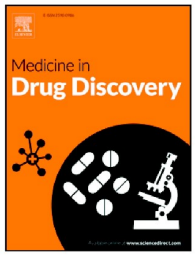
Journal Pre-proof



Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

Richard Z. Cheng

PII: S2590-0986(20)30015-4

DOI: https://doi.org/10.1016/j.medidd.2020.100028

Reference: MEDIDD 100028

To appear in: *Medicine in Drug Discovery*

Received date: 19 March 2020

Revised date: 23 March 2020

Accepted date: 24 March 2020

Please cite this article as: R.Z. Cheng, Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?, *Medicine in Drug Discovery* (2020), https://doi.org/10.1016/j.medidd.2020.100028

Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

Richard Z. Cheng*

Cheng Integrative Health Center, Columbia, SC 29212, U.S.A.

*Corresponding author: richzc@gmail.com

The COVID-19 (SARS-2-Cov) pandemic, first reported in Wuhan, China, is now spreading to many continents and countries, causing a severe public health burden. Currently, there is no vaccine or specific antiviral drug for this deadly disease. A quick, deployable and accessible, effective and safe treatment is urgently needed to save lives and curtail the spreading. Acute respiratory distress syndrome (ARDS) is a key factor of fatality. Significantly increased oxidative stress due to rapid release of free radicals and cytokines is the hallmark of ARDS which leads to cellular injury, organ failure and death. Early use of large dose antioxidants, such as vitamin C (VC) may become an effective treatment for these patients. Clinical studies also show that high-dose oral VC provides certain protection against viral infection. Neither intravenous nor oral administration of high-dose VC is associated with significant side-effects. Therefore, this regimen should be included in the treatment of COVID-19 and used as a preventative measure for susceptible populations such as healthcare workers with higher exposure risks.

Coronaviruses and influenza are among the pandemic viruses that can cause lethal lung injuries and death from ARDS [1-3]. Viral infections could evoke “cytokine storm” that leads to lung capillary endothelial cell activation, neutrophil infiltration and increased oxidative stress (reactive oxygen and nitrogen species). ARDS, characteristic of severe hypoxemia, is usually accompanied by uncontrolled inflammation, oxidative injury and damage to the alveolar-capillary barrier [4]. Increased oxidative stress is a major insult in pulmonary injury including acute lung injury (ALI) and ARDS, two clinical manifestations of acute respiratory failure with substantially high morbidity and mortality [5,6].

In a report of 29 patients with COVID-19 pneumonia, 27 (93%) showed increased hsCRP, a marker of inflammation and oxidative stress [7]. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. VC, an important component of the cellular antioxidant system [8], is beneficial to critical care management [9]. Cytokine storm is observed in both viral and bacterial infections [3] and results in increased oxidative stress via a common and non-specific pathway. Since the prevention and management of oxidative stress could be realized by large dose of antioxidants, this approach may be applicable to COVID-19 with intravenous high-dose VC based on the outcome of three previous clinical studies involving a total of 146 patients with sepsis [10].

Hemila and colleagues reported that various high-dose intravenous VC infusions (e.g., 200 mg/kg body weight/day, divided into 4 doses) shortened the intensive care unit (ICU) stay by

97.8% [11], accompanied by a significant reduction in the mortality rate [12]. Such an experience was reproduced among patients ill with severe influenza [13,14]. Indeed, dietary antioxidants (VC and sulforaphane) were shown to decrease oxidative stress induced acute inflammatory lung injury in patients receiving mechanical ventilation [15]. In addition, oral VC (e.g., 6 g daily) was able to reduce viral infection risk [16] or to improve symptoms [17].

High-dose intravenous VC has also been successfully used in the treatment of 50 moderate to severe COVID-19 patients in China. The doses used varied between 2 g and 10 g per day, given over a period of 8 to 10 hours. Additional VC bolus may be required among patients in critical conditions. The oxygenation index was improving in real time and all the patients eventually cured and were discharged [18]. In fact, high-dose VC has been clinically used for several decades and a recent NIH expert panel document states clearly that this regimen (1.5 g/kg body weight) is safe and without major adverse events [19].

Because the development of efficacious vaccines and antiviral drugs takes time, VC and other antioxidants are among currently available agents to mitigate COVID-19 associated ARDS. Given the fact that high-dose VC is safe, healthcare professionals should take a close look at this opportunity. Obviously, well-designed clinical studies are absolutely needed to develop standard protocols for bedside use.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-Infected pneumonia in Wuhan, China. JAMA (2020), 323, 1061–9.

2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (2020), 395, 507–13.

3. Fowler III AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, Fisher BJ, Syed A, DeWilde C, Priday A, Kasirajan V. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med (2017), 6, 85–90.

4. Meng L, Zhao X, Zhang H. HIPK1 Interference attenuates inflammation and oxidative stress of acute lung injury via autophagy. Med Sci Monit (2019), 25, 827–35.

5. Yan X, Fu X, Jia Y, Ma X, Tao J, Yang T, Ma H, Liang X, Liu X, Yang J, Wei J. Nrf2/Keap1/ARE signaling mediated an antioxidative protection of human placental mesenchymal stem cells of fetal origin in alveolar epithelial cells. Oxid Med Cell Longev (2019), 2019:2654910.

6. Hecker L. Mechanisms and consequences of oxidative stress in lung disease: therapeutic implications for an aging populace. Am J Physiol Lung Cell Mol Physiol (2018), 314, L642–53.

7. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi (2020), 43, E005.

8. Liu Q, Gao Y, Ci X. Role of Nrf2 and its activators in respiratory diseases. Oxid Med Cell Longev (2019), 2019:7090534.

9. Nabzdyk CS, Bittner EA. Vitamin C in the critically ill - indications and controversies. World J Crit Care Med (2018), 7, 52–61.

10. Li J. Evidence is stronger than you think: a meta-analysis of vitamin C use in patients with sepsis. Crit Care (2018), 22, 258.

11. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. Nutrients (2019), 11, 708.

12. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest (2017), 151, 1229–38.

13. High dose vitamin C and influenza: a case report. ISOM, cited on Feb 9 2020 (https://isom.ca/article/high-dose-vitamin-c-influenza-case-report/?from=groupmessage&isappinstalled=0).

14. Levy T. Primal Panacea. MedFox Publishing; 350 p. (Kindle Edition).

15. Patel V, Dial K, Wu J, Gauthier AG, Wu W, Lin M, Espey MG, Thomas DD, Jr CRA, Mantell LL. Dietary antioxidants significantly attenuate hyperoxia-induced acute inflammatory lung injury by enhancing macrophage function via reducing the accumulation of airway HMGB1. Int J Mol Sci (2020), 21, 977.

16. Kim TK, Lim HR, Byun JS. Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. BMJ Mil Health (2020), DOI: 10.1136/bmjmilitary-2019-001384.

17. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. J Manipulative Physiol Ther (1999), 22, 530–3.

18. Shanghai Expert Panel, cited on Mar 23, 2020 (http://mp.weixin.qq.com/s?__biz=MzA3Nzk5Mzc5MQ==&mid=2653620168&idx=1&sn=2352823b79a3cc42e48229a0c38f65e0&chksm=84962598b3e1ac8effb763e3ddb4858435dc7aa947a8f41790e8df2bca34c20e6ffea64cd191#rd).

19. High-dose vitamin C (PDQ®)–Health professional version. National Cancer Institute, cited on Feb 9 2020 (https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq).