

Possible effect of epinephrine in minimizing COVID-19 severity: a review

Journal of International Medical Research
48(9) 1–5

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DOI: 10.1177/0300060520958594

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Mahnaz Derakhshan^{1,2} ,
Hamid Reza Ansarian^{1,3,4,5} and
Mory Ghomshei^{1,6}

Abstract

Objective: Coronavirus disease 2019 (COVID-19) shows a wide range of severity, ranging from an asymptomatic presentation to a severe illness requiring intensive care unit admission. Identification of a strategy to manage the severity of this disease will not only help to reduce its case fatality but also help to remove some of the burden from the already overwhelmed health care systems. While successful management of symptoms in general is important, identifying measures to modify the severity of the illness is a key factor in the fight against this pandemic.

Methods: This paper presents a short literature review to suggest a new treatment modality for COVID-19.

Results: COVID-19 is less severe and rarely fatal in children than in adults, which could be caused by greater fluctuations of plasma epinephrine in children. Our literature survey endorses this hypothesis according to both the epidemiological and immunological findings.

Conclusion: Application of epinephrine pulses with a specific amplitude may be considered an intervention to minimize the severity of COVID-19.

Keywords

COVID-19, epinephrine, CD8+ T cells, circadian rhythm, adrenaline, epinephrine pulse

Date received: 1 May 2020; accepted: 21 August 2020

¹Conovita Technologies Inc., Winnipeg, Canada

²Queen Mary University of London Alumni, London, UK

³Easton Place Medical Center, Silkirk, Canada

⁴Interlake Medicentre, Stonewall, Canada

⁵University of Manitoba Alumni, Winnipeg, Canada

⁶British Columbia Institute of Technology, Burnaby, Canada

Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) began in December 2019 in China and has spread throughout many countries worldwide. The clinical

Corresponding author:

Mahnaz Derakhshan, Conovita Technologies Inc, 807 John Bruce Rd, Winnipeg, MB Canada R3X 1Y3; Queen Mary University of London Alumni, London, UK.

Email: mahnaz.derakhshan@gmail.com



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presentations of the disease are remarkably similar to those of viral pneumonia, and analysis of respiratory tract samples showed that it is caused by severe acute respiratory syndrome coronavirus 2.¹

The clinical spectrum of COVID-19 varies from asymptomatic to severe respiratory failure with a high risk of mortality, requiring intensive care unit (ICU) admission. Chinese guidelines define three levels of severity for COVID-19: mild, severe, and life threatening or critical.² In a recent study in China, 81% of cases were mild, with symptoms of the common cold, without pneumonia or with mild pneumonia; 14% were severe, with dyspnea, tachypnea, or other signs of significant pneumonia; and 5% were critical, requiring intensive care because of respiratory failure or multiple organ dysfunction.³

The relatively rapid spread of the disease is challenging the intensive care capacity of hospitals and exacerbating case fatality rates. Therefore, identification of a strategy to manage the severity of this disease will not only help to save more lives, but also could reduce the burden on already overwhelmed health care systems. Current studies indicate that the severity of the disease and case fatality ratio increase substantially with age, but young people are not at lower risk of infection than adults.⁴

There are several examples of a virus producing different degrees of severity in patients of various ages. As an example, most Epstein–Barr virus (EBV) infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis. In contrast, more than 70% of infections in adolescents present as infectious mononucleosis.⁵ This paper presents a brief study to highlight the differences among groups with different disease severities while focusing on finding a strategy to change the course of severe COVID-19 to a mild disease. Our literature review suggested that epinephrine

micro-pulses should be considered by clinical experts as a trial treatment.

Methods

We searched the literature for studies reporting epidemiological and immunological characteristics of COVID-19 patients to identify demographic groups in which COVID-19, or the common cold and flu in general, exhibited less severe presentations. We focused on identifying common underlying immuno-hormonal features across these demographic groups, particularly in children, soldiers on active duty, and people with asthma or Parkinson's disease.

Findings and discussion

According to the studies published to date, COVID-19 has an age selective pattern of severity. The Centers for Disease Control and Prevention reported that less than 3% of patients aged ≤ 19 years were hospitalized, with no ICU admissions or fatalities, while approximately $\geq 31\%$ of patients aged ≥ 85 years were admitted to hospitals, resulting in 6% to 29% ICU admissions and 10% to 27% case fatalities.⁶

In a cohort of 2500 cancer patients in France evaluated by M. Henry and colleagues, none of the patients developed a COVID-19 or an influenza-like infection. The authors attributed the lack of infection to the effect of methylene blue.⁷ However, we considered another cause, a possible constitutional difference in the immune response of cancer patients.

Likewise, although the incidence of the viral respiratory disease is higher among soldiers under stress than in civilians, the acute phase of the common cold is less severe, and the recovery is much faster in soldiers (who are under sustained operational stress) than in office workers.⁸

Kawaguchi and colleagues⁹ showed that people with Parkinson's disease are less susceptible to infection with colds than the general population, and those infections are also generally milder. This lack of susceptibility has no relationship with the severity of the disease, the time after onset of the disease, or the type of medications used. Although it is difficult to discern one causal factor to explain this finding, it is noteworthy that in Parkinson's disease patients, epinephrine pulses occur, resulting in tremor.^{10,11} This feature of autonomic dysfunction has no relationship with the severity of the disease, the time after onset of the disease, or the type of medications used. Similarly, we noticed that soldiers under sustained operational stress show a progressive increase in catecholamine levels.⁸ The common factor among these groups of people is pulses in the serum epinephrine level.

As for the effect of age, COVID-19 is clearly less severe in children than in adults. A report of 72,000 cases from China showed no COVID-19 fatalities among children, while the fatality rate was the highest in the group aged 70 years or older.³ There are many mechanisms involved in the age-selective pattern of severity. We noticed that one difference between these two age groups is the circadian variation of the epinephrine level. The circadian amplitude of the epinephrine rhythm is higher in children than in the elderly.¹² We assume that the difference in COVID-19 severity in children, compared with adults, could be related, to some extent, to their greater epinephrine fluctuations.

To evaluate the effect of epinephrine fluctuations, it would be of a great value to determine whether any difference in COVID-19 severity exists among those using β_2 -agonist asthma inhalers versus others. In a recent study, Chhiba and colleagues¹³ showed that although asthma is

considered a high medical risk factor for susceptibility to COVID-19 infection, it is not associated with an increased severity or higher risk of hospitalization. To explain this paradox, Cashman¹⁴ assumed that EDTA excipients in nebulized β_2 -agonist medicines were responsible for the decreased severity of COVID-19 in patients with asthma. We suggest that this effect could be related to nebulized β_2 -agonist medication use per se, which mimics the micro-pulses of epinephrine. However, in light of emerging data from physiological research, the severity of COVID-19 could, theoretically, be related to the kinetics of the immune response in the human body, similar to the manner in which the severity of EBV infection correlates with the CD8+ T cell level in the blood.⁵

In a recent study, Thevarajan and colleagues¹⁵ showed how the kinetics of the immune response in COVID-19 affect the clinical outcome. Similarly, Wang and colleagues¹⁶ showed the importance of robust CD8+ T cells in protecting against severe H7N9 disease. They provided evidence that in H7N9 disease, patients who rapidly recovered had early CD8+ T cell responses, and those who succumbed to the disease had little evidence of T cell activation. Their study also showed that natural killer cell activation depends on CD8+ T cell involvement.

In another review, Bucsek and colleagues¹⁷ summarized numerous studies and concluded that adrenergic stress can significantly affect the processes of many diseases by regulating immune cell activity. Although many studies have shown that adrenergic stress has an immune suppressive effect, Kohut and colleagues¹⁸ indicated that for mounting an anti-viral immune response, a certain degree of adrenergic signaling by catecholamines is required. Dimitrov and colleagues¹⁹ noted that effector CD8+ T cells were positively correlated with epinephrine oscillations, and their

population increased after low-dose epinephrine infusion.

These observations strongly suggest a positive effect of serum epinephrine pulses on attenuating the severity of COVID-19. They also indicate that this effect likely occurs through alteration of immune reactions.

Immune responses in COVID-19 appear to be a complex combination of different responses rather than a single cellular response, and many more studies are required to understand the kinetics of these immune responses. Discussing the full breadth and kinetics of the immune responses in COVID-19 is therefore beyond the scope of this work. Nevertheless, considering the above epidemiological information together with the other pieces of the immunological evidence that were presented, we suggest that epinephrine micro-pulses should be considered in trial treatments as a new measure for treatment of COVID-19.

Conclusion

As shown in the reviewed studies, we believe that epinephrine pulses, with a specific amplitude,¹⁹ could offer a protective effect against severe infection by a spectrum of cold and flu-like diseases including COVID-19. Collectively, it seems that epinephrine micro-pulses could be used to rearrange various immune defenses into a virus-focused response. This process could ameliorate the course and symptoms of severe COVID-19 infection. This treatment also could be used to improve the outcome of a prospective vaccination.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Mahnaz Derakhshan  <https://orcid.org/0000-0003-1369-3443>

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