



A closer look at endothelial injury-induced platelet hyperactivity and the use of aspirin in the treatment of COVID infection

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Abstract

In this commentary, we make a case that the mechanism of COVID pathogenesis is related to virus-induced endothelial injury resulting in platelet activation and the formation of microthrombi both systemically and in cardiac and pulmonary circulation which result in major causes of COVID morbidity and mortality. Aspirin by virtue of its irreversible inhibition of platelet COX-1, should reverse these platelet-induced pathogenic changes associated with COVID infection for the 6–9 day lifetime of the platelet. We also cite recent findings of a retrospective analysis that supports the use of low-dose (81 mg) aspirin to treat the symptoms associated with the early stages of COVID infection.

Keywords Aspirin · Platelet · Endothelial · COVID

It is now well established that COVID patients suffer from the development of multiple microthrombi and associated thrombotic complications (Klok et al. 2020). Thrombi are usually formed if there is a vascular endothelial injury (Tolstanova et al. 2012), and in COVID-19, vascular damage was reported both in acute and chronic phases of the disease (Dupont et al. 2021; Lee et al. 2021), leading to the pronouncement that “COVID-19 is, in the end, an endothelial disease” (Libby and Luscher 2020). There is also compelling evidence that COVID-19 infection induces both local and systemic platelet activation displaying increased aggregation, adhesion and microvesiculation to subthreshold concentrations of thrombin (Lichtenberger and Vijayan 2021; Zaid et al. 2020). This results in disseminated intravascular coagulation (DIC), a condition where blood clots form throughout the body and in the development of pulmonary and cardiac embolism which are major causes of COVID-associated morbidity and mortality (Tang et al. 2020).

As initially described by Vane and associates (Vane and Botting 2003), aspirin possesses powerful anti-platelet actions notably, by irreversibly inhibiting platelet COX-1, via acylation of serine 530 in the catalytic pocket of the enzyme, thereby blocking the formation of thromboxane a powerful clotting agent that promotes platelet aggregation at a site of endothelial injury. Because of this action, a number of groups have evaluated the therapeutic efficacy of aspirin to treat COVID patients on admission, with equivocal results possibly due to the fact that aspirin was administered at range of doses to patients of various stages of the disease and was added to a cocktail of other ant-clotting/anti-viral drugs—making a clear determination of a drug-induced effect challenging (Group 2022).

We found Chow et al.’s recent findings published in JAMA on aspirin’s effect on early-stage patients with moderate COVID disease (Chow et al. 2022) both compelling and potentially of important clinical significance. In summary, they performed a retrospective analysis from 64 health systems in the US, that placing 112,269 hospitalized COVID patients with moderate symptoms on low-dose 81 mg aspirin over the first 5 days of hospitalization significantly lowered both the development of pulmonary edema and mortality with the benefits enhanced in patients with multiple comorbidities. Taking aspirin vs. those patients not taking the drug made a significant difference the above parameters even though the patients were prescribed an anti-COVID cocktail of dexamethasone, remdesivir, tocilizumab, heparin

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and enoxaparin. It is also important to note that Chow et al. reported that GI and cerebral hemorrhagic complications did not occur by placing COVID patients on a 5-day course of low-dose aspirin.

Thereby aspirin's efficacy to irreversibly inhibit platelet COX-1 may be proven to be the mechanistic basis of the benefit when COVID patients are placed on this OTC available drug shortly after symptoms appear. We also agree with Chow et al. that aspirin's positive effects should continue for at least 1 week after being withdrawn from the drug, as aspirin-treated platelets remain in a non-active state due to irreversible inhibition of COX-1 for 6–9 days for the lifetime of the platelet until recycled by the process of megakaryopoiesis (Lichtenberger and Vijayan 2019). We also feel it important to emphasize that most available OTC aspirins are enteric-coated in which recent studies indicate reduction of anti-platelet bioavailability and delays action vs. immediate-release aspirin (Bhatt et al. 2017). Thus, it is likely that the beneficial effect on COVID patients will be more pronounced if they take an immediate-release aspirin (generic chewable aspirin or Vazalore®, a recently launched GI safer immediate-release aspirin product) (Cryer et al. 2011; Angiolillo et al. 2019). It is also important to note that Chow et al. also reported that patients in their study treated with low-dose aspirin had no evidence of GI or cerebral bleeding. In summary, based on the above findings, we suggest future studies should evaluate the potential therapeutic benefit of placing COVID patients on one of the above immediate-release aspirin drugs shortly after COVID infection is diagnostically confirmed or on hospital admission.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest Dr. Lichtenberger declares he was Scientific Founder of PLx Pharma Inc that is commercializing a lipid-associated aspirin and has shares in the company.

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