

EDITORIAL VIEW

CORONA EXPERIENCE

NSAIDs in COVID-19, friend or foe?

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Abstract

At the beginning of COVID-19 pandemic the use of NSAIDs was avoided. This was because the previous studies suggesting that NSAIDs may be linked to an increased risk of lower respiratory tract infection consequences. Later on studies involved the patients who used NSAIDs for some chronic conditions and showed no additional harm among these patients. Then many studies assessed the benefit of using NSAIDs in COVID-19 patients for management of pain and fever and showed no additional risk among these patients.

Key words:

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Coronavirus disease 2019 (COVID-19) is still one of the most important challenges to the healthcare systems all around the world. The mode of transmission of coronavirus 2 (SARS CoV2) is direct, person-to-person via respiratory droplets. The most prevalent signs of this condition are respiratory symptoms including coughing and dyspnea, as well as fever.¹ Digestive symptoms are also very common such as diarrhea, anorexia, and vomiting.

It is believed that the port of entry of COVID-19 is through binding of SARS-CoV-2 to target cells through angiotensin-converting enzyme 2 (ACE2). Since NSAID use may be associated with upregulation of ACE2 leading, an increased risk of infection was hypothesized, it was recommended to avoid its usage.¹

It is well known that cytokine storm, an excessive immune reaction, is usually associated with marked patient deterioration. During the of cytokine storm, there is elevated levels of proinflammatory cytokines, such as, interleukin-1b (IL-1b), IL-6, interferon gamma (IFN-g), and tumor necrosis factor alpha (TNF-a), as well as chemokines such as CCL2, CCL4, CXCL9, and CXCL10.² Therefore, immune suppression or reduction may be beneficial, which justified the corticosteroid use

in COVID-19 infection. NSAIDs could decrease the hyperinflammatory process of COVID-19.

Furthermore, Ibuprofen, a commonly prescribed NSAID, was found several years ago to reduce interleukin-6 (IL-6) in human tissues and in sputum.³

Mechanism of action of NSAIDs is to inhibit the cyclooxygenase (COX) isoforms COX-1 and COX-2. COX-1 is expressed in most cells, while COX-2 expression is induced with stimulation of inflammatory process. COX-1 and COX-2 metabolize arachidonic acid into prostaglandin H₂, which may be converted to several different types of prostaglandins (PGs), including PGD₂, PGE₂, PGF_{2a}, and PGI₂. PGs act on specific receptors to perform different roles, such as regulating immune responses and gastrointestinal barrier integrity.⁴

Based on unpublished findings, it was suggested on March 2020 in France that NSAIDs be avoided since they may worsen the result in COVID-19 patients. This was supported by past research demonstrating that NSAIDs may be related with an increased risk of lower respiratory tract infection consequences. NSAIDs may conceal early indicators of infection, such as fever, resulting in delayed identification and treatment.⁵

Furthermore, NSAIDs may cause selective inhibition of interferon gamma production by natural killer and T-cells leading to worse clinical outcome during viral infections. Also, NSAIDs have been found to inhibit antibody production in response to viral infection, but it is unclear if this affects disease severity or not.⁶

NSAIDs may cause nephrotoxicity, which is more likely to worsen the condition in patients seriously affected by COVID-19 and may be exacerbated by fever and dehydration.⁷

A review article, done by Sodhi M, found that studies performed to find association between use of NSAIDs and COVID-19 illness severity are often at risk of several types of biases. Biases include that correlation between ibuprofen administration and increased severity of COVID-19 disease is more likely to be inaccurate as deterioration may be caused by disease's natural course of severity rather than NSAIDs administration. Furthermore, NSAIDs may not be used unless in the setting of more severe symptoms. Also, many patients receiving NSAIDs for long period of time likely suffer from other chronic medical conditions that can increase their risk profile resulting in poor COVID-19 outcomes.⁸

Several studies concluded that patients receiving drugs that upregulate ACE-2 such as NSAIDs, ACEIs, or ARBs, have no increased risk of severe pneumonia. Furthermore, they found that upregulating ACE-2 might have beneficial effects.⁹

Angiotensin II levels were observed to be considerably higher in plasma samples from infected patients compared to healthy persons in a research published early in the COVID-19 epidemic. The levels were directly proportional to viral load and lung injury. The authors suggested that angiotensin receptor blocker (ARB) drugs may be used in treatment of COVID-19. This study is against the theory that upregulation of ACE2 is associated with poorer outcomes, as ACE2 acts as a negative regulator and lowers angiotensin II levels.¹⁰

No harmful effect of NSAID use among patients with COVID-19 was reported by a study done in 2020 on patients who were already receiving NSAIDs for other medical conditions.¹¹

A cohort study done in England last year recommended that patients who receive NSAIDs for their long-term conditions should continue their medications because there is no association between NSAIDs and COVID-19 related death when comparing current NSAIDs users to non-users.¹²

An observational study done in Saudi Arabia, included 503 COVID-19 patients and found no association between the acute and chronic use of NSAIDs and increased risk of mortality, severe COVID-19 disease, or the need for oxygen support, with no difference in time

to clinical improvement and length of hospital stay compared to non-NSAID users in admitted patients.⁷

A retrospective cohort study of 403 patients, was conducted to evaluate whether ibuprofen administration to individuals with COVID-19 was associated with worse clinical outcomes, compared with paracetamol or no antipyretic. Authors did not observe an increased risk for mortality or the need for respiratory support in patients who received ibuprofen. Although the need for respiratory support was higher in patients treated with paracetamol with borderline significance, this might be due to that elderly patients with more severe chronic illnesses were more likely to be treated with paracetamol to avoid ibuprofen induced renal injury.¹³

Additionally, a systematic review and meta-analysis done by Moore N. et al. reported that use of NSAIDs does not cause an increased risk in COVID-19 patients, and the previous irrelevant experimental data might have deprived patients of an effective drug for pain and fever management.¹⁴

Finally, a recently published systematic review and meta-analysis, in April 2022, concluded that NSAIDs use was not found to be associated with higher mortality, ICU admission rate, need for respiratory support or mechanical ventilation. Furthermore, there is no clear evidence to support that NSAID might worsen the prognosis of COVID-19.¹⁵

The use of NSAIDs in patients with COVID-19 is not associated with higher risk regarding mortality or mechanical ventilation. Patients receiving NSAIDs benefit from the upregulation of ACE-2, and management of pain and fever.

Conflict of interest

No conflict of interest declared by the authors.

Authors' contribution

All authors shared intellectual input in this editorial, and in preparation of the final draft.

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