Effectiveness of vitamin C to treat COVID-19: an overview

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Disclaimer: this report has not been peer-reviewed.

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Executive summary

1. Background
The Coronavirus disease 2019 (COVID-19) is a public health emergency of international concern. As there is currently no effective treatment, the evidence from randomised controlled trials to support treatment against COVID-19 is urgently needed. The Institute for Complementary and Integrative Medicine (Zurich, Switzerland) has prepared this overview to summarise the effectiveness of vitamin C for treating patients with COVID-19, and to identify the ongoing randomised controlled trials.

2. Methods
Narrative review of relevant studies. We conducted literature searches to identify documents published till 8 April 2020. We consulted electronic databases, evidence-based collections, websites of relevant organisations, and trial registries.

3. Conclusions
Effectiveness of vitamin C for treating patients with COVID-19
We have not found scientific evidence of the beneficial effects of vitamin C (oral or intravenous) for treating COVID-19.

Ongoing randomised controlled trials of vitamin C for treating patients with COVID-19
One ongoing randomised placebo-controlled trial (ClinicalTrials.gov Identifier: NCT04264533) on the intravenous infusion of vitamin C in patients with COVID-19 is being conducted in China. Its results will not be available before October 2020.
1. Introduction

Coronavirus disease 2019 (COVID-19), previously called '2019 novel coronavirus' (2019-nCoV), is an acute respiratory disease. It is caused by the coronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2).

An outbreak of COVID-19 was first reported in Wuhan in December 2019. COVID-19 has rapidly spread to other parts of China and globally, including Switzerland. As declared by the World Health Organization (WHO) on 11 March, COVID-19 is "public health emergency of international concern". The pandemic is overloading healthcare facilities worldwide.

There is currently no effective treatment against COVID-19. The optimal selection of antiviral agents and interventions targeting the virus is unknown. Therefore, evidence from randomised controlled trials (RCTs) to support specific treatment against COVID-19 is urgently needed.

There is a widespread belief that vitamin C strengthens the immune system and therefore, could work for treating or preventing respiratory infections, such as the common cold. Besides, there is some evidence that suggests that vitamin C might help to manage the immunopathologic responses contributing to the pathogenesis of severe respiratory viral infections (1, 2).

The Institute for Complementary and Integrative Medicine has prepared this report to summarise the available evidence concerning vitamin C for the treatment of COVID-19.

2. Aims of the report

This report has two specific objectives.

1. To summarise the effectiveness of vitamin C to treat patients with COVID-19.
2. To identify the ongoing RCTs of vitamin C in patients with COVID-19.

3. Methods

Narrative review.

Sources consulted (March 8th, 2020): UpToDate, Epistemonikos, MEDLINE (via PubMed), and The Cochrane Library. Screening the bibliography of relevant studies.

4. Results

Appendix 1 details the documents that we assessed for this report.

Objective 1: effectiveness of vitamin C to treat patients with COVID-19

a. Indirect evidence: effectiveness of vitamin C to treat non-COVID-19 viral infections

The effectiveness of vitamin C to treat non-COVID-19 viral infections has not been proven in recent Cochrane reviews (3, 4) and randomised controlled trials (RCTs) (5, 6).

One Cochrane review published in 2013 (3) meta-analysed seven placebo-controlled comparisons (7-13) testing 0.2 g/day or more of vitamin C administered orally starting after the onset of the cold symptoms. This review showed no consistent effect on the duration or severity of common cold symptoms.

Another Cochrane review (4) identified two trials evaluating the effects of vitamin C compared to not giving vitamin C (14) or placebo (15) in patients with community-acquired pneumonia (14) or pneumonia and bronchitis (15). One trial studied adults with a wide age range and found a dose-dependent reduction in the duration of pneumonia with two vitamin C doses; however, the trial presented a high risk of bias (14). The other trial was adequately randomised and found lower mortality and reduced severity in the vitamin C group, but this benefit was restricted to the most severely ill patients (15).

The CITRIS-ALI trial:

The CITRIS-ALI (6) is a randomised placebo-controlled trial (n=167) published in 2019. This trial evaluated the 96-h infusion of vitamin C in patients with sepsis and non-COVID-19 acute respiratory distress syndrome (ARDS). Vitamin C did not improve the primary outcome of organ dysfunction scores or the markers of inflammation and vascular injury. However, it reduced the secondary outcome 28-day mortality from 46.3% to 29.8%. This absolute risk reduction of 16.5% [95% CI: 2% to 31.1%] implies that 165 deaths would be avoided.
per 1000 patients treated with vitamin C (ranging from 20 to 311).

The reported reduction in mortality in this trial might stimulate the interpretation that the infusion of high doses of vitamin C in patients with COVID-19 might reduce mortality. However, this evidence is indirect, as the patients in this trial did not suffer from COVID-19. Moreover, 28-day mortality was just one of the forty-six pre-specified secondary endpoints evaluated in this trial (no other outcome showed statistically significant differences between treatment conditions).

The VITAMINS Trial:
This international multicentre RCT, published in 2020, concluded that treatment with intravenous vitamin C, hydrocortisone, and thiamine in intensive care patients with septic shock did not lead to a more rapid resolution of the septic shock, as compared with intravenous hydrocortisone alone (5).

b. Direct evidence: effectiveness of vitamin C to treat COVID-19 infections
It has been claimed that large doses of vitamin C might be beneficial in the treatment of COVID-19 (16). However, we have not found current scientific evidence to support the usage of vitamin C to prevent or treat COVID-19.

This absence of evidence does not imply that vitamin C is not effective. It means that we still don’t know for sure if it’s effective or not. However, in the case of vitamin C, if we extrapolate the highly certain evidence about its lack of effectiveness in other infections (see above), the conclusion is that vitamin C probably does not benefit patients with COVID-19.

Objective 2. To identify ongoing trials of vitamin C to treat COVID-19
To identify treatment options as soon as possible is critical to alleviating the impact of the COVID-19 outbreak. The WHO has published a list of candidate therapeutics (17), which does not include any vitamin C intervention.

We have found one ongoing RCT that could provide more information on the effects of vitamin C in the treatment of COVID-19 (ClinicalTrials.gov Identifier: NCT04264533). Prof. Peng (Wuhan University) leads this study, which started in February 2020 at Zhongnan Hospital of Wuhan University (China). As the date of this report (8th April 2020) the trial was still recruiting patients. The estimated final data collection date for the primary outcome is 30th September 2020.

This RCT will evaluate the effects of high doses of intravenous vitamin C in intensive care adult patients with severe or critical ARDS due to 2019-nCoV infection. The study will compare the infusion of vitamin C (12 grams in a total volume 50ml of sterile water), twice a day for seven days, as compared to placebo (infusion of 50 ml of sterile water only, also twice a day for seven days).

We have not found serious methodological limitations in the design of this study. It is a phase 2 parallel RCT (allocation ratio 1:1). According to the study register, participants, care providers and outcomes assessors will be blinded, which will give more confidence in the study results. One potential study limitation is its small sample size (a total of 140 patients), which implies that the study may not be properly powered to detect differences in the primary outcome (28-days mortality), if they exist. Another potential limitation will be the applicability of the study results. The RCT will exclude some patients that are frequent in the ICU, such as patients with dyspnoea due to cardiogenic pulmonary oedema or patients who had previous home oxygen therapy. Besides, the trial will exclude “patients with expected life is less than 24 hours”, but the registry does not report the criteria to identify such patients.

5. Conclusions
We have not found scientific evidence of the effects of vitamin C for treating COVID-19. This absence of evidence does not imply that vitamin C is not effective. It just means that we don’t have data supporting its effectiveness. However, if we extrapolate the highly certain evidence about the lack of effectiveness of vitamin C in non-COVID-19 infections, we conclude that vitamin C probably does not benefit patients with COVID-19.
One ongoing randomised placebo-controlled trial on intravenous administration of vitamin C might provide more information on the effects of vitamin C in the treatment of COVID-19 ([ClinicalTrials.gov Identifier: NCT04264533](https://clinicaltrials.gov/ct2/show/NCT04264533)). The trial is ongoing in China and its results will not be available before October 2020.
Appendix 1: Documents that were assessed for this report

a. Clinical guidelines
1. WHO Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Interim guidance. 13 March 2020 (18)
2. Handbook of COVID-19 Prevention and Treatment, the First Affiliated Hospital, Zhejiang University School of Medicine
3. CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) (19)
4. ECDC. COVID-19 (20)

b. Systematic reviews

c. Evidence summaries
Bibliography

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