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 hypoxic 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 α₂-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.

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

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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. 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.

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. 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. The delirium can be a manifestation of the central nervous system (CNS), and appears to be coupled with stimulatory Gs-proteins.

**DEX Mechanisms of Action**

DEX, a lipophilic imidazole derivative, is an α₂-AR agonist with a selective sedative action. α₂-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 α₂A, α₂B, α₂C, and α₂D α₂AR, have been characterized. α₂-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, α₂-ARs have postsynaptic functions in inhibition of sympathetic outflow to the periphery. Upon activation, presynaptic α₂-ARs are coupled to the members of the pertussis toxin (PTX)-sensitive Gαi and Gκ 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 synthesis inhibits cAMP-dependent kinase (PKA) in neurons, which may be responsible for α₂-ARs inhibitory effect on secretion of neurotransmitters and neuropeptides.

In addition, under some conditions, α₂-ARs have been shown indirectly activate voltage-gated Ca²⁺ channels and enhance Ca²⁺-dependent neurotransmitter release through coupling with stimulatory Gs-proteins. The α₂A-AR and α₂C-AR subtypes are found mainly in the central nervous system (CNS), and appears to be
responsible for sedation, analgesia, and sympatholytic effects. The α₂-B-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. Stimulation of presynaptic α₂-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 α₂-AR agonist combines various effects through both presynaptic and postsynaptic activation of α₂-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.

**Putative therapeutic benefits of dexmedetomidine in COVID-19**

**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.

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. 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. Anti-inflammatory and lung-protective effects of volatile anesthetics like isoflurane and sevoflurane make them a plausible sedative alternative for COVID-19 patients. But their administration requires special scavenging system, which may be not available in many situations. 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 α₂-ARs agonist, DEX, has versatile sedative, anxiolytic, sympatholytic and hypnotic effects. Administration of DEX is reported to be associated with...
shorter time to extubation\textsuperscript{30} as well as lower incidence of delirium\textsuperscript{27} and mortality compared to other sedative agents.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

\textbf{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.\textsuperscript{32}

As an \(\alpha_2\)-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.\textsuperscript{34} 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.\textsuperscript{34-37} Available studies suggest that this immune-modulatory effect is achieved by a reduction in the pro-inflammatory mediators (IL-1\(\beta\), IL6 IL-8, and TNF-\(\alpha\)), inhibition of TLR4/NF-kB binding activity, JAK2-STAT3, and NF-kB/COX-2 pathways.\textsuperscript{36,38-40} DEX also promotes the release of acetylcholine (ACh) through an antisympathetic effect. This also can be combined with \(\alpha_7\)nAChR on immune cytomembranes and lead to anti-inflammatory effects via the cholinergic pathway.\textsuperscript{31,42} Moreover, DEX exerts antioxidant and anti-apoptosis effects through regulation of the GSK-3\(\beta\)/MKP-1/Nrf2 pathway.\textsuperscript{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.\textsuperscript{44-47}

\textbf{Dexmedetomidine 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 benefit 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.\textsuperscript{46} 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.\textsuperscript{47} DEX has also been indicated to be proper sedative agent for management of atrial fibrillation with rapid ventricular response in COVID-19 patient.\textsuperscript{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. There have already been reports regarding DEX-associated hyperpyrexia in critically ill COVID-19 patients. As hyperpyrexia seems to be associated with an adverse impact on COVID-19 patients, 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, 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. 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. 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.

**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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**Author Contributions**

SS: Developed the theoretical concept, contributed to the final version of the manuscript. AJ: Assisted with data collection, contributed to the final version of the manuscript. AZ: Contributed to the design and implementation of the research, supervised the findings of this work. AS: Contributed to the design and implementation of the research, supervised the findings of this work. EB K: Developed the theory and performed the literature research, contributed to the final version of the manuscript. RA: Developed the theory and performed the literature research, contributed to the final version of the manuscript. RJK: Supervised the project, contributed to the design and implementation of the research. DO: Contributed to the interpretation of the results. All authors discussed the results and contributed to the final manuscript.

**Conflict of Interest**

The authors declare no competing interests and any financial relationship in this study.

**References**

1. Guan WJ, Zhong NS. Clinical characteristics of covid-19 in china. Reply. N Engl J Med. 2020;382(19):1861-2. doi:10.1056/NEJMct2005203
2. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of covid-19 - a systematic review. Life Sci. 2020;254:117788. doi:10.1016/j.lfs.2020.117788
3. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504. doi:10.1016/j.intimp.2020.106504
4. Mangalmurti N, Hunter CA. Cytokine storms: Understanding covid-19. Immunity. 2020;53(1):19-25. doi:10.1016/j.immuni.2020.06.017
5. Safari S, Salimi A, Zali A, Jahangirifard A, Bastanhagh E, Aminnejad R, et al. Extracorporeal hemoperfusion as a potential therapeutic option for severe covid-19 patients; a narrative review. Arch Acad Emerg Med. 2020;8(1):e67-e.
6. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with covid-19 - preliminary report. N Engl J Med. 2020;384(8):693-704. doi:10.1056/NEJMoa2021436
7. Poston JT, Patel BK, Davis AM. Management of critically ill adults with covid-19. JAMA 2020;323(18):1839-41. doi:10.1001/jama.2020.4914
8. Mahmoodpoor A, Shadvar K, Ghamari AA, Mohammadzadeh Lameh M, Aghari Ardebili R, Hamidi M, et al. Management of critically ill patients with covid-19: What we learned and what we do. Anesth Pain Med. 2020;10(3):e104900-e. doi:10.5812/aapm.104900
9. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, et al. Delirium and encephalopathy in severe covid-19: A cohort analysis of icu patients. Critical Care. 2020;24(1):491. doi:10.1186/s13054-020-03200-1
10. Pun BT, Badenes R, Horas La Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with covid-19 (covid-d): A multicentre cohort study. Lancet...
11. Marra A, Ely EW, Pandharipande PP, Patel MB. The abcd ef bundle in critical care. Crit Care Clin. 2017;33(2):225-43. doi:10.1016/j.ccc.2016.12.005

12. Kottis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. Covid-19: Icu delirium management during sars-cov-2 pandemic. Critical Care 2020;24(1):176. doi:10.1186/s13054-020-02882-x

13. Liu K, Nakamura K, Katsukawa H, Elhadi M, Nydahl P, Ely EW, et al. Abcd ef bundle and supportive icu practices for patients with coronavirus disease 2019 infection: An international point prevalence study. Crit Care Explor. 2021;3(3):e0353. doi:10.1097/ cce.0000000000000353

14. Andrews LJ, Benken ST. Covid-19: Icu delirium management during sars-cov-2 pandemic—pharmacological considerations. Critical Care. 2020;24(1):375. doi:10.1186/s13054-020-03072-5

15. Mahmoodpoor A, Ekrami E, Soleimanpour H. Dexmedetomidine: an all sedation-in-one drug in critically ill patients with covid-19. Pharm Sci. 2020;26:801-1. doi:10.34172/PS.2020.53

16. Eason MG, Kurose H, Holt BD, Raymond JR, Liggert SB. Simultaneous coupling of alpha 2-adrenergic receptors to two g-proteins with opposing effects. Subtype-selective coupling of alpha 2c, alpha 2c4, and alpha 2c2 adrenergic receptors to gi and gs. J Biol Chem. 1992;267(22):15795-801.

17. Gál A, Ducza E, Minorics R, Klukovits A, Gálik M, Falkay G, et al. The roles of alpha2-adrenoceptor subtypes in the control of cervical resistance in the late-pregnant rat. Eur J Pharmacol. 2009;615(1-3):193-200. doi:10.1016/j.ejphar.2009.04.067

18. Berg T. B- and a(2)-adrenoceptor control of vascular tension and catecholamine release in female normotensive and spontaneously hypertensive rats. Front Neur. 2017;8:130-. doi:10.3389/ fneneur.2017.00130

19. RAZAVI S, Nejad RA, Mohajerani SA, Talebian M. Risk factors of unplanned extubation in pediatric intensive care unit. Tanaffos. 2013;12(3):11.

20. Hanidiar D, Bittner EA. Sedation of mechanically ventilated covid-19 patients: Challenges and special considerations. Anesth Analg. 2020;131(1):e40-e1. doi:10.1213/ANE.0000000000004887

21. Azeem TMA, Yosif NE, Alansary AM, Esmat IM, Mohamed AK. Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial. Saudi J Anaesth. 2018;12(2):190-7. doi:10.4103/sja.SJA_303_17

22. Mahjoobifard M, Heidari M, Dahmardeh M, Mirtajani SB, Jahangirifard A. Comparison of dexmedetomidine, lidocaine, and fentanyl in attenuation hemodynamic response of laryngoscopy and intubation in patients undergoing cardiac surgery. Anesthesiol Res Pract. 2020;2020:4814037. doi:10.1155/2020/4814037

23. Jabaudon M, Boucher P, Imhoff E, Chabanne R, Faure J-S, Roszyk L, et al. Sevoflurane for sedation in acute respiratory distress syndrome. A randomized controlled pilot study. Am J Respir Crit Care Med. 2017;195(6):792-800. doi:10.1164/rcrm.201604-0686OC

24. De Conno E, Steurer MP, Wittlinger M, Zalunardo MP, Weder W, Schneider D, et al. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology. 2009;110(6):1316-26. doi:10.1097/ALN.0b013e3181a10731

25. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Volatile anesthetics. Is a new player emerging in critical care sedation? Am J Respir Crit Care Med. 2016;193(11):1202-12. doi:10.1164/rcrm.201512-2435CP

26. Constantin J-M, Momon A, Mantz J, Payen J-F, De Jonghe B, Perbet S, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: A meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med. 2016;35(1):7-15. doi:10.1016/j.accp.2015.06.012

27. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: A randomized clinical trial. JAMA. 2016;315(14):1460-8. doi:10.1001/jama.2016.2707

28. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fukue A, Hashimoto A, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: A randomized clinical trial. JAMA. 2017;317(13):1321-8. doi:10.1001/jama.2017.2088

29. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: A systematic review and meta-analysis of randomized trials. Crit Care Med. 2013;41(9):S30-8. doi:10.1097/ CCM.0b013e3182a16898

30. Mahmoud M, Mason KP. Dexmedetomidine: Review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015;115(2):171-82. doi:10.1093/bja/aev226

31. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients requiring mechanical ventilation with sepsis: A randomized controlled pilot study. Intensive Care Med. 2019;380(26):2506-2514. doi:10.1007/s00134-019-05686OC
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34. Sukeyama S, Higuchi H, Inoue M, Nagatsuka H, Maeda S, Miyawaki T. Locally injected dexmedetomidine inhibits carrageenin-induced inflammatory responses in the injected region. Anesth Analg. 2014;118(2):473-80. doi:10.1213/ane.000000000000060

35. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001;86(5):650-6. doi:10.1093/bja/86.5.650

36. Hofer S, Steppen J, Wagner T, Funke B, Lichtenstern C, Martin E, et al. Central sympatholytics prolong survival in experimental sepsis. Critical Care. 2009;13(1):R11. doi:10.1186/cc7709

37. Cavalcanti V, Santos CL, Samary CS, Araújo MN, Heil LBB, Morales MM, et al. Effects of short-term propofol and dexmedetomidine on pulmonary morphofunction and biological markers in experimental mild acute lung injury. Respir Physiol Neurobiol. 2014;203:45-50. doi:10.1016/j.resp.2014.08.008

38. Wang K, Li C. Effects of dexmedetomidine on inflammatory factors, lymphocyte subsets and expression of nf-kb in peripheral blood mononuclear cells in patients receiving radical surgery of colon carcinoma. Oncol Lett. 2018;15(5):7153-7. doi:10.3892/ol.2018.8205

39. Xiang H, Hu B, Li Z, Li J. Dexmedetomidine controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. Inflammation. 2014;37(5):1763-70. doi:10.1007/s10753-014-9906-1

40. Tan F, Chen Y, Yuan D, Gong C, Li X, Zhou S. Dexmedetomidine protects against acute kidney injury through downregulating inflammatory reactions in endotoxemia rats. Biomed Rep. 2015;3(3):365-70. doi:10.3892/br.2015.425

41. Kong W, Kang K, Gao Y, Liu H, Meng X, Yang S, et al. Dexmedetomidine alleviates lps-induced septic cardiomyopathy via the cholinergic anti-inflammatory pathway in mice. Am J Transl Res. 2017;9(11):5040-7.

42. Kang K, Gao Y, Wang SC, Liu HT, Kong WL, Zhang X, et al. Dexmedetomidine protects against lipopolysaccharide-induced sepsis-associated acute kidney injury via an a7 nachr-dependent pathway. Biomed Pharmacother. 2018;106:210-6. doi:10.1016/j.biopharm.2018.06.059

43. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Crit Care Med. 2004;32(6):1322-6. doi:10.1097/00003152-200406000-00038

44. Jiang L, Hu M, Lu Y, Cao Y, Chang Y, Dai Z. The protective effects of dexmedetomidine on ischemic brain injury: A meta-analysis. J Clin Anesth. 2017;40:25-32. doi:10.1016/j.jclinane.2017.04.003

45. Liu Y, Yu Y, Zhang J, Wang C. The therapeutic effect of dexmedetomidine on protection from renal failure via inhibiting kdm5a in lipopolysaccharide-induced sepsis of mice. Life Sci. 2019;239:116868. doi:10.1016/j.lfs.2019.116868

46. Castillo RL, Ibacache M, Cortinez I, Carrasco-Pozo C, Farias JG, Carrasco RA, et al. Dexmedetomidine improves cardiovascular and ventilatory outcomes in critically ill patients: Basic and clinical approaches. Front Pharmacol. 2020;10:1641. doi:10.3389/fphar.2019.01641

47. Bao N, Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. Mediators Inflamm. 2020;2020:6136105. doi:10.1155/2020/6136105

48. Stockton J, Kyle-Sidell C. Dexmedetomidine and worsening hypoxemia: A case report. Am J Emerg Med. 2020;38(10):2247.e1-2. doi:10.1016/j.ajem.2020.05.066

49. Cruz Salcedo EM, Rodriguez LM, Patel J, Seevaratnam AR. Use of dexmedetomidine in early prone positioning combined with high-flow nasal cannula and non-invasive positive pressure ventilation in a covid-19 positive patient. Cureus. 2020;12(9):e10430. doi:10.7759/cureus.10430

50. Talib U, Ahmad I. Dexmedetomidine-associated bradycardia: A blessing in disguise for management of atrial tachyarrhythmias in patients with covid-19 requiring sedation. Chest. 2020;158(4):A417-A. doi:10.1016/j.chest.2020.08.406

51. Krüger BD, Kurmann J, Corti N, Spahn DR, Bettex D, Rudiger A. Dexmedetomidine-associated hyperthermia: A series of 9 cases and a review of the literature. Anesth Analg. 2017;125(6):1898-906. doi:10.1213/ane.0000000000002353

52. Czepiel KS, Lucas AT, Whalen MJ, Mojica JE. Dexmedetomidine-associated hyperpyrexia in three critically ill patients with coronavirus disease 2019. Crit Care Explor. 2020;2(9):e0213. doi:10.1097/ccc.0000000000000213

53. Suwanwongse K, Shabarek N. Hyperpyrexia in patients with covid-19. J Med Virol. 2020;92(11):2857-62. doi:10.1002/jmv.26154

54. Zhao Y, Zhou H, Tan W, Song Y, Qiu Z, Li S, et al. Prolonged dexmedetomidine infusion in critically ill patients: A retrospective analysis of a large clinical database multiparameter intelligent monitoring in intensive care iii. Ann Transl Med. 2018;6(15):304-.

55. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. Anesth Analg. 2003;96(4):1054-5. doi:10.1213/ane.0000050773.70232.08

56. Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: Sedative and cardiovascular effects. Intensive Care Medicine. 2004;30(12):2188-96. doi:10.1007/s00134-004-2417-z

57. Bouajram RH, Bhatt K, Croci R, Baumgartner L, Puntillo
K, Ramsay J, et al. Incidence of dexmedetomidine withdrawal in adult critically ill patients: A pilot study. Crit. care explor. 2019;1(8):e0035. doi:10.1097/cco.0000000000000035

58. Kukoyi A, Coker S, Lewis L, Nierenberg D. Two cases of acute dexmedetomidine withdrawal syndrome following prolonged infusion in the intensive care unit: Report of cases and review of the literature. Hum Exp Toxicol. 2013;32(1):107-10. doi:10.1177/0960327112454896