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Consideration of immunomodulatory actions of morphine in COVID-19 – Short report

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Abstract. – Cytokine storm in COVID-19 is linked to disease severity and mortality. 40% of patients with severe COVID-19 require mechanical ventilation. Analgesia and sedation are used for treatment of pain, facilitation of mechanical ventilation, or management of acute agitation. Herein, we present the immunomodulating actions of morphine that may either improve or worsen the clinical course of COVID-19 once cytokine storm develops. A literature search was performed to find articles on potential immunomodulatory effects of morphine. Taken together, the results of *in vitro* and *in vivo* models in non-COVID-19 conditions suggest that morphine could have a beneficial effect by mitigating the cytokine storm in the early stages of severe COVID-19. In contrast, it could be potentially harmful in late stages of severe COVID-19, especially in the presence of septic shock.

Key Words:
Morphine, Immunomodulating effect, Cytokine storm, COVID-19.

Coronavirus (CoV) is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of CoVs include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV.

In late December 2019, cases of serious respiratory illness and death were first reported in Wuhan, China. Soon after, the number of cases soared dramatically, spreading across China and worldwide.

The World Health Organization (WHO) announced the official name of the disease as "coronavirus disease 2019 (COVID-19)". Since then, this potentially fatal disease with high transmission rates has become a great global public health concern. The analysis of the viral genome has revealed that the novel CoV is phylogenetically close to SARS-CoV. Therefore, the novel CoV has been named "SARS-CoV-2" by the International Committee on Taxonomy of Viruses (ICTV)[1].

Clinical features of COVID-19 include a wide spectrum of respiratory, cardiac, gastrointestinal, and renal symptoms. Laboratory findings oftentimes demonstrate leucopenia with lymphopenia [especially natural killers (NK)], elevated C-reactive protein (with normal procalcitonin), elevated ferritin and D-dimers. Clinical findings[2,3] showed exuberant inflammatory responses during SARS-CoV-2 infection, further resulting in uncontrolled pulmonary inflammation (diffuse alveolar disease), likely a leading cause of case fatality.

Significantly high blood levels of cytokines and chemokines were also noted in patients with COVID-19 infection. These included IL1-β, IL-1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA[4]. These cytokines are reasoned to promote disease severity[4]. In fact, cytokine storm (hyperinflammation, macrophage activation syndrome-like disease) has been linked to disease severity and increased fatality rates.

Predictors of fatality in a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included increased IL6 concentration, suggesting that mortality might be due to virally driven hyperinflammation which in consequence ends with general hypercytokinemia and multiorgan failure[5,6].

Hence, immunotherapy is being tested as one option of therapeutic interventions in COVID-19. Currently ongoing studies evaluate the efficacy of various immunomodulating agents, e.g.,

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convalescent plasma, immunoglobulins, glucocorticoids, recombinant human IL-6 receptor monoclonal antibody (Tocilizumab), JAK inhibitors (Jakotinib, Ruxolitinib), and chloroquine/hydroxychloroquine among others[7].

15% of patients with severe COVID-19 develops acute respiratory distress syndrome (ARDS) and 6% develops septic shock. About 40% of patients with severe COVID-19 requires mechanical ventilation[8]. Provision of analgesia and sedation is a core pharmacotherapeutic aspect of the care of critically ill patients. Patients in the intensive care units commonly require analgesia and sedation for treatment of pain, facilitation of mechanical ventilation, or management of acute agitation and psychoses. In addition to relieving discomfort, early treatment of pain with IV opioid agents (namely morphine or fentanyl) may allow patients to reach a desired light level of sedation without the additional need for increasing the dosage of IV sedatives.

Opioids produce analgesia by acting on receptors located on neuronal cell membranes. Three major types of opioid receptor, m, d and k (mu, delta and kappa), were defined. Opioid receptors are present in many regions of the nervous system that are involved in pain transmission and control, including primary afferent neurons, spinal cord, midbrain and thalamus. Morphine has considerably higher affinity for m receptors than for other opioid receptors[9].

In addition to pain management, consideration should be given to specific pharmacological treatment strategies for breathlessness. Low dose morphine has been shown to reduce safely and effectively breathlessness in patients with severe chronic obstructive pulmonary disease and refractory dyspnea. Numerous guidelines recommend opioids in this clinical setting. Breathlessness is a subjective experience derived from interactions between multiple physiological, psychological, social and environmental factors. It leads to significant distress, impaired physical and mental functioning[10].

Opioids are the most frequently prescribed class of medications to treat refractory breathlessness. The exact mechanisms by which opioids alleviate breathlessness are not fully understood. Possible mechanisms include altered central perception of breathlessness, reduced spontaneous respiratory drive, reduction in total ventilation, increased ventilatory efficiency with exercise, a reduction in responses to hypoxemia and hypercapnia, and an effect on bronchoconstriction[11].

The fear of respiratory depression and hastened death might be a major barrier to the use of opioids as first-line treatment for refractory breathlessness. To date, there have been no reports of respiratory depression from low dose oral opioids for dyspnea in the medical literature. While morphine has a role in palliating refractory breathlessness, the additional complexity and challenges of morphine prescription to respiratory patients reinforce the urgent need for further research in this clinical setting[11].

In vivo administration of morphine has been shown to depress delayed-type hypersensitivity reaction, cytotoxic T-cell activity, T-cell antigen expression, antibody production, NK cell activity, and neutrophil activity. Morphine produces immunosuppressive effects both at the proteomic and cellular levels. It affects both the innate and adaptive immunity *via* mu opioid receptor. It has been suggested that morphine can either exacerbate or improve infection. Of note, morphine treatment increases susceptibility of mice to bacteria or lipopolysaccharide (LPS). In contrast, morphine administered subcutaneously suppresses infections by *Mycobacterium* spp[12].

Fukuda et al[13] suggested that one of the factors that determine whether morphine exacerbates or inhibits infection is the timing of administration. Morphine treatment in mice before lipopolysaccharide (LPS) challenge suppressed lethal endotoxic shock. In contrast, when we administered after LPS, morphine exacerbated lethal endotoxic shock.

Histologic examination revealed a marked increase in the accumulation of infiltrates comprising polymorphonuclear leukocytes and mononuclear cells in the lung accompanied by the destruction of alveoli[13].

Plasma levels of TNF-α, INF-γ, MCP-1, and IL-12 in the group treated with morphine after LPS challenge were higher than those treated with morphine before LPS challenge. Morphine treatment before shock improved the survival rate of mice with LPS-mediated lethal endotoxic shock, and morphine treatment after shock decreased the rate of survival[13].

Zubelewicz et al[14] reported a significant increase of plasma corticosterone following morphine injection in adjuvant arthritis rats. Anti-inflammatory effects of centrally-injected morphine may arise from the activation of hypothalamic-pituitary-adrenal (HPA) axis resulting in the release of anti-inflammatory glucocorticoids.

The authors highlighted that central or peripheral injection of morphine may activate HPA axis and exert a potent anti-inflammatory action by

inhibiting NK cells activity and pro-inflammatory cytokines secretion (sequential suppression of INF-γ and TNF-α)[14].

Finally, the development of tolerance to endotoxin prevents sustained hyperinflammation during systemic infections. Banerjee et al[15] reported that chronic morphine treatment tempers endotoxin tolerance resulting in persistent inflammation, septicemia and septic shock.

Morphine was found to downregulate endotoxin/LPS induced miR-146a and 155 in macrophages. However, only miR-146a overexpression, but not miR-155 abrogates morphine mediated hyper-inflammation. Conversely, antagonizing miR-146a (but not miR-155) heightened the severity of morphine-mediated hyper-inflammation. These results suggest that miR-146a acts as a molecular switch controlling hyper-inflammation in clinical and/or recreational use of morphine[15].

Conclusions

Taken together, the results of *in vitro* and *in vivo* models in non-COVID-19 conditions suggest that morphine could have a beneficial effect by mitigating the cytokine storm in the early stages of severe COVID-19. In contrast, it could be potentially harmful in late stages of severe COVID-19, especially in the presence of septic shock.

This article has raised many issues in need of further investigation. More research using controlled trials is needed to determine the effect and timing of morphine administration in COVID-19 patients.

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Conflict of Interest
The Authors declare that they have no conflict of interests.

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