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LETTER TO THE EDITOR

# Colchicine may not be effective in COVID-19 infection; it may even be harmful?

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Dear Editor,

Nowadays, the novel coronavirus disease 2019 (COVID-19) pandemic is spreading rapidly all over the world. The search for drugs against COVID-19 is continuing. Colchicine is used in many inflammatory diseases such as familial Mediterranean fever, Behçet's, gout, and pericarditis [1]. Colchicine disrupts the microtubule formation and reduces chemotaxis, phagocytosis, and migration of neutrophils [2].

COVID-19 enters the cell using the angiotensin-converting enzyme 2 (ACE2) as a host receptor and causes infection. Severe progression of COVID-19 infection in the elderly, patients with hypertension and obesity, and smokers suggests that the virus causes more severe infection at low cytosolic pH [3]. When the cytosolic pH is low, the virus increases its entry into the cell by penetrating to ACE2 [3]. Hydroxychloroquine, the synthetic derivative of quinine, increases cytosolic pH by effects $K^+/H^+$ exchanger and decreases viral load [3–5]. Colchicine is a microtubule inhibitor; microtubules play an important role in intracellular protein trafficking. $Na^+/H^+$ exchanger (NHE) is a powerful intracellular pH regulator ion pump [6]. NHE is abundant in microtubules and is involved in regulating intracellular and extracellular pH. Colchicine directly affects H-ATPase, causes volume loss, and also indirectly affects NHE [7]. Colchicine binds to microtubules in between acidic pH 6.7 and 6.8. Colchicine is binding very low in microtubules at other pH values [8]. Colchicine decreases intracellular pH for a short period after binding to microtubules; then, it increases intracellular pH [8, 9]. Its net effect is the increase in intracellular pH. However, as the pH increases, the binding of colchicine to microtubules decreases. As the colchicine level that binds to the microtubule decreases, the pH decreases again, and colchicine is re-bonded to the microtubule. Since colchicine is less bound to microtubule at alkaline pH, it cannot make intracellular pH highly alkaline [8, 9]. Therefore, colchicine may not be able to increase the intracellular pH to a level that prevents the virus from binding to ACE2. If the intracellular pH is low in the patient exposed to COVID-19, the viral load will increase. Angiotensin II ensures that intracellular pH is kept at optimum alkali values [9]. The effect of angiotensin II is very strong, and following acid loading, angiotensin II immediately brings the pH to normal or alkaline values [9]. Colchicine inhibits the intracellular pH-increasing effect of angiotensin II [10]. Colchicine slightly alkalizes the intracellular pH since it binds to the microtubule at acidic pH and suppresses the pH alkalizing effect of angiotensin II [7]. ACE2 displays its catalytic activity at pH 6.7 [11]. It is estimated that the virus binds ACE2 at acidic pH since hydroxychloroquine reduces the viral load by making pH elevation. The viral load reduction effect of colchicine can be quite weak since colchicine cannot strongly raise the pH like hydroxychloroquine. Recently, it has been suggested that colchicine may be effective in COVID-19 infection and reduce cytokine storm seen during the COVID-19 infection. Cytokine storms of COVID-19 often occur in patients with comorbid conditions, such as the elderly, hypertension, diabetes, obesity, and smoking. The cytokine suppressive effect of colchicine is also weak [12]. Since colchicine does not decrease intracellular pH enough, there will be a high viral load. As the viral load increases, the cytokine storms will be more severe.

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One of the most common causes of death in COVID-19 infection is acute respiratory distress syndrome (ARDS). Toxic doses of colchicine affect alveolar type II pneumocytes, inhibiting the release of surfactants and causing ARDS [13]. Even at therapeutic doses, colchicine may decrease the secretion of the surfactants. Multiorgan failure and disseminated intravascular coagulation (DIC) are also frequently observed during COVID-19 infection. Toxic doses of colchicine may cause multiorgan failure and DIC. The colchicine use in patients with COVID-19 may increase the risk of ARDS and DIC. Colchicine also interacts with macrolides and human immunodeficiency virus (HIV) drugs used to treat COVID-19 and may increase their serum levels [14]. In conclusion, colchicine may not be beneficial in patients with COVID-19 since its effects of increasing cytosolic pH and preventing cytokine storms are very weak. Colchicine may increase ARDS and multiorgan failure in COVID-19. We suggest that colchicine is not used in COVID-19.

## Compliance with ethical standards

**Disclosures** None.

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