PubMed) and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on IV Vitamin C on COVID-19 and two articles on non-COVID-19 critically-ill patients.

Effectiveness of IV vitamin C in COVID-19 patients

Hiedra et al conducted case series of 17 patients found positive for SARS-CoV-2 via single-test nasopharyngeal swab PCR, who were requiring 30% or more fraction of inspired oxygen (FiO₂) and who received IV vitamin C as part of the COVID-19 treatment.⁵ These patients were treated in the progressive care and medical intensive care units. The inflammatory markers including D-dimer and ferritin, were compared pre- and post-treatment. Vitamin C was administered at a dose of 1 g every 8 h for three days. Inpatient mortality rate was reported to be 12% with 17.6% rates of

intubation and mechanical ventilation. There was a significant decrease in inflammatory markers, including ferritin and D-dimer, and decreasing trend of FiO₂ requirements, after vitamin C administration.⁵

Another article was a case report on a 74 year old woman with no recent sick contacts or travel history presented with fever, cough, and shortness of breath.⁶ Chest radiography revealed air space opacity in the right upper lobe, suspicious for pneumonia. A nasopharyngeal swab for SARS-CoV-2 came back positive while the patient was in the airborne-isolation unit. Laboratory data showed lymphopenia and elevated lactate dehydrogenase, ferritin, and interleukin-6. The patient was initially started on oral hydroxychloroquine and azithromycin. On day 6, she developed ARDS and septic shock, for which mechanical ventilation and pressor support were started, along with infusion of high-dose intravenous vitamin C. The patient improved clinically and was able to be taken off mechanical ventilation within 5 days.⁶

An unpublished Malaysian study was conducted among critically ill COVID-19 patients in two different tertiary hospitals, comparing those treated with high dose vitamin C against those without.⁷ Both groups showed similar clinical background, comorbidity, illness severity, and severity score on admission. All of the patients were on oxygen support in which 12 out of the 14 were on ventilator support. The mortality rate in the group treated with vitamin C was lower (14.3%) compared to those not treated (71.4%). Duration of days on the ventilator were shorter in the vitamin C group compared to non-vitamin C group (14 vs 19.6 days). Similarly, the duration to complete weaning of oxygen therapy was also shorter in vitamin C group (16 vs 23.5 days).⁷

A multicenter randomised controlled trial is currently underway evaluating the effectiveness of high-dose IV vitamin C for the treatment of severe COVID-19.⁸

Effectiveness of IV vitamin C in Non-COVID-19 patients

There were two articles on effectiveness of IV vitamin C on non-COVID-19 patients were retrieved. A recent meta-analysis study assessed the effect of Vitamin C on ventilation time among patients in the intensive care unit.⁹ Based on eight studies (685 patients) included in the meta-analysis, the researchers found that vitamin C shortened the length of mechanical ventilation on average by 14% ($p < 0.0001$). Significant heterogeneity in the effect of vitamin C existed between the trials, which was fully explained by the ventilation time in the untreated control group. Vitamin C was found most beneficial in patients with the longest ventilation, corresponding to the most severely ill patients. Among 471 patients (in five trials) requiring ventilation for more than 10 hours, a dosage of 1 to 6g/day of vitamin C shortened ventilation time on average by 25% ($p < 0.0001$).

Another meta-analysis included 18 controlled trials with a total of 2004 patients, evaluated the effect of IV vitamin C in critically-ill patients without COVID-19, in terms of length of stay in the

intensive care unit (ICU) and duration of mechanical ventilation.¹⁰ Patients undergoing cardiac surgery were studied in 13 trials, patients with sepsis in two trials, lung contusion patients in two trials, and burns patients in one trial. In 12 trials with 1766 patients, vitamin C reduced the length of ICU stay on average by 7.8% (95% CI: 4.2%, 11.2%; $p = 0.00003$). In six trials, orally administered vitamin C in doses of 1–3 g/day (weighted mean 2.0 g/day) reduced the length of ICU stay by 8.6% ($p = 0.003$). In three trials in which patients needed mechanical ventilation for over 24 hours, IV vitamin C shortened the duration of mechanical ventilation by 18.2% (95% CI 7.7%, 27%; $p = 0.001$).

Evidence on Safety

There was no adverse event directly related to the administration of vitamin C were reported from the included studies.^{6,10}

CONCLUSION

The retrieved low level of evidence suggested that IV vitamin C may have potential to be used in patients with moderate to severe COVID-19 disease. There was high level of evidence on non-COVID-19 critically-ill patients which suggested that IV vitamin C shortened the length of mechanical ventilation and reduced the length of ICU stay.

While robust evidence for the treatment of COVID-19 patients with IV vitamin C is not yet available, a randomised controlled trial is underway. Until then, evidence from non-COVID-19 suggested that IV vitamin C may be a safe and promising adjunct therapy for critically-ill patients with sepsis and related complications.

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Disclosure: The authors of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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