Short communication

Potential Crucial Role of COX-1 and/or COX-2 Inhibition, NSAIDs or Aspirin Triggered Lipoxins and Resolvins in Amelioration of COVID-19 Mortality.

Mina T. Kelleni, MD, PhD

Pharmacology Department, College of Medicine, Minia University, Egypt.

Mobile: +201200382422

drthabetpharm@yahoo.com, mina.kelleni@mu.edu.eg

https://orcid.org/0000-0001-6290-6025

Highlights

Low dose aspirin is frequently used in management of COVID-19.

Low dose aspirin was suggested to reduce risk of COVID-19 complications and mortality.

COX-1 and COX-2 enzymes might play an important role in COVID-19 pathogenesis.

NSAIDs have been proved safe to manage COVID-19 and we suggest they also save lives.

Aspirin triggered lipoxins and resolvins generated with higher doses of aspirin might prove beneficial.

Abstract

Aspirin has been recently suggested to be independently associated with reduced risk of mechanical ventilation, ICU admission and in-hospital mortality of COVID-19. However, we claim that the molecular interpretation of these important results was not scientifically valid, and we provide our academic interpretation that is also basing on our real-life

practice using non-steroidal anti-inflammatory drugs in management of COVID-19 and we suggest that inhibition of COX-1 and/or COX-2 enzymes might play a life saving role in COVID-19 management and we further discuss the potential of aspirin triggered lipoxins and resolivns in the same context.

Keywords: COVID-19, COX-1, COX-2, NSAIDs, aspirin triggered lipoxins, aspirin triggered resolvins.

Introduction

The results of the study performed by Chow et al. which demonstrated that aspirin use was independently associated with reduced risk of mechanical ventilation, ICU admission and in-hospital mortality while there were no differences in major bleeding or overt thrombosis between aspirin and non-aspirin users[1], have some major flaws in their interpretation and should be properly interpreted from a pathophysiologic and pharmacologic point of view for the best interests of the prospective medical research and more importantly the welfare of our precious COVID-19 patients. Thus, we wish to share some insights about their interpretation as regards to use of low dose aspirin and more importantly to cyclooxygenase inhibition potential crucial role in management of COVID-19 aiming at further exploration of its pathophysiology that might guide us in our vigorous quest for a highly anticipated cure.

Low dose aspirin and COVID-19 coagulopathy

Chow et al. have cited numerous references that correlated SARS CoV-2 induced hypercoagulable state and subsequent development of platelet rich thrombi with severe COVID-19 and mortality and they have cited a study performed by Paranjpe et al.[2] which has suggested that systemic treatment-dose anticoagulation may be associated with improved outcomes among hospitalized COVID-19 patients hospitalized with COVID-19 to suggest that their reported aspirin beneficial outcomes might be due to its well-known antithrombotic properties. However, Paranjpe et al. have clearly enumerated numerous limitations of their study, the effect of the prophylactic low dose aspirin tested by Chow et al. might differ from that of the systemic treatment dose anticoagulants studied by Paranjpe et al. to be also noted that a large observational study has demonstrated no significant association between ongoing use of direct oral anticoagulants and severe COVID-19 and wisely suggested that therapies should be better directed against thrombogenic inflammation, the cause, rather than against hypercoagulability; the symptom[3]. Importantly, Chow et al. have not found a difference in incidence of overt thrombosis between aspirin and non-aspirin users and thus, we would like to discuss some sub-overt mechanisms that might be attributed to reason for the potential aspirin beneficial effects in COVID-19 as expressed by Chow et al.

Low dose aspirin and COVID-19 inflammation

Chow et al. have stated that aspirin, as a cyclooxygenase-1 (COX-1) inhibitor, modifies both inflammatory and coagulation responses and they cited a review written by Warner et al.[4] However, in that cited reference, no mention to a link between COX-1 inhibition and inflammation was found and it was clearly stated, at that reference as elsewhere, that COX-1 is the constitutive form of the enzyme which is also exclusively or dominantly expressed in the anucleated platelets and that COX-2 is the inducible one associated with inflammation. Moreover, Chow et al. have cited a resourceful review and meta-analysis written by Panka et al. [5] to reason for the aspirin's anti-inflammatory mechanisms including lipoxin formation. However, in that reference these mechanisms were evident in murine or in in-vitro preclinical models, which in some used aspirin by local administration and in all of these models aspirin was used, as also stated, in high doses in contrast to the low doses used in clinical studies including that of Chow et al. and thus the evidence cited from Panka et al. does not reason for Chow et al. aspirin's anti-inflammatory properties. Additionally, Panka et al. discussed some contradictory results found in sheep and murine models and chow et al. have also wisely confirmed that aspirin showed mixed results when tested for acute respiratory distress syndrome and cited few studies though only thoroughly discussed the positive ones.

Similarly, Chow et al. have also cited a study performed by Ikonomidis et al. [6] in which 300 mg daily aspirin was administered for six weeks and decreased IL-6 and CRP to reflect on their 81 mg aspirin dose and this is also not scientifically justified as low dose aspirin cannot inhibit the inflammatory COX-2, as stated by Chow et al., and inhibits COX-1 almost selectively. Moreover, Ikonomidis et al. have also mentioned that aspirin exhibits anti-inflammatory action in a dose dependent manner and its greatest effects occur at doses as high as 2 g.

Potential benefits of low dose aspirin in COVID-19

In our opinion, the results presented by Chow et al. should be interpreted and built upon by researching potential aspirin's non COX dependent anti-inflammatory effects through modulation of the immune and inflammatory function of platelets[7] as well as its peculiar

ability to trigger induction of the beneficial anti-inflammatory and immunomodulatory lipoxins and resolvins which are synthesized through acetylated COX-2[8].

Notably, while COX-2 acetylation, and the subsequent formation of lipoxins and resolvins, is not achievable by low dose aspirin, induction of COX-1 upregulation in COVID-19 might be considered for further research as it has been previously described, with potential benefits of its inhibition under certain conditions, in some neuroinflammatory and neurodegenerative diseases. Additionally, COX-1 and/or COX-2 potential role in SARS CoV-2 replication should be assessed and NSAIDs were also suggested, in a preprint, to directly affect SARS CoV-2 replication[9].

Potential therapeutic role of NSAIDs in COVID-19

On the other hand and basing on our academic and real-life experience, we have recommended adoption of large clinical trials that adopt therapeutic doses of NSAIDs in management of COVID-19 and postulated prevention of complications and significant reduction of mortality [10,11], explained in two preprints, the potential molecular mechanisms upon which their COVID-19 efficacy might be reasoned[12,13] and updated our real-life clinical protocol that adopts NSAIDs as integral part of COVID-19 managment[14] to be noted that we recommend against the concomitant use of prophylactic low dose aspirin and NSAIDs, or at least some of them[15] while conducting the anticipated clinical trials, while obviously opting for NSAIDs over low dose aspirin.

Conflicts of interest and sources of funding

The author states that there are no conflicts of interest to disclose.

References

1. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin Use Is Associated With Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients With Coronavirus Disease 2019. Anesthesia & Analgesia. 2021;132(4).
2. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. Journal of the American College of Cardiology. 2020 2020/07/07/;76(1):122-124.
3. Flam B, Wintzell V, Ludvigsson JF, et al. Direct oral anticoagulant use and risk of severe COVID-19 [https://doi.org/10.1111/joim.13205]. Journal of Internal Medicine. 2021 2021/03/01;289(3):411-419.

4. Warner TD, Nylander S, Whatling C. Anti-platelet therapy: cyclo-oxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy [https://doi.org/10.1111/j.1365-2125.2011.03943.x]. British Journal of Clinical Pharmacology. 2011 2011/10/01;72(4):619-633.
5. Panka BA, de Grooth H-J, Spoelstra-de Man AME, et al. Prevention or Treatment of Ards With Aspirin: A Review of Preclinical Models and Meta-Analysis of Clinical Studies. Shock. 2017;47(1):13-21.
6. Ikonomidis I, Andreotti F, Economou E, et al. Increased Proinflammatory Cytokines in Patients With Chronic Stable Angina and Their Reduction By Aspirin. Circulation. 1999 1999/08/24;100(8):793-798.
7. Sonmez O, Sonmez M. Role of platelets in immune system and inflammation. Porto Biomedical Journal. 2017 2017/11/01/;2(6):311-314.
8. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nature Reviews Immunology. 2008 2008/05/01;8(5):349-361.
9. Chen JS, Alfajaro MM, Wei J, et al. Cyclooxgenase-2 is induced by SARS-CoV-2 infection but does not affect viral entry or replication. bioRxiv : the preprint server for biology. 2020:2020.09.24.312769.
10. Kelleni MT. ACEIs, ARBs, ibuprofen originally linked to COVID-19: the other side of the mirror. Inflammopharmacology. 2020 Dec;28(6):1477-1480.
11. Kelleni MT. Early use of non-steroidal anti-inflammatory drugs in COVID-19 might reverse pathogenesis, prevent complications and improve clinical outcomes. Biomed Pharmacother. 2021 Jan;133:110982.
12. Kelleni MT. Non-steroidal Anti-inflammatory Drugs/nitazoxanide/azithromycin Potential Beneficial COVID-19 Effects: Preventing the Cytokine Storm via Mitigation of the Interleukin-6 Amplifier and Monocytic Immunological Dysrhythmia. OSFPREPRINTS (Preprint). 2021.
13. Kelleni MT. NSAIDs, SARS CoV-2 ORF Proteins, Caspases, and CARD14: Solving the Mystery of COVID-19 and Beyond. OSFPREPRINTS (Preprint),. 2021, March 31.
14. Kelleni MT. NSAIDs/Nitazoxanide/Azithromycin Immunomodulatory Protocol Used in Adults, Children and Pregnant COVID-19 Patients: An Egyptian Prospective Observational Study. OSFPREPRINTS (Preprint). 2021.
15. Gurbel P, Tantry U, Weisman S. A narrative review of the cardiovascular risks associated with concomitant aspirin and NSAID use. Journal of Thrombosis and Thrombolysis. 2019 2019/01/01;47(1):16-30.