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Potential Sedative and Therapeutic Value of Dexmedetomidine in Critical COVID-19 Patients

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Abstract:

The coronavirus 2019 disease (COVID-19) is an ongoing outbreak of respiratory disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus can invade various tissues and organs, causing multiple organ dysfunctions. Critically ill COVID-19 patients may develop acute respiratory distress syndrome and pneumonia, which are the major causes of hypoxemic respiratory failure and death due to SARS-CoV-2 infection. Thus, ventilation support (invasive or noninvasive), has become a common practice in respiratory treatment of COVID-19 patients. Patients receiving mechanical ventilation usually require sedation to alleviate anxiety, pain and discomfort. On the other hand, current clinical reports have indicated that a significant number of COVID-19 patients require prolonged intensive care unit (ICU) care and ventilation, which increases the risk of delirium. Thus, selection of appropriate sedative medications during this period is of utmost importance. Dexmedetomidine (DEX) is a sedative, anxiolytic and analgesic agent that acts through the α_2-adrenoceptor. Its sedative property is notable due to the lack of respiratory depression. In addition, its cytoprotective, immunoregulatory and anti-inflammatory properties have been well established in preclinical settings. Based on these features, a number of recent studies have proposed DEX as a beneficial sedative agent that simultaneously mitigates the excessive inflammation and protects vital body organs in patients with severe COVID-19. In current brief review, we aimed to discuss the therapeutic benefits of DEX in managing different indications of COVID-19.

Keywords: SARS-CoV-2, sedation, multiple organ dysfunctions, ventilation, dexmedetomidine, inflammation

1. Introduction:

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, and subsequently spread worldwide. Currently, there is no certain and approved antiviral agent against the SARS-CoV-2 pneumonia named "coronavirus disease 2019" or "COVID-19". Clinical manifestations of COVID-19 range from asymptomatic infection to critical illness. The most common clinical symptoms in the patients are fever and cough, anorexia, weakness, shortness of breath in addition to other nonspecific symptoms, including headache, dyspnea, fatigue, muscle pain, and digestive symptoms such as diarrhea and vomiting. The patients are prone to developing lymphopenia, increased neutrophil count and thrombocytopenia. Moreover, elevated levels of infection-related markers, including C-reactive protein (CRP), fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), D-dimer, pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-a), creatinine and liver enzymes have also been associated with the severity of the COVID-19 in several studies.[1-3]

In the majority of cases the infections may be asymptomatic, mild, self-limiting, but in some cases the respiratory symptoms can rapidly progress to dyspnea, hypoxemia, and acute respiratory distress syndrome (ARDS) with a high risk of multi-organ dysfunction and death. General treatment strategies include bed rest, maintain nutritional and hemodynamic support, close monitoring of vital signs (including heart rate, temperature, blood pressure, pulse oximetry, respiratory rate, etc.).

Most of the current reports highlighted an elevated cytokine patterns among severely ill COVID-19 patients, suggesting the potential role of "cytokine storm" in pathogenesis of SARS-CoV-2 and COVID -19 patients' poor outcomes[4]. Therefore, anti-cytokine therapies, appears to be considered as a treatment option for inhibition of cell death and multi-organ failure in these patients. Although a number of pharmacological (cytokine antagonists) and mechanical strategies (hemoperfusion) are already being considered or implemented in clinical practice for patients with severe COVID-19 so far, only few treatments such as dexamethasone and methylprednisolone, have been sufficiently promising to improve patient survival[5,6].

In the absence of specific therapeutic drug option against SARS-CoV-2, early diagnosis and timely appropriate supportive therapy are essential in the care of severe COVID-19 patients[7,8]. The available clinical reports have indicated that the respiratory support through non-invasive or

invasive mechanical ventilation is a cornerstone of the management of critically ill COVID-19 patients. Furthermore, sever COVID-19 patients typically require a longer periods of ventilation, which vastly increases a person's risk for delirium. Although the true prevalence of delirium in critically ill patients with COVID-19 is unclear, the results from cohorts and large, international studies have found that delirium is common and often last for twice the duration in acute respiratory patients without COVID-19.[9,10] The delirium can be a manifestation of direct neuroinvasion of SARS-CoV-2, induction of central nervous system (CNS) inflammatory mediators, secondary consequence of other organs failure, effect of sedative strategies, prolonged mechanical ventilation (MV), unfortunate environmental factors including physical restraint and social isolation.

Despite advances in multidisciplinary set of evidence-based practices and supportive cares in ICUs, such as the ABCDEF (Assess, Prevent, and Manage Pain, Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT), Choice of analgesia and sedation**,** Delirium: Assess, Prevent, and Manage, Early mobility and Exercise, and Family engagement and empowerment) bundle, to improve duration of mechanical ventilation, delirium, and survival of ICU patients[11], as the novel (SARS-CoV-2) rapidly changed ICU practice world wild, data regarding the rate of implementation of the ABCDEF bundle and supportive care provided to patients with COVID-19 infections in ICUs is limited. However, it appears that due to lack of sufficient knowledge, strained workforce or scarcity of resources ABCDEF bundle is not used routinely in clinical practice for COVID-19 patients[12,13].

The choice of drug and delirium monitoring are two main concepts of ABCDEF bundle implantation for ICU patients, including critically ill COVID-19 patients. For instance, use of benzodiazepine, opioid, vasopressor, and antipsychotics are reported to be associated with a higher risk of delirium in COVID-19.[9,10] Noteworthy, administration of benzodiazepine a sedative commonly prescribed for anxiety, has been demonstrated to be associated with a 59% higher risk of developing delirium in COVID-19 patients[14], which makes the choice of sedative agents quite challenging.

Dexmedetomidine (DEX), a highly selective alpha2-adrenergic receptor (α_2-AR) agonist exerts sympatholytic, anxiolytic, sedative, and analgesic effects with minimal incidence of delirium and respiratory depression. It is frequently used for analgesic adjuvant and sedation during the

performance of awake intubation. Recent studies have suggested its potential benefit in non-intubated COVID-19 patients being managed with noninvasive ventilation (NIV) or high flow nasal cannula (HFNC).

In addition, to its sedative properties, DEX has anti-apoptotic, cytoprotective and anti-inflammatory effects. Based on molecular basis of COVID-19 pathogenesis, DEX might be advantageous to attenuate the initial organ damages and disease severity in COVID-19 patients.

In current mini-review, we aimed to explore the potential value of DEX, in terms of sedative benefits, anti-inflammatory properties and organ protective effects, for management of ICU COVID-19 patients.[15] (Fig 1).

2. DEX Mechanisms of Action

DEX, a lipophilic imidazole derivative, is an α_2-AR agonist with a selective sedative action. α_2-ARs are a type of adrenergic receptors, which belong to the superfamily of G-protein coupled receptors (GPCRs). They are important mediators of neurotransmitter function in the central and peripheral nervous system.

On the basis of their binding profiles and amino acid sequence, four distinct subtypes of α2-ARs including α_2A, α_2B, α_2C, and α_2D α_2AR, have been characterized. α_2-ARs were initially identified as presynaptic receptors being involved in a negative feedback loop to regulate the release of norepinephrine. However, further investigation revealed that in addition to their presynaptic action, α_2- ARs have postsynaptic functions in inhibition of sympathetic outflow to the periphery. Upon activation, presynaptic α_2-ARs are coupled to the members of the pertussis toxin (PTX)-sensitive Gαi and Gαo families and inhibit adenylyl cyclase activity. This leads to decrease of intracellular cyclic adenosine monophosphate (cAMP) production, followed by hyperpolarization of noradrenergic. Reduction of cAMP synthesize inhibits cAMP-dependent kinase (PKA) in neurons, which may be responsible for α_2-ARs inhibitory effect on secretion of neurotransmitters and neuropeptides.

In addition, under some conditions, α_2-ARs have been shown indirectly activate voltage-gated Ca^{2+} channels and enhance Ca^{2+}-dependent neurotransmitter release through coupling with stimulatory Gs-proteins[16,17].

The α_2A-AR and α_2C-AR subtypes are found mainly in the central nervous system (CNS), and appears to be responsible for sedation, analgesia, and sympatholytic effects. The α_2B-AR subtype has low expression in specific areas of the CNS, while it is present in the majority of peripheral tissues, including vascular smooth muscle, where mediates vasopressor effects.[18]

Stimulation of presynaptic α_2-AR, which regulates the release of norepinephrine and adenosine triphosphate (ATP) by negative feedback, is of the greatest clinical significance of this receptor. Activation of this negative feedback loop attenuates the sympathetic stress response and reduces the heart rate and blood pressure.

DEX as a potent and highly selective α_2-AR agonist combines various effects through both presynaptic and postsynaptic activation of α_2-ARs. With such multi-target mechanism of action, DEX produces analgesia, sedation, and anxiolysis, while avoiding some of the side effects associated with use of multiple anesthetic agents.

3. Putative therapeutic benefits of dexmedetomidine in COVID-19

3.1 Dexmedetomidine as a sedative and analgesic drug in COVID-19 patients

In a minority of COVID-19 patients, severe acute hypoxemic respiratory failure or respiratory distress syndrome necessitates oxygenation and ventilation therapies, including nasal catheter, oxygen inhalation, masked oxygen inhalation, high flow oxygen therapy (HFNO), invasive or noninvasive mechanical ventilation (NIV). Patients receiving assisted MV, commonly require sedation to decrease stress response, optimize patients' tolerance to the endotracheal tube and facilitate their ventilator adaptation. This can help to avoid prolongation of MV, length of intensive care unit (ICU) stays and need for tracheostomy. In order to achieving patient-ventilator synchrony, controlling pain and minimizing the risk for self-extubation, moderate to deep sedation/analgesia is used in COVID-19 patients subjected to MV, like all other patients undergoing mechanical ventilation.[19]

Due to high sedation requirements and possible drug interactions between antiviral medications and drugs that are used for sedation, choosing appropriate method for COVID-19 sedation during MV can be challenging.[20]

Opioids exhibit particular efficacy as analgesic drugs, but have some complications including vomiting, nausea, and intolerance to feeding due to gut hypomotility which may lead to

malnutrition and the risk of aspiration during prolonged ICU stay. Besides, opioids and benzodiazepines appear to increase the odds of delirium in susceptible patients and can negatively interfere with respiration.[21,22]

Anti-inflammatory and lung-protective effects of volatile anesthetics like isoflurane and sevoflurane make them a plausible sedative alternative for COVID-19 patients.[23-25] But their administration requires special scavenging system, which may be not available in many situations.[20] Thus, with unusually high sedation requirements in a large proportion of MV dependent COVID-19 patients and possibility of critical drug shortages, alternative options and additional guidelines for sedation of these patients are desperately needed.

The highly selective α_2-ARs agonist, DEX, has versatile sedative, anxiolytic, sympatholytic and hypnotic effects. Administration of DEX is reported to be associated with shorter time to extubation[26] as well as lower incidence of delirium[27] and mortality compared to other sedative agents.[28,29] An important feature of DEX -based sedation is that it induces adequate sedation while preserving a degree of responsiveness and arousability in ICU patients. This aspect, combined with the minimal influence on respiration, makes DEX a compelling alternative agent for patients with respiratory failure, whom the preservation of spontaneous ventilation and maintaining airway tone is vital[30]. However, actual clinical relevance of these beneficial effects remains to be fully elucidated as an available study reported that the early administration of DEX did not result in lower 90-day mortality in ICU patients compared to patients who were assigned to receive other sedatives.[31] Apart from the controversy between available reports, there is a strong rationale for clinical studies investigating the potentials of DEX as a sedative agent in ICU patients with COVID-19.

3.2 Dexmedetomidine as an Anti-Inflammatory and Organ-Protective

Despite promising results for a number of antiviral medications, no specific and effective treatment for COVID-19 is available. Current clinical management of COVID-19 relies mainly on life-sustaining therapies that support organ functions during the course of viral infection elimination by patient's immune system.

Growing body of evidence has suggested that along with the pathogenic effect of the SARS-CoV-2, an excessive and destructive inflammatory response plays a crucial role in the clinical

manifestations of COVID-19. Such uncontrolled immune response may result in pulmonary interstitial arteriolar walls damage, reduction of lung capacity and deterioration of lung capacity and overall lung performance.

SARS-CoV-2 not only induces the diffused alveolar injury and acute respiratory failure, but many other organs, including liver, heart, intestine, kidney, CNS and muscle have also been found to be injured by the infection. Such multi-organ failure appears to be the consequence of pathophysiological changes such as alveolar macrophage activation, lymphopenia, cytokine release syndrome, thrombosis endothelial dysfunction and coagulation. It is therefore apparent that a viral infection-related inflammation and the subsequent cytokine storm in severe COVID-19 cases play crucial roles in disease outcomes. Thus, therapeutic approaches that modulate inflammatory pathways, potentially lead to substantial improvements in reducing the mortality of COVID-19 patients.[32]

As an α_2-AR agonist, DEX is suggested to decrease central sympathetic nerve activity, which obviously affect inflammation and immune function either directly via cell surface receptors or indirectly by shifting sympathetic-parasympathetic balance towards parasympathetic.[33]

Results from several studies on inflammatory animal models including sepsis models (caecal ligation and puncture (CLP), and lipopolysaccharide (LPS), acute lung injury models (ALI), and ischemia/reperfusion injury (IRI) models supported cytoprotective and anti-inflammatory effects of DEX[34-37]. Available studies suggest that this immune-modulatory effect is achieved by a reduction in the pro-inflammatory mediators (IL-1β, IL6 IL-8, and TNF-α), inhibition of TLR4/NF-κB binding activity, JAK2-STAT3, and NF-κB/COX-2 pathways.[36,38-40] DEX also promotes the release of acetylcholine (ACh) through an antisympathetic effect. This also can be combined with α7nAChR on immune cytomembranes and lead to anti-inflammatory effects via the cholinergic pathway.[41,42] Moreover, DEX exerts antioxidant and anti-apoptosis effects through regulation of the GSK-3β/MKP-1/Nrf2 pathway.[37,43]

Since the confirmation of DEX's anti-inflammatory and anti-oxidative stress properties, its organ-protective effects have become a popular topic of research. Several promising results have already demonstrated the neuroprotective, cardioprotective, hepatoprotective, pulmonoprotective and renoprotection properties of DEX.[44-47]

3.3 DEX as a Sedative and Therapeutic Agent in COVID-19

As mentioned, excessive immune activation and systemic hypoxia caused by lung injury plays significant roles in multi-organ dysfunction and poor outcomes of COVID-19 patients. Besides, on a behavioral level, social isolation and dyspnea-related fear place COVID-19 patients at a higher risk for anxiety and agitation. This becomes major area of concern, especially when the patient is fully dependent on supplemental oxygen. In such critical conditions, anti-delirium and sedative properties of DEX make it a potential drug for management of agitated patients.

In addition to the sedative beneficial of DEX, its well-established cytoprotective, anti-inflammatory and organ protective effects, have been reported by several studies. All of the above-mentioned effects of DEX suggest it as a reasonable agent for managing sedation in COVID-19 patients. In this respect, a number of recent studies have investigated the potential benefits of DEX in these patients.

A new study has demonstrated that DEX infusion in a critically ill COVID-19 patient with worsening hypoxemia despite maximal HFNC oxygen support, aided the patient to avoid intubation by improving compliance with oxygen devices (HFNC and nasal cannula) and promoting saturations.[48] In other study, administration of DEX for patient already on supplemental oxygen, HFNC, or NIPPV improved compliance and comfort with self-proning and allowed improved tolerance to oxygenation devices [49]. DEX has also been indicated to be proper sedative agent for management of atrial fibrillation with rapid ventricular response in COVID-19 patient.[50] As arrhythmias and bradycardia are of the COVID-19 major complications, DEX appeared to be appropriate sedation or anesthesia agent for COVID -19 patients with refractory atrial fibrillation. Due to DEX's central antihypertensive, sedative and organ-protective effects as well as its minimal effects on respiratory function, a number of clinical trials are ongoing to investigate the immunomodulatory profile of this agent in patients recovering from COVID-19 or for moderate sedation of COVID-19 patient in the palliative situation (NCT04413864 and NCT04350086). Pending the results of these and other clinical trials, unique pharmacologic properties of DEX make it a medication of choice for COVID-19 patients' sedation.

However, some important points need to be considered in light of convincing evidence for DEX benefit in COVID-19 patients. A number of studies have reported that high dose of DEX is associated with an increased risk of developing hyperthermia.[51] There have already been reports

regarding DEX-associated hyperpyrexia in critically ill COVID-19 patients.[52]. As hyperpyrexia seems to be associated with an adverse impact on COVID-19 patients[53], attention should be made in its administration. On the other hand, while available studies have reported that prolonged DEX infusion is not associated with increased in-hospital mortality in critically ill patients[54], DEX withdrawal syndrome, characterized by tachycardia, hypertension and agitation, raises a concern. This is particularly can be problematic for COVID-19 patients that often have longer ICU stays and greater sedation time. However, available studies have reported that DEX can be used safely for up to 7 days, in critically ill patients without withdrawal symptoms, increased in-hospital mortality, adverse events, or sequelae.[55,56] On the other hand, the possible incidence of withdrawal or increase risk of in-hospital mortality is reported to be associated with its total cumulative dose of DEX, rather than duration of therapy.[54,57] These suggest that such events can be prevented by careful dosing of DEX. It is noteworthy to mention that the possible acute withdrawal syndrome can be managed or significant improved by administration of oral clonidine, as an alternative substituted α2-AR agonist.[58]

Conclusion:

According to the aforementioned researches, DEX can be considered when sedation of COVID-19 patients is required, not only for its safety, but also for its immunomodulatory properties. However, further clinical investigation to establish the effects of dexmedetomidine on outcomes in critically ill COVID-19 patients is highly recommended.

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Authors' contributions:

S.S Developed the theoretical concept, contributed to the final version of the manuscript.

A.J Assisted with data collection, contributed to the final version of the manuscript

A.Z: Contributed to the design and implementation of the research, supervised the findings of this work

A.S: Contributed to the design and implementation of the research, supervised the findings of this work

E.B .K: Developed the theory and performed the literature research, contributed to the final version of the manuscript

R.A: Developed the theory and performed the literature research, contributed to the final version of the manuscript

R.J.K: Supervised the project, contributed to the design and implementation of the research

D.O: Contributed to the interpretation of the results

All authors discussed the results and contributed to the final manuscript.

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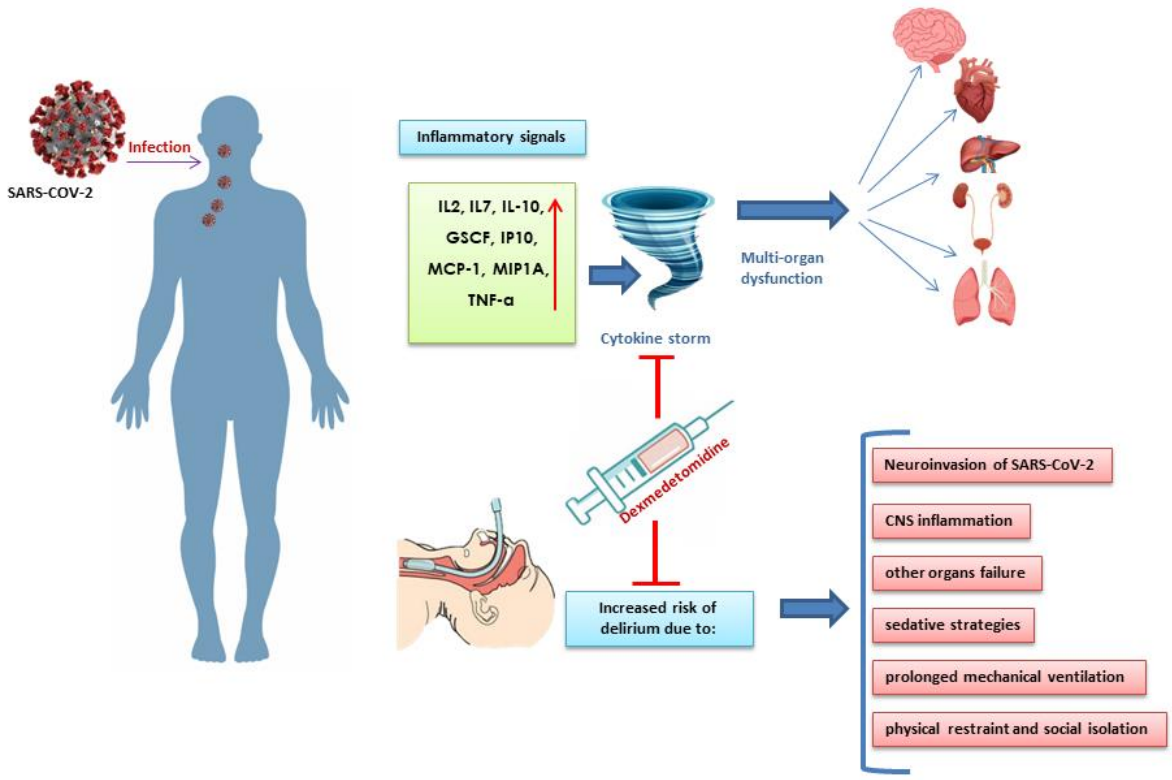

Figure 1.