



# Perioperative Nonsteroidal Anti-Inflammatory Agents in the COVID-19 Orthopedic Patient

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**Abstract** *Background:* SARS-CoV-2 infection can cause serious complications beyond lung injury and respiratory failure, including sepsis, cardiovascular injury, renal failure, coagulation abnormalities, and neurologic injury. Widely used medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) have been flagged as having the potential to cause harm in the context of COVID-19. It is unknown if the benefits of NSAID use in the orthopedic population will outweigh the potential risks of increased morbidity in COVID-19 orthopedic patients. *Methods:* We conducted a narrative review of the use of NSAIDs in the orthopedic patient with COVID-19, focusing on the effects of NSAIDs on the inflammatory process, the role of NSAIDs in orthopedics, and the associations between NSAID use and complications of pneumonia. *Results:* We found that it may be appropriate to consider NSAID use in otherwise healthy orthopedic patients with COVID-19 and significant pain. *Conclusions:* In this context, we recommend that NSAIDs be used at the lowest effective dose for the shortest duration possible in orthopedic patients with COVID-19. However, pending further data and based on the concerns outlined in this review, we recommend avoiding NSAIDs in orthopedic patients with significant comorbidities and those who are undergoing major orthopedic surgery.

**Keywords** nonsteroidal anti-inflammatory agents · COVID-19 · orthopedic

## Introduction

As the coronavirus disease 2019 (COVID-19) pandemic unfolded, it became clear that SARS-CoV-2 infection can cause serious complications beyond lung injury and respiratory failure, including sepsis, cardiovascular injury, renal failure, coagulation abnormalities, and neurologic injury. Such complications may be particularly severe in elderly people and those with underlying health conditions [47]. One of the hallmarks of severe COVID-19 is the contribution of a dysfunctional immune response to disease progression as a result of an aggressive inflammatory response [38]. In the absence of an effective vaccine or treatment for COVID-19, many commonly available drugs have been examined for potential utility in managing this complicated disease. However, other widely used medications have been flagged as having the potential to cause harm in the context of COVID-19 [13]. In March 2020, the French Health Minister, Olivier Véran, claimed on Twitter that anti-inflammatory medications such as ibuprofen or cortisone might aggravate COVID-19, stimulating widespread global concern about these classes of otherwise useful drugs [43]. Approximately 1 in 15 adults in the USA use prescription nonsteroidal anti-inflammatory drugs (NSAIDs), and nearly half have used nonprescription NSAIDs during the COVID-19 pandemic [28]. In the realm of acute and chronic pain management, the potential impact of empiric avoidance of NSAIDs could be vast.

As part of a multimodal regimen [42], NSAIDs are an important analgesic option for orthopedic patients and an integral part of many orthopedic enhanced recovery pathways [36, 37]. NSAIDs are among the most effective analgesics available [24] and may be associated with a significant reduction in opioid use and critical respiratory failure in high-risk orthopedic patients with obstructive sleep apnea (OSA) [8].

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Nevertheless, NSAID use is not without risk (renal, coagulation, gastrointestinal, cardiovascular), particularly in orthopedic patients with significant comorbidities. It is unknown if the benefits of NSAID use in the orthopedic population will outweigh the potential risks of increased morbidity in COVID-19 orthopedic patients. In this review, we discuss the effects of NSAIDs on the inflammatory process, the role of NSAIDs in orthopedics, the associations between NSAID use and complications of pneumonia, and the available literature on NSAIDs in relation to COVID-19 orthopedic patients.

### NSAIDs, the Inflammatory Process, and COVID-19

NSAIDs act in large part through inhibition of the prostaglandin synthases cyclooxygenase (COX)-1 and -2. Prostaglandins (PGs) mediate diverse physiologic effects in different tissues, ranging from allergic responses and bronchoconstriction to vasoconstriction/vasodilation, platelet aggregation, sleep regulation, pain, inflammation, and maintenance of the gut mucosa [23]. Thus, while NSAIDs are appealing for their antipyretic and analgesic effects, the potential deleterious effects of selective and non-selective COX inhibition in various tissues must be considered. The most common complications of NSAIDs encountered in clinical practice are gastric ulceration, gastrointestinal bleeding, renal injury, and coronary vascular events (especially with COX-2 inhibitors).

Given the widespread use and study of NSAIDs over many decades, it is notable that novel effects and mechanisms of these compounds continue to be discovered. NSAIDs have been shown to have COX-independent inflammatory effects, including effects on leukocyte adhesion and chemotaxis as well as modification of transcription factors involved in regulation of inflammatory cytokines [9]. Unexpectedly, in 2006, the potent NSAID indomethacin was shown to have direct antiviral effects on SARS-CoV and a related coronavirus, independent of its immunomodulatory effects [1].

However, NSAIDs as a class may be considered to be a potential risk factor for increased COVID-19 susceptibility and severity. One concern is that SARS-CoV-2, the virus that causes COVID-19, has a viral envelope with glycoprotein spikes that bind to angiotensin-converting enzyme-2 (ACE-2) on cell surfaces and fuse with cell membranes [2]. ACE-2 is expressed in high levels on alveolar epithelial cells and is considered to be both an essential infectious route for SARS coronaviruses and a key contributor to associated lung pathology [19, 30]. It has been widely reported that NSAIDs may increase COVID-19 risk by increasing expression of ACE-2 [6, 22]. However, this hypothesis hinges entirely on data from a diabetic mouse model of cardiac fibrosis in which abnormally low ACE-2 levels were corrected by ibuprofen administration [31]. It is unclear how or if this study is relevant to human ACE-2 expression in the lung or any other tissue in diabetic or non-diabetic patients. It is also not clear if the observed experimental effect was specific to ibuprofen or applicable to other

NSAIDs. Moreover, even should NSAIDs be shown to increase ACE-2 expression similarly to the use of ACE-1 inhibitors and angiotensin II receptor blockers (ARBs) [2], preliminary evidence does not support an association with increased risk or severity of COVID-19. A database analysis of approximately 5894 COVID-19 patients (2573 who had hypertension) found no association between any single medication class (ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics) and an increased risk of severe COVID-19 [32]. Previous treatment with anti-hypertensive medications also was not associated with a higher risk of testing positive for COVID-19 [32].

While there is little evidence to suggest that NSAIDs increase COVID-19 risk via ACE-2, significant COVID-19-related clinical concerns remain. In severe cases of COVID-19, acute respiratory distress syndrome (ARDS) is often associated with the development of a cytokine release syndrome characterized by persistent fevers with increased levels of inflammatory markers such as ferritin, interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  [11, 12]. As PGs can both promote and attenuate inflammation, the impact of various NSAIDs on the inflammatory pathology of COVID-19 remains unclear. Moreover, severe COVID-19 is strongly associated with risk of renal injury, myocardial events, and thrombotic complications [14, 15, 45], any of which may be exacerbated by the known risk profiles of various NSAIDs [17, 20, 23]. Observational studies suggest a higher rate of acute kidney injury in COVID-19 inpatients, with 75% having abnormal urine dipstick test results, 44% with proteinuria, 27% with hematuria, and approximately 14% with elevated serum creatinine/blood urea nitrogen and estimated glomerular filtration under 60 mL/min [5, 29, 48]. Acute kidney injury occurs in approximately 5 to 15% of COVID-19 inpatients [5, 48]. Evidence of myocardial injury has been reported in 7 to 20% of hospitalized COVID-19 patients [10, 16, 35]. Incidence of deep venous thrombosis (DVT) has been described in as many as 46% of inpatients, with 31% incidence reported in an intensive care unit (ICU) population despite thromboprophylaxis, and evidence of cardiac injury is seen in approximately 20% in hospitalized and critically ill patients [18, 35].

### The Role of NSAIDs in Orthopedic Peri-operative Care

NSAIDs are potent analgesics that have demonstrated equivalent analgesia to opioids in combined systematic reviews of randomized, double-blind, single-dose studies in patients with moderate to severe pain. For example, oxycodone immediate release 10 mg with acetaminophen 650 mg provides equivalent analgesia to ibuprofen 400 mg [27]. The combination of acetaminophen with an NSAID may offer superior analgesia compared with either drug alone [26].

NSAIDs are typically used as part of a multimodal analgesic regimen in orthopedic patients and the use of NSAIDs in this population is associated with improved outcomes [36, 37, 42]. In a large database analysis, 85.6% ( $N = 1,318,165$ ) of total hip and knee arthroplasty patients received multimodal analgesia, and total hip arthroplasty patients who

received more than 2 non-opioid analgesics (versus opioids only) had significantly fewer respiratory complications, less gastrointestinal morbidity, and decreased opioid prescriptions and lengths of stay [24]. NSAIDs, including selective COX-2 inhibitors, were the most effective analgesic modalities in improving outcomes [24]. In high-risk orthopedic patients, such multimodal analgesic regimens may be of particular value. For example, in a database analysis of OSA patients, use of multimodal analgesia was associated with a significant decrease in need for mechanical ventilation and ICU admission than an opioid-only approach to pain management [8].

As in the general population, care must be taken to minimize the potential adverse events associated with NSAID use in orthopedic patients. A recent meta-analysis suggested that current exposure to NSAIDs was associated with an increase in the odds of developing acute kidney injury (AKI) in the general population with higher risk in the elderly and people with chronic kidney disease [46]. All NSAIDs may result in gastrointestinal toxicity which may be reduced by taking a concomitant gastroprotective agent [7]. In addition, while selective COX-2 inhibitors have been associated with the greatest risk of adverse cardiac events, many non-selective NSAIDs are associated with some degree of cardiovascular risk (e.g., heart failure, elevated blood pressure) and thrombotic events [33].

### **NSAIDs and Pulmonary Infections in Non-COVID-19 Patients**

Although pulmonary complications are not typically associated with NSAID use, a review of the few published observational studies suggests that NSAID use may be associated with higher rates of complicated pneumonia [41]. The largest published dataset utilized the Danish National Patient Registry (1997–2011) to identify 59,250 patients with a first-time diagnosis for community-acquired pneumonia (CAP) [3]. Of these patients, 15% had filled an NSAID prescription within 60 days before the index date. The authors found an association between NSAID intake and increased risk of pleuropulmonary complications (pneumonia, lung abscess, pyothorax, or pleural effusion) with the highest risk observed in patients with a recent NSAID prescription filled within 0–7 days before CAP [3]. An observational study ( $n = 106$ ) in CAP patients requiring ICU admission found that the 20 patients who received NSAIDs within 4 days of ICU admission were younger with fewer comorbidities but were more likely to have complicated pleural effusions or pleuropulmonary complications [25]. Finally, in a small observational study of 90 CAP inpatients admitted to the ICU, stepwise logistic regression analysis revealed that patients who had taken NSAIDs prior to hospital admission had a higher rate of pleuropulmonary complications, such as pleural empyema and lung cavitation [40]. It is unclear whether the anti-inflammatory and immunomodulatory effects of NSAIDs directly affect the clinical course of CAP or if the observed complications

result from delayed treatment in the context of suppression of symptoms [21, 25, 40].

### **NSAIDs in the COVID-19 Orthopedic Patient**

Despite claims that NSAIDs might exacerbate COVID-19 [43], both the US Food and Drug Administration (FDA) and the World Health Organization (WHO) have stated that they are not aware of scientific evidence linking the use of NSAIDs with worsening COVID-19 symptoms [34, 39]. An official announcement from the FDA did note that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections” [39]. In response to concerns on the use of NSAIDs in the context of COVID-19, the WHO recently reported on a systematic review of 73 studies examining the use of NSAIDs in viral infections [44]. This review revealed no severe adverse effects associated with NSAID use and was unable to draw conclusions about the potential risk of cardiovascular events.

It is difficult to determine whether the benefits outweigh the risks of NSAID use in the orthopedic COVID-19 population. There is currently no compelling scientific evidence indicating that COVID-19 patients who have mild symptoms are harmed by the use of NSAIDs. For orthopedic patients who test positive for COVID-19 but are otherwise healthy, it may be appropriate to continue to use NSAIDs. This option is especially important to consider in patients who have severe acute or significant chronic pain and would otherwise face the need for opioid pain management. In contrast, in patients expected to experience minimal pain, it may be prudent to minimize or avoid NSAIDs in the setting of COVID-19, even in healthy patients.

Hospitalized COVID-19 patients or patients with significant related comorbidities (renal, gastrointestinal, coagulation, cardiovascular) are at higher risk for complications including respiratory failure, kidney injury, myocardial damage, and thrombotic events [4]. This profile of organ injury overlaps significantly with complications independently associated with both complex orthopedic surgery and with the use of certain NSAIDs. Given these overlapping risk profiles, it may be appropriate to avoid NSAIDs in orthopedic COVID-19 patients hospitalized for major surgery or with significant related comorbidities.

In summary, as part of a multimodal analgesic regimen, NSAIDs are a valuable and integral analgesic option for the management of pain in the orthopedic patient. The primary mechanism of action (COX inhibition) for NSAIDs is well-defined as are both its beneficial and deleterious effects. There are hypothetical mechanisms by which NSAIDs may exacerbate COVID-19 but none have been definitively proven. It may be appropriate to consider NSAID use in otherwise healthy orthopedic patients with COVID-19 and significant pain. In this context, we recommend that NSAIDs be used at the lowest effective dose for the shortest duration possible. However, pending further data and based



on the concerns outlined in this review, we recommend avoiding NSAIDs in orthopedic patients with significant comorbidities and those who are undergoing major orthopedic surgery.

### Compliance with Ethical Standards

**Conflict of Interest:** Christopher L. Wu, MD, Kethy M. Jules-Elysee, MD, Meghan A. Kirksey, MD, PhD, and Gregory A. Liguori, MD, declare that they have no conflict of interest.

**Human/Animal Rights:** N/A

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