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COVID-19, PAIN AND ANTIINFLAMMATORY AGENTS: WHAT HAS CHANGED?

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ABSTRACT

Introduction: Fever, headache, muskuloskeletal pain are symptoms recorded commonly in patients with COVID-19. Although preferred as the first line in these conditions, nonsteroidal anti-inflammatory drugs (NSAID) are questioned the pandemic era, with the concerns of up-regulation of ACE2 receptors. This review aims to shed light to this aspect of COVID-19 clinical course, with a special emphasis on the use and safety of NSAIDs in the pandemic era. **Methods:** Currently available literature on the nature of painful and inflammatory conditions related to COVID-19, and NSAID use was identified by searches of available databases. Usage of these agents in the management of patients with a diagnosis or suspicion of COVID-19 was addressed in the literature data found by searches of databases. The findings were presented in different subheadings. **Results:** There are not well-designed, population-based randomized, controlled studies demonstrating the net effects and safety situation of NSAIDS specifically in patients with a definitive or presumptive diagnosis of COVID-19. Paracetamol and the NSAID group “profens” (ibuprofen / ketoprofen / dexketoprofen / flurbiprofen) are active agents effective in all viral infections including pandemic ones. **Conclusion:** Safety precautions related to COVID-19

have not been supported by evidence-based studies. COVID-19 patients can benefit from effects of paracetamol and NSAIDs following specific precautions.

KEYWORDS: COVID-19, treatment, pain management, nonsteroidal anti-inflammatory drugs, ACE2 receptors. Ibuprofen.

INTRODUCTION

COVID-19 affected the world as a whole in 2020. As of July 2020, it infected more than 15.000.000 people in the world and caused more than 600.000 deaths. The steady and rapid increase in the total number of cases in seven months has pointed out that COVID-19 has turned into a pandemic threatening the world's well-being.

Since the number of cases involved by this infection boosted in a short time window, treatments in subjects other than COVID-19 are also affected negatively. For example, it has been speculated that ACE inhibitors and antihypertensive agents should not be used due to the fact that the virus binds to ACE-2 receptors, and this theory has been quickly refuted with evidences, as it has been demonstrated that patients' outcomes are more favorable when they continue their treatment with ACE inhibitors.

A similar situation has been experienced in the treatment of pain and fever. The use of antipyretic, analgesic and NSAIDs has been extensively discussed.

Pneumonia and ARDS triggered by increased pulmonary inflammation in COVID-19 cases led to thickened lung secretions, widespread lung damage and obstruction of the airways, and entry into the fatal path begins with this mechanism. Increased proinflammatory cytokines (cytokine storm) in serum and microthrombi also play a role in this mechanism.

Although there are few data to enlighten the specific situation of NSAIDs in patients with a definitive or presumptive diagnosis of COVID-19, the utilization of antipyretic, analgesic and NSAIDs are widespread in the treatment of pain and fever. These signs and symptoms are precipitated mainly by cytokine storm, major pathophysiologic pathway inflicting these patients. It is well established that **cytokine storm**, which is a hyperactive inflammatory response, triggers COVID-19 symptoms such as **fever, muscle pain, sore throat**. This has also been postulated as the link to the severity of the disease.

Many experts think that severity of the course of the disease is associated with an exaggerated immune response. It is suggested that excessive activation of neutrophil leukocytes is one of the main causes (Barnes, 2020). The high levels of CRP and other inflammatory markers indicate that the pro-inflammatory response plays a pivotal role in COVID-19 infection (Martinez, 2020).

Table. Supportive therapies other than antiviral / antibiotics in a non-hospitalized patient with or suspected COVID infection.

Agent / strategy	Description
Fever management	It is effective to take plenty of fluids and a warm shower at intervals of several hours. It would be correct to ventilate the house / environment, dress fine, keep it at room temperature (18-22C).
Antipyretic-pain medications:	Paracetamol can be preferred primarily. It is claimed that caution should be taken since the NSAID group profens (ibuprofen / ketoprofen / dexketoprofen / flurbiprofen) are active antipyretic NSAID agents, as they can disguise / increase the signs and symptoms of COVID-19 infection (Micallef, 2020). However, this opinion was not supported on the basis of evidence.
The anti-interleukin-6 receptor antibody tocilizumab	The agent can be used as an immunomodulator, to suppress inflammation and to alleviate fever. Its effect is more pronounced during the cytokine storm period.
Corticosteroids	Methylprednisolone is useful in patients with ARDS Due to its anti-inflammatory effects, it may be effective on inflammatory muscle pain. It is recommended only in the treatment of ARDS (Wu, 2020). Corticosteroid agents are mostly not recommended unless there are not any other indications.
Vitamin supplements	The net benefits of vitamins C and D have not been proven in routine administration, it is useful to give these substances only in people with deficiency, malnutrition and debility.

People who would not benefit from these measures (e.g., those unable to get fluid or with persistent vomiting) or have respiratory distress should be admitted to the hospital.

Paracetamol and NSAIDs

Although it has been claimed that the profen group, which is widely used as an anti-inflammatory agent worldwide, can facilitate the adhesion of the virus to the cell by up-regulation of ACE2 receptors in patients with COVID-19, it has not been supported by concrete evidence. There are no clear data to support that NSAIDs should not be used specifically in patients diagnosed with or suspected to have COVID-19 (Pergolizzi, 2020).

The most serious complications of COVID-19 infection is sepsis, as well as cardiovascular and / or respiratory complications. This situation is predominantly seen in elderly and patients

with comorbidities (Zhou, 2020). Long-term use of NSAIDs such as ibuprofen, naproxen and diclofenac are associated with higher rates of CVD, such as myocardial infarction, heart failure and stroke (Bhala, 2013).

Acute respiratory infections are associated with an already increased risk of stroke and myocardial infarction, and short-term use of NSAIDs during illness is associated with an increased risk (Wen, 2018). For example, the use of NSAIDs in acute respiratory infections has been reported to increase the propensity for AMI (OR: 3.41), but it is thought that there may be no significant increase of the risk with NSAIDs since the OR value for AMI is considered to be 2.65, even if NSAIDs are not used at all (Wen, 2017).

It is not known whether any of these proposed factors apply to the COVID-19 pandemic. Evidence to date is not strong enough to support the full refusal of the use of NSAIDs.

Why is the profen group used in COVID-19 and other infections?

NSAIDs may be needed if paracetamol's analgesic effect is insufficient, or for conditions such as severe musculoskeletal pain or resistant fever (Besedovsky, 2019).

Should aspirin be used?

People taking low-dose aspirin should continue their treatment for secondary prevention of cardiovascular disease (Little 2020).

What about pregnant women?

It has also been reported that aspirin and NSAIDs given prophylactically should not be interrupted in pregnant women (Kwiatkowski, 2020). It was also repeated that there is no suggestion that NSAIDs from profen group should be withheld in pregnant patients with suspected or diagnosed COVID-19.

Kakodkar et al. also reported in their article published in April 2020 that WHO also stated that it had not issued a negative interpretation for ibuprofen and/or other NSAIDs and that it was appropriate to continue the medication (Kakodkar, 2020).

Renin-Angiotensin System (RAS) **inhibitors and NSAIDs**

The idea that RAS inhibitors and ibuprofen increase ACE2 receptors is based on the results of a study by giving high doses of ibuprofen in diabetic rats, such as 40 mg / kg (Qiao, 2015). This dose is deliberately an overdose such as 3 g in a 70 kg person. This does not mean that

these findings can be extrapolated to an outcome associated with the usual dose of ibuprofen in man.

Headache and COVID-19

Headache has been reported in 11% to 34% of cases with COVID-19 in different series (Borges do Nascimento. 2020, Zhang 2020, Chen 2020, Xu 2020). Headache is one of the principal indications in which NSAIDS are preferred as the first-line agent. In the article published in April 2020, Maassen VanDen Brink et al. reported that there was no data preventing the use of **RAS** inhibitors and NSAIDS such as ibuprofen in suspected patients with COVID-19 with headache (Maassen VanDenBrink, 2020).

Musculoskeletal pain and NSAIDS: Orthopedists from Italy, De Girolamo et al. stated that the warnings for not using ibuprofen in May 2020 lead to a point that reduces the quality of life of orthopedic patients (De Girolamo, 2020).

Is NSAIDs safe to use?

In the last IDSA report, the issue regarding the use of NSAID agents in COVID-19 cases was also examined and it was stated that there is no warning that NSAIDs should not specifically used in patients with COVID-19, however, possible adverse effects need to be taken into consideration (Bhimraj, 2020). It has been mentioned that any cause-effect relationship regarding the use of NSAID has not been established in patients with deterioration. GI hemorrhage is the best known widespread adverse effect of NSAIDS. Nonetheless, profen group has been shown to cause fewer GI hemorrhages when compared to other NSAIDs (*British National Formulary, 2014).*

In the UK, **"The Expert Working Group on the Commission of Human Medicines"** stated that no link could be proven between ibuprofen and severe course or exacerbation of COVID-19 (Gov.UK.). Again, the UK health authority NHS emphasized that paracetamol may be the first choice and there is no clear data preventing the use of ibuprofen in the treatment of acute pain and fever (NHS England, 2020). Previously, it is reported that there is no definite data on NSAIDs increasing the complications of community-acquired pneumonia (Basille 2017).

Another critical issue regarding safety is that the feared side effects of NSAIDs are **dose-related** consequences of the agents. In other words, a comparison of short-term oral NSAID

and IV continuous infusion in a severely symptomatic patient will certainly yield different results. For example, IV administered NSAID significantly increases the risk of stroke / CVA in patients with critical condition and/or respiratory distress, but there is no such risk in oral administration (Voiriot, 2018). In a new article, Zolk et al. also suggested that NSAIDs should be used in the COVID-19 pandemic period at the lowest effective dose and for a short time and reported that no untoward effects are expected (Zolk, 2020).

The differences between the agents

Diclofenac, one of the most commonly used NSAIDs, has been accused of marked local neurotoxicity (in IM use) in the last decade, the risk of GI bleeding and -due to the sodium content - exacerbations of heart failure and hypertension, and therefore, its use has been considerably reduced.

Paracetamol has been promoted as a safe alternative to NSAIDs, but the agent has well-established causal links with liver damage or toxicity for decades. In other words, paracetamol is a treatment that can cause problems if posology is not considered. Therefore, NSAIDs can be used with caution after paracetamol if necessary (Belgium, 2020, Little, 2020).

Conclusion sentence about security; There are definitely COVID-19 cases where NSAIDs would not be appropriate to use, such as those prone to GI bleeding. However, a scientific basis for not using them in other cases has not been established.

Table. As with many drugs, questions to be asked before prescribing in optimizing the safety profile of NSAIDs. With this six-item approach, which can be called the 3W2H1C system, a safer profile will be created for patients.

Q	Explanation
To Whom?	Make sure it is given to the right patient
Why?	With what indication?
Which drug?	Choose the agent with the best profile of effect/adverse events
How much?	In what dosage?
How?	IV / oral route
Caution!	Drug interactions and allergies

In conclusion, the use of NSAIDs as antipyretic, analgesic and anti-inflammatory agents appears to be indicated in viral infections such as COVID-19, also during pandemic periods. There is no evidence to support NSAIDs not to be used in COVID-19 infections

due to their side effects. NSAIDs are used after paracetamol, if necessary, to manage the symptoms of COVID-19.

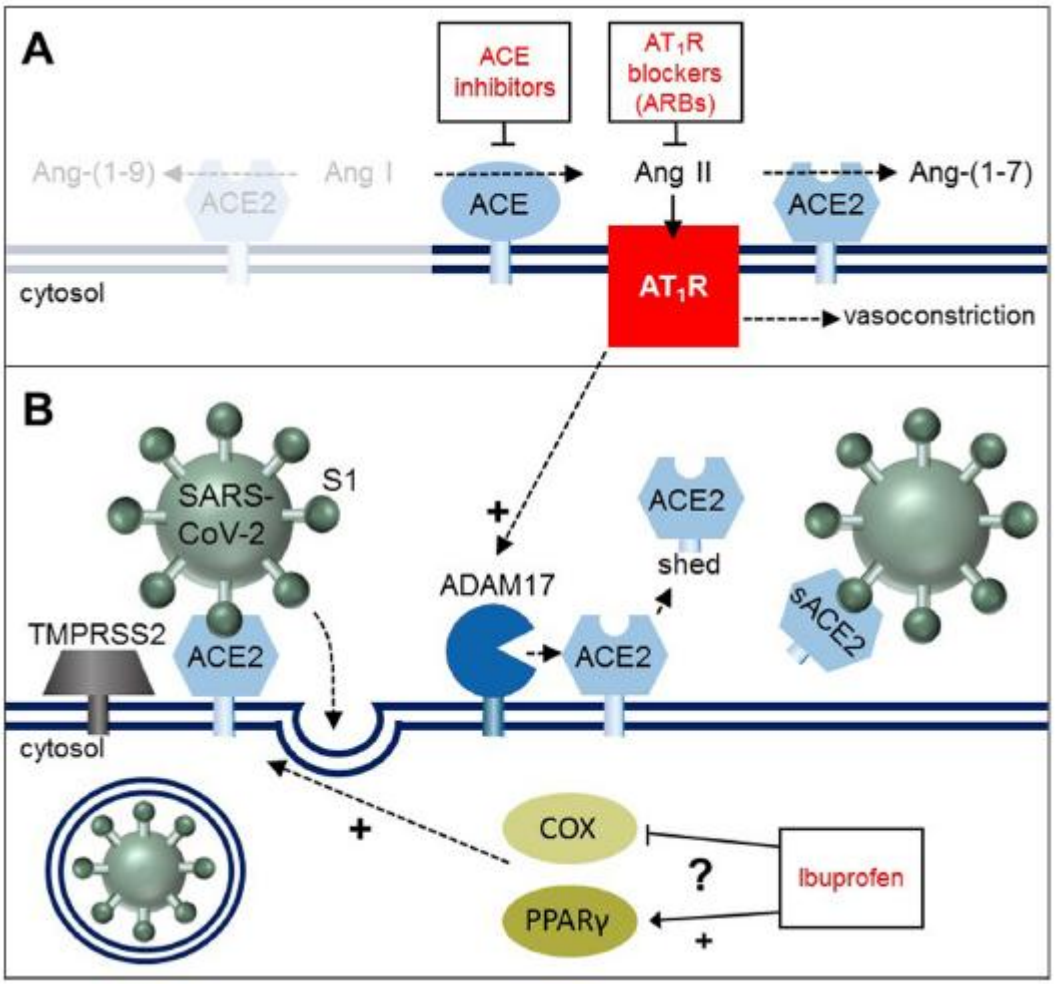

Figure. Angiotensin (AT) -converting enzyme-2 (ACE2) converts AT-I to AT- (1-9) and AT-II to AT- (1-7) (Panel A). If ACE inhibitors (ACEI) exist in the tissue, the conversion of AT-I to AT-II is inhibited (Panel B). ACE2 is also bound to SARS-Cov-2 after treatment with "serine protease transmembrane protease, serine 2" (TMPRSS2). If disintegrin and metalloprotease 17 (ADAM17) and membrane-bound ACE2 are cleaved, soluble (s) ACE2 appears and they cannot facilitate SARS-Cov-2 entry, they keep the virus in the solution. With AT-II type-1 receptors (AT1R), they increase ADAM17 activity, and AT1R blockers (ARB) inhibit this. Ibuprofen increases the synthesis of ACE2, possibly via cyclooxygenase (COX) inhibition and Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) activation.

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