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NSAIDs may increase the risk of thrombosis and acute renal failure in patients with COVID-19 infection

Keywords COVID-19; NSAID; Cyclooxygenase; Thrombosis; Acute renal failure; Prostaglandin

Abbreviations

ACE2	angiotensin-converting enzyme 2
ARDs	acute respiratory distress syndrome
COVID-19	novel coronavirus disease 2019
COX	cyclooxygenase
NSAIDs	non-steroidal anti-inflammatory drugs
PG	prostaglandin

We read with great interest the article by Micallef J et al. ''Non-steroidal anti-inflammatory drugs, pharmacology, and COVID-19 infection'' [1]. As the authors point out, non-steroidal anti-inflammatory drugs (NSAIDs) can lead to resistant superinfection during novel coronavirus disease 2019 (COVID-19) infection [1]. The risk of thrombosis and multiorgan failure is high in severe COVID-19 infection. NSAIDs during COVID-19 infection can also lead to complications such as thrombosis and acute renal failure. We would like to mention several harmful effects of NSAIDs use during COVID-19 infection.

The cyclooxygenase (COX) pathway plays a role in many physiological and pathophysiological events such as regulation of vascular tone, pulmonary fibrosis, and tissue remodeling, surfactant homeostasis, pulmonary defense, bronchial mucus secretion in the lung. By producing COX-2, prostaglandin (PG)E_2, and PGI_2, it is responsible for vasodilation, inflammation, fever, and pain. COVID-19 infection spreads rapidly all over the world and causes deaths. Recently published several articles reported that ibuprofen increased angiotensin-converting enzyme 2 (ACE2). ADAM17 is a metalloprotease that causes ACE2 shedding and thus ACE2 upregulation. ADAM17 activation may increase COVID-19 infection [2]. Non-selective NSAIDs activate ADAM17, causing ACE2 shedding [3]. NSAIDs can increase viral load in this way.

Selective or non-selective NSAIDs two-fold or greater increase the risk of venous thromboembolism [4]. NSAIDs increase the risk of not only venous but also arterial thromboembolism [4]. PGI_2 inhibition, which has an antithrombotic effect with COX-2 inhibition, may increase the thrombosis risk [5]. Thrombosis tendency is higher in COX-2 selective inhibitors. COX-2 suppression disrupts thromboxane A_2/PGI_2 balance in favor of thromboxane A_2. By suppressing COX-1 over 95%, an antithrombotic effect occurs. Only aspirin or high-dose naproxen may perform this antithrombotic effect [5]. NSAIDs inhibit PG synthesis, leading to the Na^+/K^+ exchanger (NHE) activation. Activation of NHE increases the thrombosis risk. The risk of arterial and venous thromboembolism is increased during COVID-19 infection. COVID-19 infection enhances the von Willebrand factor release by infecting the vascular endothelium, increasing the thrombosis risk [6]. Also, ACE2 becomes dysfunctional when the virus binds to ACE2. Since ACE2 degrades angiotensin II, ACE2's dysfunction increases angiotensin II levels. Angiotensin II activates NHE and NHE activation also shows a procoagulant effect. Angiotensin II binds to AT1 receptors, leading to increased levels of endothelin 1 and bradykinin [7]. Increased endothelium 1 pathway activates the coagulation cascade. Bradykinin increases the tendency of arterial thrombosis [7]. In addition, angiotensin IV formation increases because of elevated angiotensin II. When angiotensin IV levels increase excessively, angiotensin IV binds to AT1 receptors, causing thrombotic effects [8]. The risk of arterial and venous thromboembolism is already increased in COVID-19 infection, using NSAIDs in infected patients with the virus may more increase the embolism risk.

COX-1 primarily functions in the control of kidney hemodynamics and glomerular filtration rate, while COX-2 functions principally affect salt and water excretion. COX-2-inhibition enhances the pressure effect of angiotensin II [9]. NSAIDs increase blood pressure by causing sodium and water retention. Besides, they cause vasoconstriction by decreasing the formation of vasodilator prostacyclin in the vascular wall [5]. NSAIDs can lead to acute and chronic kidney failure. Angiotensin II level in patients with COVID-19 increased with the mechanisms mentioned above. COX inhibition due to NSAID use potentializes the negative effects of angiotensin

II on the kidney and may increase the risk of acute renal failure.

NSAIDs in COVID-19 can cause some other complications. PGE_2 blocks the release of leukotriene through its receptors in mast cells. Inhibition of the COX-1 with non-selective NSAIDs activates the formation of the leukotrienes from arachidonic acid. Increased leukotriene release may trigger bronchoconstriction and acute respiratory distress syndrome (ARDS) [10]. COVID-19 infection often causes ARDS. Using NSAIDs can cause serious side effects, especially in patients infected with severe COVID-19.

Disclosure of interest

The authors declare that they have no competing interest.

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