

NARRATIVE REVIEW

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 associated with increased risk of complications of lower respiratory tract infections. Later on studies involved the patients who used NSAIDs for some chronic conditions and showed no additional harm among these patients. Then many studied 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: COVID-19; pandemic; NSAIDs

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1. Introduction

Coronavirus disease 2019 (COVID-19) still remains to be one of the most important challenges to the healthcare systems all around the world.¹ The mode of transmission of coronavirus 2 (SARS CoV2) is direct, person-to-person via respiratory droplets.² The most common symptoms of this disease are respiratory symptoms such as cough and dyspnea with fever.³ Digestive symptoms are also very common such as diarrhea, anorexia, and vomiting.⁴

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.⁵ Although ibuprofen was proved to cause upregulation of ACE 2, as found in an experimental study in rats,⁶ this effect has not been confirmed in humans.⁷

It is well known that cytokine storm, an excessive immune reaction, is usually associated with marked patient deterioration. During the event 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), in addition to chemokines such as CCL2, CCL4, CXCL9, and CXCL10.^{8,9} Therefore, immune suppression or reduction may be beneficial,¹⁰ which justified the use of corticosteroids in COVID-19 infection.¹¹ NSAIDs could decrease the hyperinflammatory process of COVID-19.¹² Furthermore, Ibuprofen, a commonly prescribed NSAID, was found several years ago to reduce IL-6 in human tissues,¹³ and in the sputum.¹⁴

2. Pharmacology

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.¹⁵

3. NSAIDS as an enemy?

On 14 March 2020 in France, it was recommended that NSAIDs use should be avoided as it might worsen the outcome in COVID-19 patients based on unpublished reports.¹⁶ This was based on previous studies suggesting that NSAIDs may be associated with increased risk of complications of lower respiratory tract infections.¹⁷⁻²¹ NSAIDs can mask initial signs of infection such as fever leading to delayed diagnosis and treatment.²²

Furthermore, NSAIDs may cause selective inhibition of interferon gamma production by natural killer and T-cells leading to worse clinical outcome during viral infections.²³ 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.^{24,25}

NSAIDs may cause nephrotoxicity,^{26,27} which is more likely to worsen the condition in patients seriously affected by COVID-19 and may be exacerbated by fever and dehydration. It was recommended that NSAIDs should not be used as the first-line treatment for fever and pain in patients with COVID-19 according to an editorial done by Little P.²⁸

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 periods of time likely suffer from other chronic medical conditions that can increase their risk profile resulting in poor COVID-19 outcomes.²⁹

4. NSAIDS as a friend?

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.³⁰⁻³²

Naproxen was believed to have both antiviral and anti-inflammatory properties so it may be added to the standard COVID-19 treatment.³³

In a study published early in the COVID-19 pandemic, significantly higher angiotensin II levels were found in samples of plasma of infected patients compared to healthy individuals. 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.³⁴

Additionally, it was reported that among COVID-19 patients requiring hospitalization, individuals treated with ibuprofen or naproxen were less likely to require ventilation.¹⁰

No harmful effect of NSAID use among patients with COVID-19 was reported by several studies done in 2020.³⁵⁻³⁷

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.¹⁶

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.³⁸

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.³⁹

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.⁴⁰

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-19.⁴¹

5. Conclusion

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.

6. Conflict of interest

Nil declared by the authors.

7. Author contribution

AA: Bibliography

RF: Data collection and revision

MAM: Searching and sorting of references

OM: Scientific writing and revision

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