Review Article

Nonsteroidal Anti-Inflammatory Drugs in Viral Infections Disease, Specially COVID-19

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Abstract

During the current SARS-CoV-2 (COVID-19) pandemic, some reports were presented based on those nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may exacerbate symptoms in COVID-19 patients. According to this, we aimed to collate information available in published articles to identify any evidence behind these statements with the aim of helping clinicians on how best to treat patients. We could not find published conclusive evidence for or against the use of NSAIDs in COVID-19 patients. Meanwhile, there appeared to be some evidence that corticosteroids may be beneficial if utilized in the early acute phase of infection, however, conflicting WHO (World Health Organization) evidence surrounding corticosteroid use in certain viral infections means this evidence is not conclusive. Given the current availability of literature, caution should be exercised until further evidence emerges surrounding the use of NSAIDs and corticosteroids in COVID-19 patients. However, the availability of reliable information for clinicians and patients is paramount.

Keywords: Corticosteroid, COVID-19, nonsteroidal anti-inflammatory drugs, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus was declared as a main threat to global health in December 2019.[1] The WHO referred to this novel pneumonia-like disease in Wuhan, China as COVID-19.[2] The coronavirus is a type β virus and its genetic sequence has a 70% similarity to the SARS virus.[3] After entering the body, the coronavirus binds to the beta coronavirus receptor angiotensin-converting enzyme 2 (ACE2) and invades healthy cells. It begins to multiply rapidly and eventually kills its host cell. The continued proliferation of the virus and the subsequent death of cells will lead to pneumonia, dyspnea, and in more severe cases, acute respiratory distress syndrome (ARDS).[4]

The most common symptoms of COVID-19 include fatigue, tiredness, muscle pain, dry cough, dyspnea or shortness of breath, fever, and gastrointestinal problems. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a subset of a drug class that acts as a pain killer, antipyretic, anticoagulant, and in higher doses act as an anti-inflammatory drug. Side effects involve an increased chance of gastrointestinal ulcers and bleeds, heart attack, and kidney disease.[4-6]

The idiomnonsteroidal recognized these drugs from steroids, which while having a like eicosanoid-depressing, anti-inflammatory activity, and many other effects. First used in 1960, the term served to distinguish these medications from steroids, which were especially brand at the time as the overhead with anabolic steroid misuse.[7] NSAIDs by inhibiting the activity of cyclooxygenase enzymes (COX-1 or COX-2) that are involved in the synthesis of prostaglandins play their main role in the inflammation process and blood clotting.

There are two types of NSAIDs accessible: nonselective and COX-2 selective.[8] Most NSAIDs are nonselective who can obstruct the activity of both COX-1 and COX-2. These NSAIDs, whereas reducing inflammation, also suppress

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platelet aggregation and increase the chance of gastrointestinal ulcers/bleeds.[8] COX-2 selective inhibitors have less gastrointestinal side effects but advertise thrombosis and some of these agents extensively increase the risk of a heart attack. As a result, assured older COX-2 selective inhibitors are no longer used due to the high risk of undiagnosed vascular disease.[8] These differential reactions are due to the different roles and tissue localizations of each COX isoenzyme.[8] By inhibiting physiological COX activity, all NSAIDs increase the chance of kidney disease and heart attack.[9,10] In addition, NSAIDs can block the creation of erythropoietin resulting in anemia, since hemoglobin needs this hormone to be produced.

The largest prominent NSAIDs are aspirin, ibuprofen, and naproxen, all available over the counter (OTC) in most countries.[11] Paracetamol (acetaminophen) is generally not considered an NSAID because it has only minor anti-inflammatory activity. Paracetamol treats pain mainly by blocking COX-2 and inhibiting endocannabinoid reuptake almost exclusively within the brain, but not much in the rest of the body.[12,13]

In COVID-19 patients with hypertension, using ACE1 inhibitors and angiotensin receptor blocker (ARB) reduces the production of angiotensin II (ANG II), thus lowering the levels of inflammatory factors.[2-4] Despite concerns regarding using renin-angiotensin-aldosterone system in COVID-19 patients, it is still considered in these patients for improving their conditions.[14-16]

Studies have shown that people with preexisting conditions such as cardiovascular diseases, nephropathy, hypertension, and diabetes are at a higher risk of more severe symptoms.[17] The mortality rate of COVID-19 is lower compared to SARS or MERS.[18] COVID-19 shares some symptoms with other β coronaviruses, such as Ebola (EVD). COVID-19 patients have been shown to have a higher leukocyte count, more severe respiratory problems, and higher levels of proinflammatory cytokines.[19]

Materials and Methods

The present mini-review study has been written based on 61 articles available in popular databases including PubMed, Google Scholar, Science Direct, and Scopus.

Results

Inflammation is the body's physiological response to tissue damage caused by pathogenic infections, chemical irritation, and other harmful agents. As inflammation progresses, various cells are activated by a signaling network and attracted to the inflamed tissue. This process involves many mediators, including growth factors, cytokines, and chemokines. All the recruited cells at the site of damage take part in the defense mechanism. However, their persistence or prolonged recruitment in the tissue will lead to further tissue damage and, consequently, to worsening the inflammation regardless of its etiology.[20,21]

Cyclooxygenase (COX) is one of the most important structural enzymes in producing inflammatory mediators. So far, two COX isoenzymes have been discovered: COX-1 and COX-2. COX-1 is constantly involved in regulating homeostatic functions of the gastrointestinal mucosa, renal function, and accumulation of platelets. COX-2 is produced because of inflammatory responses of mitogens and cytokines. COX-2 is the main producer of prostanoids, which are lipid mediators involved in vasodilation, increasing vascular permeability, and leukocyte chemotaxis.[22]

COX-1 and COX-2 have fundamental yet contradictory roles in the host immune response to influenza infection that are possibly due to the inadequate production of prostaglandins and leukotrienes because of infection. Prostaglandins and leukotrienes cause the local secretion of lipoxins, particularly Polymorphonuclear leukocyte polymorphonuclear neutrophils (PMNs), which can interact with leukocyte receptors. This process leads to inhibition of PMN inflammation and improving PMN phagocytosis by macrophages.[23,24]

Selective inhibition of COX-2 or COX-1/COX-2 decreases the secretion and extraction of inflammatory cells of the pleural membrane after 2 h but worsens the lung inflammation in 48 h.[25] COX inhibitors can affect the adaptive immune response by inhibiting the expression of interleukin-4 (IL-4) in T cells (CD4) and hinder the initial IFN-γ production by nonimmune cells, an effective strategy against viral infection.[26]

Inadequate inhibition of COX-1 results in an increased inflammatory response and early release of proinflammatory cytokines. In contrast, inadequate inhibition of COX-2 reduces inflammation and proinflammatory cytokines which in turn will reduce symptoms and improve survival even though selective COX-2 inhibitors may have benefits for patients with viral infections.[27] COX-2 plays an important role in the pathogenesis and inflammatory response to the influenza virus. The same is true in COVID-19 infection, which in its more severe forms can cause a cytokine storm.[27] Kirkby *et al*. conducted a study on COX-deficient mice to examine the role of prostanoids in regulating the inflammatory response to bacterial and viral pathogen-associated molecular patterns. The results indicated that eliminating the COX-2 gene in Lipopolysaccharides LPS-treated mice considerably inhibits IL and interferon responses. On the other hand, eliminating the COX-1 gene did not affect the cytokine response to LPS.[28] The tissue concentration of COX-2 protein is higher in patients with viral infections.[29] A study by Carey *et al*. found that eliminating COX-1 and COX-2 genes results in reduced mortality in influenza-infected mice and worsens the infection, respectively.[30] However, many cases of Epstein–Barr virus-associated malignancies have been observed in patients with inflammation and regulated COX-2 levels, suggesting the possible role of COX-2 in viral tumorigenesis.[31]

NSAIDs reduce the production of prostaglandin in the body through inhibiting endoperoxide synthase enzymes, including

COX.[1] NSAIDs are among the most widely used medicines for treating pain and inflammation, including chronic inflammatory disorders such as rheumatoid arthritis and osteoarthritis.[32] NSAIDs may have side effects on cardiovascular, renal, and digestive functions.[33,34] These drugs are used by practically 96% of patients older than 65 years.[35] Great care should be taken regarding the effects of these drugs on the human body as there are limited controlled clinical trials on NSAIDs. Although several studies have examined the protective effect of NSAIDs against viral infections, the role of inflammation in regulating the proliferation and survival of the virus remains unknown.[31] The Medicines and Healthcare products Regulatory Agency in England has changed the previous recommendations regarding NSAIDs and stated that "there is currently insufficient evidence to establish a link between use NSAIDs, and susceptibility to contracting COVID-19 or the worsening of its symptoms."[36,37]

Pathological findings on pulmonary edema consider the use of corticosteroids and ventilators in severely ill COVID-19 patients to inhibit the progression of ARDS.[38] Liu *et al*. investigated the anti-inflammatory effects of NSAIDs and inhibiting the COX-2 enzyme on the survival of patients with influenza. There is also evidence on the adverse effects of corticosteroids in COVID-19 patients.[39]

NSAIDs may increase the number of ACE2 receptors, allowing the COVID-19 virus to infect cells faster and more easily, thus exacerbating the symptoms of the disease. Ibuprofen (an extremely common NSAID) is particularly likely to worsen the infection in COVID-19 patients.[40] Drug interactions between NSAIDs and aspirin, antidepressants, and other commonly used drugs may lead to adverse drug reactions (ADRs). It is therefore vital to carefully monitor the medication dosage and the duration of treatment with NSAIDs.[41] A study by Langhendries *et al*. showed that repeated acetaminophen and ibuprofen exposure in children may lead to an increase in immune deviations.[42]

They can also inhibit the action of IL-6, which is the main inflammatory cytokine. One theory state that ibuprofen may prevent immune-mediated cytokine storm in severely ill patients with multiple organ failure.[43] Moreover, NSAIDs (including ibuprofen) inhibit the TNF-induced transcription of NFκB, contributing to reducing the secretion of pro-inflammatory cytokines such as IL-8.[44-46]

Ibuprofen is a less potent anti-inflammatory compared to steroids. Some influenza viruses can trigger potentially fatal cytokine storms.[47] They therefore may be used in COVID-19 patients, provided that the "Five Rights" of medication administration are observed: the right patient, right drug, right time, right dose, and right route.[48] In France, health authorities have warned against using ibuprofen in COVID-19 patients. This warning is mostly based on outdated, unconfirmed reports, whose supporting theories are explained further in the following. Ibuprofen increases ACE2, which is a receptor for SARC-CoV-2 virus, thus increasing the entrance of the virus into the cells. The European Medicines Agency has also cautioned against high-dose ibuprofen therapy.[49] One animal study on streptozotocin-induced diabetic rats indicated that ibuprofen helped decrease cardiac fibrosis.[40,50]

A study was conducted on 12,808 patients tested for SARC-CoV-2 in five hospitals in Massachusetts, USA. The test results of 2271 patients came out positive; 707 patients were hospitalized, and mechanical ventilators were used for 213 patients. Overall, patients who had used ibuprofen, naproxen, atenolol, or oseltamivir before testing had a lower rate of hospitalization. Furthermore, exposure to ibuprofen decreased the risk of ventilation. SARC-CoV-2 infection is asymptomatic even in moderately severe cases; it may then suddenly lead to (sometimes irreversible) pulmonary damage and immune system reduction or suppression.[51]

Although the use of paracetamol (acetaminophen) in COVID-19 patients is also very common, it is not mentioned in any of the studies on the use of ibuprofen. Ibuprofen may be used in patients with a more severe infection and higher fever, where paracetamol is not sufficiently effective. It is also true for soft-tissue infections. No report has indicated a higher risk of severe pneumonia in patients with long-term exposure to ACE-2 boosting drugs, including ARBs, ANG - converting enzyme inhibitors ACEIs, or NSAIDs.[52]

Excluding ibuprofen and solely using paracetamol to control symptoms may expose patients to higher doses of paracetamol, leading to a higher risk of hepatic damage. Currently, there is no scientific evidence to confirm the role of ibuprofen in increasing the severity of SARC-CoV-2 or COVID-19 infection.[52] In case of chloroquine, a rigorous scientific study is required to examine the benefits and risks of using ibuprofen for COVID-19. At this time, it is not possible to conduct a prospective randomized study. Studying the databases and medical records may help in understanding the effects of chronic use of drugs, but it may not be helpful in examining the use of OTC medications such as paracetamol or ibuprofen for relieving the early symptoms in COVID-19 patients.[52]

Based on previous studies, the National Health Commission of China recommended the use of ribavirin and interferon-α for COVID-19 patients.[33] The use of other antivirals such as protease inhibitors (PIs) in the treatment of hepatitis C and HIV/AIDS has been examined.[34] Remdesivir and chloroquine have shown promising effects on COVID-19 infections in vitro. Moreover, studies have shown the efficacy of these drugs on various viruses and in people with a history of other illnesses.[32]

Studies by Elfiky have suggested that RNA synthesis inhibitors ribavirin, remdesivir, and sofosbuvir could prevent the proliferation of the virus and treat viral infections.[53]

A prospective observational study on 57 consecutive patients infected with pneumonia showed that the possible complications affected with prolonged prehospital use of NSAIDs which lead to longer hospitalization duration and more complicated pleural effusions.[54]

Capuano *et al*. investigated the protective effects of NSAIDs. COX inhibition significantly increases nitric oxide levels, thus reducing the replication of porcine sapovirus (the virus responsible for severe acute gastroenteritis). Therefore, NSAIDs may be recommended in the treatment of sapovirus infection.[55]

Rinott *et al*. assess whether ibuprofen use in COVID-19 patients was related with a crucial disease, compared with individuals using paracetamol or no antipyretics. They monitored any utilize of ibuprofen from a week before diagnosis of COVID-19 across the disease in 403 patients. Primary results were mortality and the respiratory support requirerment, as well as oxygen administration and mechanical ventilation. Compaired to exclusive paracetamol users, no differences were observed in mortality rates or the need for respiratory support amid patients using ibuprofen.[56]

The fundamental mechanism of NSAIDs is through blocking prostaglandin synthesis from arachidonic acid, which has turned into a harmful treatment agent.[48] However, Davis and Robson state that NSAIDs have possible ADRs responsible for almost 30% of hospital admissions for ADRs. These are mainly due to gastrointestinal bleeding, myocardial infarction, stroke, and renal damage.[8]

During the inflammation process, NSAIDs can modify the adhesion, degranulation, phagocytosis, and production of reactive oxygen species by PMNs. In general, NSAIDs reduce the uptake of PMNs and refine their innate functions. In addition, in acute pleural effusion models, treatment with ibuprofen, indomethacin, and flurbiprofen led to a significant decrease in secretion and migration of cytokines.[31,57,58]

Protein kinase RNA-activated (PKR) has a fundamental role in the antiviral mechanism of the host cell. PKR is activated at the time of viral replication and phosphorylates the α subunit of the translation initiation factor eIF2, thus suppressing protein synthesis in infected cells. Indomethacin can activate PKR, which in turn begins the phosphorylation of eIF2 in infected cell colonies to prevent cell replication.[59]

In a study by Huo *et al*. (2011), it was indicated that H5N1 infected mice treated with the polymerase basic protein 2 PB2 oligonucleotides or in combination with anti-inflammatory celecoxib have a significantly lower virus replication compared to mice who have received no treatment. Furthermore, the treatment group had significantly lower TNF-α levels compared to the control group. It can be stated that reducing inflammation and disease symptoms is the only way to reduce viral load. Moreover, combination therapy with PB2 oligonucleotides and celecoxib is more effective than single use of each.[60]

Studies have shown that the avian-origin influenza H7N9 virus can be lethal in mice as it causes severe pulmonary damage and upregulation of cytokines. However, a study by Zhao *et al*. has indicated that the combination therapy with celecoxib and zanamivir reduces pro-inflammatory cytokine activity and pulmonary damage and improves survival rates in mice.[61]

Discussion

Each medicine has its own benefits and risks which are indicated in its product information, according to EU National Treatment Guidelines, paracetamol as a first treatment choice for fever or pain. Other NSAIDs (like ibuprofen) can be used to reduce fever and treat pain or inflammation caused by many diseases. In this mini-review, we found while initial reports suggested that NSAIDs may worsen the course and outcomes of COVID-19, the World Health Organisation and Public Health England stated otherwise. Our results appear to support the latter as there is insufficient evidence to support an association of NSAID use and worsening of outcomes in viral infections. The choice of drug to treat fever or pain in COVID-19 should be based on a benefit-risk assessment for known side effects (e.g., kidney damage and gastrointestinal ulceration) and the respective treatment guidelines that in most cases recommend paracetamol as the first treatment option for fever or pain associated with infections.

Conclusion

Currently, there is no document that the acute use of NSAIDs causes an increased risk of rising COVID-19 or of getting a more cruel COVID-19 disease.

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Conflicts of interest

There are no conflicts of interest.

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