

# Perioperative pain management in COVID-19 patients: Considerations and recommendations by the Saudi Anesthesia Society (SAS) and Saudi Society of Pain Medicine (SSPM)

### ABSTRACT

The COVID-19 pandemic has swept across the world over the past few months. Many articles have been published on the safety of anesthetic medications and procedures used in COVID-19 positive patients presenting for surgery. Several other articles covered the chronic pain management aspect during the pandemic. Our review aimed to focus on perioperative pain management for COVID-19 patients. We conducted a literature search for pertinent recent articles that cover considerations and recommendations concerning perioperative pain management in COVID-19 patients. We also searched the literature for the relevant adverse effects of the commonly used medications in the treatment of COVID-19, and their potential drug–drug interactions with the common medications used in perioperative pain management. Professional societies recommend prioritizing regional anesthesia techniques, which have many benefits over other perioperative pain management options. When neuraxial and continuous peripheral nerve block catheters are not an option, patient-controlled analgesia (PCA) should be considered if applicable. Many of the medications used for the treatment of COVID-19 and its symptoms can interfere with the metabolism of medications used in perioperative pain management. We formulated an up-to-date guide for anesthesia providers to help them manage perioperative pain in COVID-19 patients presenting for surgery.

**Key words:** Acute pain; anesthesia; anesthesiology; COVID19; coronavirus; multimodal analgesia; pain

### Introduction


Coronavirus Disease 2019 (COVID-19) is a viral disease that affects the respiratory system and originated in Wuhan, China, in December 2019. It has disseminated rapidly throughout the whole world and was declared a worldwide pandemic by the WHO in March 2020.<sup>[1,2]</sup> This disease is caused by the

novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), which is related to the virus that causes severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which had outbreaks in 2003 and 2012, respectively.<sup>[3,4]</sup>

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**How to cite this article:** Alyamani OA, Bahatheq MS, Azzam HA, Hilal FM, Farsi S, Bahaziq W, *et al.* Perioperative pain management in COVID-19 patients: Considerations and recommendations by the Saudi Anesthesia Society (SAS) and Saudi Society of Pain Medicine (SSPM). Saudi J Anaesth 2021;15:59-69.

Access this article online	
<b>Website:</b> www.saudija.org	<b>Quick Response Code</b> 
<b>DOI:</b> 10.4103/sja.SJA_765_20	

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**Submitted:** 15-Jul-2020, **Revised:** 15-Jul-2020, **Accepted:** 16-Jul-2020, **Published:** 05-Jan-2021

By mid-July 2020, the estimated number of reported cases with COVID-19, according to WHO, reached almost 13 million. SARS CoV-2 differs from the zoonotic viruses SARS CoV and MERS in its higher infectivity and lower mortality rates.<sup>[3-5]</sup> However, all three viruses show similarities in their clinical picture of pneumonia, which could progress to acute respiratory distress syndrome (ARDS) with a noticeable drop in T-lymphocyte count.<sup>[6]</sup>

One study examined the outcome data of 2,634 COVID-19 patients in New York hospitals who were either discharged or deceased at the end of the study. The results showed that up to 12.2% required mechanical ventilation and 21% of them died. Unfortunately, the mortality rates of those who required mechanical ventilation were significantly higher than those who did not, which occurred in both age groups of 18 to 65 years and those above 65 years old, especially among patients with comorbid conditions such as hypertension, diabetes, and obesity.<sup>[7]</sup> Earlier studies on SARS CoV and MERS have shown that in intranasally infected transgenic mice, both viruses were heavily present in the respiratory centers at the brain stem.<sup>[8]</sup> The similarities between the three viruses may lead us to think that this novel virus may affect the respiratory centers as well.

Surgical procedures during any pandemic can be challenging. In many parts of the world, hospitals have postponed their elective procedures, allowing only emergency and urgent ones to proceed. Perioperative pain management during the COVID-19 pandemic adds considerable concerns to anesthetic management in such cases. Many cytokines have been found to have higher levels in COVID-19 patients.<sup>[9]</sup> Cytokines released and activated by inflammation are thought to have a significant contribution to postoperative pain.<sup>[10]</sup>

The management of perioperative pain commonly includes medications that may cause or worsen respiratory depression. Moreover, some of the medications used in the treatment of COVID-19 may affect the pharmacokinetics of medications used in perioperative pain management. The aim of this review article is to shed some light on these considerations and provide recommendations for anesthesia providers for the management of perioperative pain in COVID-19 patients.

## Methods

We searched the PubMed database for the terms “pain,” “pain medicine,” “pain management,” “pain control,” “postoperative pain,” “perioperative pain,” “opioids,” “and “analgesia” in combination with “COVID-19” and “SARS CoV-2”. We also searched for selected medications

and techniques combined with the terms “COVID-19” and “SARS CoV-2”. The third search method focused on the pharmacological properties and adverse effects of medications used in the management of patients with COVID-19. Lastly, the following medical societies’ websites were reviewed for their guidance, considerations, and recommendations: The American Society of Regional Anesthesia and Pain Medicine (ASRA), The American Society of Anesthesiologists (ASA), The European Society of Regional Anesthesia and Pain Therapy (ESRA), The Association of Anaesthetists of Great Britain and Ireland, The Canadian Anesthesiologists’ Society (CAS), The European Society of Anaesthesiology (ESA), The American Academy of Pain Medicine (AAPM), and The American Academy of Hospice and Palliative Medicine (AAHPM). The last day of literature search was July 15, 2020, before submission of the article.

## Results

We were unable to find any published articles dedicated to the subject of perioperative pain management in surgical patients infected with COVID-19 [see Table 1 for an overview of the articles]. Four articles that were relevant to this subject were identified. The first article was written by an international expert panel for the ASRA and ESRA statements on chronic pain practice during the pandemic, which focused on the management of chronic pain during the pandemic with sections on opioids, NSAIDs, and steroid use for COVID-19 patients.<sup>[11]</sup>

The second article discussed considerations in multidisciplinary chronic pain management during the pandemic.<sup>[12]</sup> The third article covered considerations and recommendations for neuraxial and peripheral nerve blocks in COVID-19 patients.<sup>[13]</sup> The fourth article discussed the practical considerations for regional anesthesia in an infected or suspected COVID-19 patient regarding measures of controlling cross-contamination for anesthesia personnel.<sup>[14]</sup>

### Perioperative pain management techniques and medications

Early epidemiologic studies classified the clinical conditions of COVID-19 into three categories: mild (with mild pneumonia or none), severe (with dyspnea, hypoxia, or >50% lung tissue involvement in radiological imaging), and critical (with respiratory failure, shock, or multiorgan dysfunction),<sup>[15]</sup> as shown in Table 2. In our opinion, this categorization is essential when weighing the risks and benefits of using a particular medication for the management of perioperative pain. The primary aim during this pandemic is the safety of patients and healthcare workers, so surgical procedures should be postponed with the agreement of

**Table 1: An overview of the article**

Perioperative pain management techniques and medications	
General Considerations	
Neuraxial anesthesia and peripheral nerve blocks	
Opioids	
Patient-controlled analgesia (PCA)	
Commonly used analgesic medications	
Paracetamol	
Nonsteroidal anti-inflammatory drugs (NSAIDS)	
Alpha-1 Agonists	
Gabapentinoids	
Ketamine	
Lidocaine	
COVID-19 medications and perioperative pain management	
Antimicrobials	
Chloroquine and Hydroxychloroquine	
Azithromycin	
Remdesivir	
Lopinavir/Ritonavir	
Favipiravir	
Immunomodulatory Agents	
Tocilizumab	
Interferon- $\alpha$ -2a and Ribavirin	
Immunoglobulin Therapy	
IVIG	
Supportive Medications	
Albuterol & Ipratropium	
Systemic Corticosteroids	
Loperamide	
Ondansetron	
Metoclopramide	
Dextromethorphan	

**Table 2: COVID-19 clinical condition classification**

Mild disease	No or mild pneumonia
Severe disease	Dyspnea, hypoxia, or > 50 percent lung involvement on imaging within 24 to 48 h
Critical disease	Respiratory failure, shock, or multiorgan dysfunction

all stakeholders involved (including the patient). If general anesthesia is deemed necessary, rapid sequence induction seems an appropriate option. This would minimize the time for airway instrumentation and eliminate the need for bag-mask ventilation, which may both cause aerosolization of the virus.<sup>[16]</sup>

The protocols of Enhanced Recovery After Surgery (ERAS) programs can help guide multimodal analgesia options for COVID-19 patients. The use of opioid-sparing analgesics and regional techniques should be encouraged in such patients.<sup>[17]</sup> A recent systematic review showed a reduced hospital length of stay and a lower incidence of complications following total knee or hip arthroplasty in patients who received multimodal analgesia according to ERAS protocols.<sup>[18]</sup> The commonly used opioid-sparing analgesics with relevant considerations to COVID-19 are discussed below. See Table 3 for common multimodal analgesics.

### Neuraxial anesthesia and peripheral nerve blocks

COVID-19 is not a contraindication for neuraxial anesthesia or other regional anesthesia techniques according to ASRA. Professional societies of regional anesthesia recommend prioritizing regional anesthesia techniques in suspected or confirmed COVID-19 patients since airway instrumentation is considered an aerosol-generating procedure.<sup>[13,19,20]</sup> Moreover, regional blocks are opioid-sparing and may decrease the chances for airway obstruction and respiratory depression in the postoperative period.<sup>[11,13,21]</sup>

During a regional block, conversion to a general anesthetic technique always remains a possibility. Therefore, it is recommended for the anesthesia provider to wear an N95 mask if available. It is also recommended for the suspected or confirmed patient to wear a surgical mask as well to limit the spread of the disease. Caution is advised when midazolam is used in sedation for regional anesthetic techniques as it is metabolized by hepatic CYP 3A4. Many of the medications listed below either inhibit or compete with other medications for this CYP450 enzyme.

Extreme caution should be exercised when performing peripheral regional blocks that may affect respiratory mechanics in COVID-19 patients (interscalene or supraclavicular brachial plexus blocks).<sup>[13]</sup> Careful assessment of the nerve block or neuraxial anesthesia/analgesia before surgical intervention is vital to avoid the possibility of having to instrument the airway under urgency. Ice packs used to assess the level of the block should not be reused unless carefully cleaned in order to minimize the risk of contamination.<sup>[14]</sup>

If a peripheral nerve block is indicated, we recommend the use of continuous peripheral nerve blocks when possible in order to decrease opioid consumption, provide adequate postoperative pain control, and minimize contact with infected patients.<sup>[22]</sup> It is advisable to refer to local institutional protocols and procedures for the safe administration of continuous peripheral blocks. In the treatment of post-dural puncture headache (PDPH), the inadvertent introduction of the virus to the intrathecal space with an epidural blood patch remains a possibility. Although no guidelines are currently available for the treatment of PDPH in COVID-19 patients, it may be safer in this situation to employ a conservative management of PDPH. A nasal sphenopalatine ganglion block may carry the risk of infection for healthcare workers and is inadvisable in this situation.<sup>[13,19]</sup>

### Patient-controlled analgesia (PCA)

A meta-analysis by McNichol *et al.* revealed that PCA is more effective than intermittent doses of opioids administered

**Table 3: Considerations for multimodal analgesia medications in COVID-19 patients**

Medication	Considerations and Recommendations
Opioids	Caution with patients who are at high risk of respiratory depression and to opioid side effects. Use as part of a multimodal analgesia approach. Avoid using Intramuscular and subcutaneous routs. Titrate dose to effect. Caution with intrathecal opioid administration. Pay attention to metabolism of the used opioid. Treat nausea prophylactically. Pay attention to CYP inducers and inhibitors. Monitor vital signs closely.
Paracetamol	Get base line liver enzyme in sever and critical patients. Caution use with liver dysfunction. Caution with other medications that affect the liver. Caution with older individuals. Limit it the dose to 3.25 gram daily.
Nonsteroidal anti-inflammatory drugs (NSAIDS)	Discontinue the long-term use of both, non-selective and selective COX-2 inhibitors For the short-term perioperative use: Caution with CVS patients and patients at risk for major vascular events. Caution in kidney dysfunction. Aspirin is an exception as antiplatelet therapy.
Dexmedetomidine	Avoid during hemodynamic instability. Caution with old age. Tachyphylaxis after 24-hour use.
Gabapentinoids	Questionable efficacy in opioid sparing. Emerging evidence of high incidence of pneumonia and respiratory insufficiency with long-term use. Avoid in patients with moderate to severe COVID-19.
Ketamine	Use at the usual subanesthetic doses. Caution in patients with ischemic heart diseases.
Lidocaine	With respect to its side effects and use it if applicable

by nurses in achieving postoperative analgesia after a major surgery. PCA also had superior patient satisfaction pain control and better recovery after surgery.<sup>[23,24]</sup> Although the PCA group had higher opioid consumption than the intermittent IV doses group, it did not affect the in-hospital length of stay.<sup>[24]</sup> Sedation and respiratory depression have been reported, but only due to misuse of PCA. Furthermore, it was a rare occurrence at 0.3% with PCA morphine and should not dissuade from their use.<sup>[23,25]</sup> In spontaneously breathing COVID-19 patients, the use of a background basal infusion should be avoided and monitoring of continuous pulse oximetry should be employed.<sup>[26]</sup>

The use of PCA decreases nursing visits, thus decreasing healthcare workers' exposure to COVID-19 patients. Hospitals should develop protocols for assigning and disinfecting PCA pumps and their attachments following use by COVID-19-positive patients. No specific programming or preferred agent for PCA in COVID-19 patients has been proposed. We recommend that physicians exercise caution when using PCA in COVID-19 patients and ensure that appropriate monitoring protocols are in place.

## Commonly used analgesic medications

### Opioids

Opioids are widely used in the management of moderate to severe postoperative pain in the absence of regional anesthesia. Unfortunately, these medications cause dose-dependent respiratory depression,<sup>[27]</sup> which may necessitate the use of supplemental oxygen or rescue airway maneuvers. This may lead to aerosolization of the virus and an increased risk of transmission of the disease. Furthermore, several in-vivo and in-vitro studies have indicated that the stimulation of opiate receptors may result in the depression of several components of the immune system, such as neutrophils, phagocytes, and natural killer cells. There are still knowledge gaps in the pharmacology related to the immune system for opioids other than morphine.<sup>[28,29]</sup> Nevertheless, there is no clear evidence that clinical doses of opioid therapy cause clinically significant immunosuppression.

It is essential to try to avoid depending solely on opioids for pain control by offering multimodal analgesia. On the other hand, it may not be reasonable to ban opioids completely for all COVID-19 patients undergoing surgery due to the nature of some surgeries and patient comorbidities. Anesthesia providers should not provide patients with suboptimal pain therapy to avoid using opioids. Interactable pain can delay mobilization, thus impairing respiratory function.<sup>[30]</sup> No opioid is superior to another in this situation, but a careful titration of the opioid dose in a multimodal analgesic setting is advised. Careful attention must be paid to the side effects, duration of action, and systemic involvement of COVID-19, such as renal and cardiac dysfunction.<sup>[31,32]</sup>

In patients with renal impairment, caution is advised with opioids that depend on renal excretion, which may lead to the accumulation of active metabolites. Furthermore, the dose of opioids should be titrated carefully in patients who show evidence of cardiovascular dysfunction to avoid circulatory decompensation. Patients who are chronic opioid users should continue their regimen if appropriate in order to avoid withdrawal. All patients receiving intrathecal morphine for perioperative pain control should have their vital signs checked hourly for the first 12 hours in order to prevent delayed respiratory depression. Intramuscular and subcutaneous opioids have an unpredictable onset, a longer duration of action, and are inferior when compared to other routes of administration.<sup>[33]</sup>

In COVID-19 patients, the anticipation of opioid-related side effects is prudent, and proactive management is of paramount importance. The prophylactic management of nausea is advised since retching and vomiting may lead to aerosolization of the virus. Patients at high risk of

postoperative respiratory depression should be monitored in a high dependency unit and early signs of respiratory compromise should be aggressively treated.

#### **Paracetamol (acetaminophen)**

In a review by Feng *et al.*, a considerable percentage of COVID-19 patients had increased levels of ALT and AST liver enzymes. These findings were seen more in adults than in children.<sup>[34]</sup> The US FDA Acetaminophen Advisory Committee recommended decreasing the dose of paracetamol (acetaminophen) to 3.25 grams per day to decrease the incidence of overall toxicity.<sup>[35]</sup> In COVID-19 patients, we recommend reviewing the liver enzymes, conducting a thorough medication reconciliation before starting paracetamol, and adhering to the recommended daily dose of 3.25 grams if the benefit outweighs the risk. In COVID-19 patients with no liver dysfunction, a single perioperative dose is unlikely to cause harm.

#### **Nonsteroidal anti-inflammatory drugs (NSAIDs)**

Except for naproxen, both nonselective COX inhibitors (ibuprofen and diclofenac) and selective COX2 inhibitors (celecoxib, rofecoxib, and parecoxib) can increase the risk of major cardiovascular events. All of them increase the risk of gastrointestinal bleeding and kidney dysfunction when used at a high dose and for a long term.<sup>[36]</sup> Two studies showed that the short-term perioperative use (less than two weeks) of parecoxib/valdecoxib by patients undergoing Coronary Artery Bypass Graft (CABG) surgery was associated with a significant increase in the risk of cardiovascular events and poor wound healing.<sup>[37,38]</sup>

The concern of worsening respiratory tract infections with the use of NSAIDs resurfaced when COVID-19 became a pandemic, especially since many of NSAIDs are sold over the counter.<sup>[39]</sup> In mid-April 2020, the WHO conducted a rapid systematic review and concluded that the available evidence is not sufficient to support the concern about severe adverse events, long-term survival, and quality of life when NSAIDs are used by COVID-19 patients.<sup>[40]</sup> COVID-19 patients can become seriously ill, especially those in older age groups and patients with comorbidities. These patients are at higher risk of having the adverse effects of NSAIDs. The question of whether a one-time dose or a 24-hour course of a selective COX2 inhibitor perioperatively can lead to significant harm is a one for which we did not find evidence in our search. The authors recommend discontinuing any long-term use of both types of NSAIDs and avoiding the routine use of perioperative NSAIDs in elderly patients and patients with multiple cardiovascular comorbidities with moderate to severe COVID-19.

#### **Dexmedetomidine**

Dexmedetomidine is a highly selective  $\alpha_2$ -adrenergic agonist that has several beneficial effects, including sedation and analgesia. It also has an added benefit of opioid-sparing when used perioperatively in patients undergoing abdominal surgery.<sup>[41]</sup> Several studies have shown that it may reduce the severity of different types of lung injury in rats.<sup>[42-44]</sup>

Dexmedetomidine also has other attributes that may make it an attractive option in the management of COVID-19 patients, such as preserving respiratory drive and reducing delirium. The most common adverse reactions of dexmedetomidine (with incidence higher than 2%) are hypotension, bradycardia, and dry mouth. In elderly patients and those with low baseline arterial pressure, it can lead to hemodynamic instability.<sup>[45]</sup>

Dexmedetomidine has been successfully used for sedation in COVID-19 patients with good results.<sup>[46]</sup> Due to adverse reactions associated with prolonged infusion (tachyphylaxis, respiratory failure, and agitation), its use for sedation in intensive care units is usually limited to less than 24 hours.<sup>[45,47]</sup> In conclusion, dexmedetomidine can be used as an adjunct for acute pain and sedation of COVID-19 patients in the perioperative period, but its adverse effects should always be kept in mind.

#### **Gabapentinoids**

Pregabalin and gabapentin are anticonvulsant agents that are commonly used in the management of many chronic pain conditions. Recently, they have been used increasingly in the management of acute postoperative pain. In many studies, gabapentinoids reduced postoperative pain and decreased opioid requirements when they were given preoperatively.<sup>[48]</sup> However, there is emerging evidence that recommends against the routine use of gabapentinoids as part of a multimodal analgesic regimen in enhanced recovery pathways. The opioid-sparing effect has been questioned and hardly regarded as minimal, and the adverse effects are said to be underestimated.<sup>[49,50]</sup>

In December 2019, the US FDA warned of an increased risk of pneumonia, severe respiratory insufficiency, and even death associated with the use of gabapentinoids, particularly when they are used concomitantly with opioid analgesics, hypnotics, antidepressants, and antihistamines.<sup>[51]</sup> In 2017, the EMA warned about severe respiratory depression with gabapentinoids, which affects up to 1 in 1,000 patients.<sup>[52,53]</sup> The summary of product characteristics (SPC) of gabapentin stated that the incidence of viral infections in RCTs was “very common” (more than 1 in 10), and the incidence of pneumonia and respiratory infection was “common” (between 1 in 10 and

1 in 100). The SPC of pregabalin warned that the incidence of nasopharyngitis is “common” in treated patients (between 1 in 10 and 1 in 100).<sup>[54]</sup>

Gabapentinoids should be tailored to each patient based on their comorbidities to minimize the risk of adverse effects. They may be considered selectively for surgeries with a high likelihood of substantial postoperative pain.<sup>[49]</sup> We recommend against the routine use of gabapentinoids as adjuvant medications to treat postoperative pain in patients with moderate to severe COVID-19, and caution is advised for their use by those who are asymptomatic or have mild symptoms.

### **Ketamine**

Ketamine is a noncompetitive NMDA receptor antagonist that has potent analgesic properties when administered in subanesthetic doses. It is opioid-sparing, which makes it useful when opioids pose risks to patients.<sup>[55,56]</sup> Ketamine preserves spontaneous ventilation, has a bronchodilation effect, and reduces airway resistance.<sup>[57-60]</sup> The Royal College of Anaesthetists recommended using ketamine for anesthesia induction in COVID-19 patients who have a higher risk of cardiovascular instability due to the drug’s positive effect on hemodynamics.<sup>[61]</sup>

Ketamine is recommended for patients undergoing surgeries where severe postoperative pain is expected, as well as those who are opioid-tolerant or dependent according to the guidelines of the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS), ASRA, AAPM, and ASA. They also suggest that ketamine be considered for opioid-dependent or tolerant nonsurgical patients with chronic pain conditions who have acute pain exacerbations, as well as patients with increased risk of respiratory depression or ileus. At high doses, ketamine may lead to transient tachycardia and hypertension, which is a concern for patients with pre-existing ischemic heart disease.<sup>[62]</sup> We support the use of ketamine perioperatively in subanesthetic doses as an adjuvant medication in the management of perioperative pain in patients with COVID-19 for its analgesic and opioid-sparing effects.

### **Lidocaine**

IV lidocaine infusion is widely used in perioperative multimodal analgesia for many surgical procedures.<sup>[63]</sup> We recommend its use when applicable as an adjuvant for its opioid-sparing effect. A bolus dose of lidocaine on induction can also help blunt the airway response associated with intubation, which in turn can decrease coughing and bucking.

This is beneficial for preventing cross-contamination in patients who are shedding the virus.<sup>[64,65]</sup>

### **COVID-19 medications and perioperative analgesia**

Drug–drug interaction in patients with COVID-19 is a complex topic that is rapidly evolving. Interactions may range from a mild transient effect to permanent disability or death. To our knowledge, no other paper has been dedicated to the potential drug–drug interactions in COVID-19 patients for perioperative analgesia. Table 4 summarizes the considerations of drug–drug interactions and adverse effects in this situation.

Careful drug reconciliation should be conducted before developing a perioperative pain management plan for such patients. Several online resources for checking drug–drug interactions are available. We found the University of Liverpool COVID-19 Drug Interactions website to be a valuable resource, and a link is provided in the references section.<sup>[66]</sup>

### **Antimicrobials**

#### ***Chloroquine and hydroxychloroquine***

The antimalarial drugs chloroquine and hydroxychloroquine were among the first drugs to ride the wave of drug-repurposing in the face of the pandemic and they have been falling out of favor lately. However, the authors of an article published in *Lancet* that influenced physicians in abandoning chloroquines have retracted their article for reasons that have to do with the inability to reanalyze the data by an independent reviewer.<sup>[67]</sup>

Although chloroquines are considered generally well tolerated, several articles have warned about their harmful adverse effects, such as prolongation of the QT interval.<sup>[68,69]</sup> In patients receiving chloroquines, caution is advised with the use of methadone, high-dose oxycodone, and meperidine since these opioids can prolong the QT interval as well.<sup>[70,71]</sup> Both chloroquines competitively inhibit the activity of hepatic cytochrome P450 enzyme 2D6 (CYP2D6), which may reduce the effect of prodrugs such as tramadol and codeine and promote the propagation of withdrawal symptoms in patients who are dependent on these drugs.<sup>[72]</sup>

#### ***Azithromycin***

Azithromycin is commonly used in combination with chloroquines in the treatment of COVID-19. This antibiotic inhibits the hepatic CYP3A4 enzyme and can increase the circulating levels of the active forms of opioids.<sup>[73]</sup> Moreover, prolongation of the QT interval with the concomitant use of methadone and azithromycin has been reported.<sup>[74]</sup>

**Table 4: Common COVID-19 medications and considerations for perioperative pain management**

Medication	Important drug interaction or adverse effects
<b>Antimicrobials</b>	
Chloroquine and Hydroxychloroquine	Inhibit CYP2D6, may reduce the effect of prodrug opioids such as Tramadol and Codeine. Prolong QT, caution with Methadone, Meperidine and high dose Oxycodone.
Azithromycin	Inhibits CYP3A4, may induce opioid overdose. Prolongs QT.
Remdesivir	Induces CYP3A4, no sufficient data on opioid metabolism. Most common adverse effects: nausea and acute respiratory failure.
Lopinavir/Ritonavir	Strong inhibitor of CYP3A4, caution with all opioids. Prolongs QT.
Favipiravir	Interferes with the metabolism and excretion of Paracetamol, limit Paracetamol dose to 3g/day.
<b>Immunomodulatory agents</b>	
Tocilizumab	No major adverse events or relevant drug-drug interactions reported.
INF- $\alpha$ -2a and Ribavirin	No major adverse events or relevant drug-drug interactions reported.
<b>Immunoglobulin therapy</b>	
IVIG	No major adverse events or relevant drug-drug interactions reported.
<b>Supportive medications</b>	
Albuterol & Ipratropium	No significant drug-drug interactions or adverse effects related to perioperative pain management.
Systemic Corticosteroid	Can decrease postoperative pain but should not be used for that purpose since the risks outweigh the benefit. The exception in the risk vs benefit is in Dexamethasone use in patients requiring supplemental O <sub>2</sub> or mechanical ventilation for the purpose of decreasing mortality.
Loperamide	Could prolong QT at very high doses > 100mg/day. May enhance the effect of other opioids at high doses.
Ondansetron	Metabolized by CYP2D6, could decrease efficacy of Tramadol and Codeine. Prolongs QT interval (dose dependent).
Metoclopramide	With long-term and/or high doses, it can cause somnolence and prolonged QT that is dose dependent.
Dextromethorphan	In slow metabolizers or with the concurrent use of a CYP450 inhibitor it may have a significant sedative effect.

**Remdesivir**

Remdesivir is an antiviral agent that was recently supported for its use in patients with COVID-19 in a preliminary report of one of its trials.<sup>[75]</sup> Nausea and acute respiratory failure were the most common adverse events in the SIMPLE trial. It has induction properties of hepatic CYP3A4 among other CYPs and may affect the metabolism of opioids. However, there are no data to support this drug-drug interaction yet.<sup>[76]</sup>

**Lopinavir/ritonavir**

The antiviral drug combination of ritonavir and lopinavir is approved for the treatment of Human Immunodeficiency Virus (HIV). This combination therapy is undergoing trials for its potential use in patients with COVID-19. Ritonavir is a potent CYP3A4 inhibitor and may interfere with opioid metabolism, thus increasing the chance of opioid overdose.<sup>[77,78]</sup> Prolongation of the QT interval has also been reported with this therapy. The questionable efficacy and side effect profile of this combination may hinder its approval for the treatment of COVID-19.<sup>[78]</sup>

**Favipiravir**

Favipiravir is an antiviral agent that is approved for the treatment of influenza and is undergoing several trials as a potential treatment for COVID-19. It decreases the metabolism and excretion of paracetamol in healthy

individuals. When used concomitantly with favipiravir, the dose of paracetamol should be reduced to 3 g daily.<sup>[79]</sup>

**Immunomodulatory agents****Tocilizumab**

Tocilizumab is a monoclonal antibody agent that is used for some forms of arthritis.<sup>[80]</sup> It is undergoing trials for the treatment of COVID-19 and is showing promising results in terms of decreasing ICU admission and mortality rates.<sup>[81,82]</sup> It can cause headache, hypertension, and a dose-dependent increase in liver enzymes, but no significant relevant side effects have been reported yet.<sup>[80,83,84]</sup>

**Interferon- $\alpha$ -2a and ribavirin**

The combination of interferon  $\alpha$ -2a (an immunomodulator) and ribavirin (an antiviral drug used for the treatment of hepatitis C infections) is undergoing several clinical trials for its efficacy in the treatment of COVID-19. INF- $\alpha$ -2a/ribavirin, combined with lopinavir/ritonavir, may be used in the treatment of COVID-19 based on the positive results seen in the treatment of MERS. There is no interaction with drugs used for perioperative pain apart from gastrointestinal symptoms and depression.<sup>[84]</sup>

**Immunoglobulin therapy****IVIG**

Intravenous immunoglobulin (IVIG) therapy is being investigated for use in the treatment of COVID-19. It has

been used in some chronic pain conditions with positive results.<sup>[85-87]</sup> We have not been able to find any articles showing any positive or negative effects of IVIG on acute pain. No reported drug–drug interactions were found with this therapy.

### Supportive medications

#### **Albuterol and ipratropium**

Albuterol and ipratropium are commonly used in the management of asthma and COPD. The alpha-adrenergic receptor agonist albuterol can cause tachycardia, anxiety, or agitation. The anticholinergic drug ipratropium bromide can cause sedation and tachycardia. When used in clinically appropriate doses, no side effects with analgesic agents were reported.<sup>[88]</sup>

#### **Corticosteroids**

The CDC and WHO recommend against the routine use of systemic corticosteroids for the treatment of COVID-19.<sup>[89]</sup> Nevertheless, they are still being used in critical COVID-19 patients diagnosed with severe ARDS. They are unlikely to be used in other COVID-19 patients except for those already being treated for a chronic illness. Even a single perioperative dose of a systemic corticosteroid may reduce postoperative pain and opioid consumption.<sup>[90]</sup> Furthermore, a single dose of dexamethasone is commonly used intraoperatively for the prevention of postoperative nausea and vomiting. Nevertheless, these benefits come with the cost of potential risks of systemic corticosteroids, such as higher risks of surgical wound infection, hyperglycemia, and immune suppression.<sup>[91]</sup> The most recent CDC recommendations on the use of dexamethasone in COVID-19 patients, that came out in June 2020, was to limit its use to patients who require supplemental O<sub>2</sub> or mechanical ventilation.

#### **Loperamide**

Loperamide is a peripheral  $\mu$  opioid receptor agonist used for the symptomatic treatment of diarrhea. This drug may have a place in the management of loose bowel motions that may accompany COVID-19. At high doses (100 mg/day or more, typical of substance abuse), loperamide can prolong the QT interval by a mechanism similar to that of oxycodone. This effect is not of concern with clinically appropriate doses. By competing for the same CYP450, it may enhance the effect of other opioids.<sup>[92]</sup>

#### **Ondansetron**

Ondansetron is an antiemetic agent that is metabolized by the hepatic CYP2D6 enzyme. It may compete with opioids that are metabolized by the same CYP system.<sup>[93]</sup> Concomitant use of ondansetron may decrease the efficacy of the prodrug forms of opioids (i.e., codeine, tramadol, and hydrocodone).<sup>[93-95]</sup> As

a 5-HT<sub>3</sub> receptor antagonist, ondansetron may also decrease the efficacy of tramadol since the latter works by inhibiting serotonin reuptake and noradrenaline in addition to being a weak  $\mu$  receptor agonist.<sup>[95]</sup> Fentanyl, hydromorphone, and oxycodone are mainly metabolized by CYP3A4 and are less likely to be affected by ondansetron.<sup>[96]</sup> Ondansetron is widely used in the management of perioperative nausea and vomiting. The risk of QT interval prolongation with ondansetron is dose-dependent.<sup>[97]</sup>

#### **Metoclopramide**

Metoclopramide is structurally related to the local anesthetic agent procaine but is devoid of local anesthetic properties. It is widely used as an antiemetic and a gastrointestinal prokinetic agent.<sup>[98]</sup> As a D<sub>2</sub> receptor antagonist, metoclopramide has a remarkable analgesic effect on acute migraine attacks.<sup>[99]</sup> Other than that, it does not show any analgesic properties. With long-term use at high doses, metoclopramide can cause somnolence, extrapyramidal side effects, and prolongation of the QT interval.<sup>[22]</sup> In a typical one-time small dose of metoclopramide in the perioperative course, the adverse effects are unlikely to outweigh the benefit of preventing nausea and vomiting in COVID-19 patients.

#### **Dextromethorphan**

Dextromethorphan is structurally related to opioid agonists and has NMDA receptor antagonist activity, but its analgesic effect is negligible. It is widely used as an anti-tussive agent. Dextromethorphan can cause excessive sedation in slow metabolizers, which should be kept in mind when used for patients with COVID-19.<sup>[100]</sup>

### Limitations

Literature discussing COVID-19 and perioperative pain management is scarce. Many of the considerations and recommendations in this field fall under expert opinions based on pertinent evidence. As new evidence on COVID-19 is rapidly emerging, some of it may contradict the current findings.

### Conclusion

Anesthesia providers may often encounter COVID-19 patients presenting for a surgical procedure, which can pose challenges in the management of perioperative pain from various perspectives. Regional techniques should be high on the list of analgesic modalities considered for their opioid-sparing effect and potential prevention of cross-contamination. Opioids are the most common analgesic medications used in perioperative pain management, but their use is associated with a risk of respiratory depression,



which is an added concern for patients with respiratory compromise. Furthermore, some of the medications used in the management of COVID-19 patients induce or inhibit hepatic CYP450 or compete with opioids on the same metabolic pathway, resulting in the augmentation or attenuation of their effect.

Multimodal analgesia is advantageous for COVID-19 patients since it is opioid-sparing. We have highlighted many of the potential drug–drug interactions and pertinent adverse effects that may occur in the management of perioperative pain in COVID-19 patients. As research on COVID-19 is rapidly growing and our knowledge of it is expanding, better management of perioperative pain will ensue. This review is endorsed by the Saudi Anesthesia Society (SAS) and the Saudi Society of Pain Medicine (SSPM).

### Acknowledgments

We thank Dr Amani H Yamani, MB BS, ABIM board certified in internal medicine and infectious diseases, associate consultant of internal medicine, infectious diseases, and transplant and oncology infectious diseases at King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, for her assistance with the antimicrobial section of this article.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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