Could Low Doses Acetylsalicylic Acid Prevent Thrombotic Complications in COVID-19 Patients?

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Abstract
Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) can induce inflammatory and thrombotic complications of pulmonary district (interstitial pneumonia), sometimes evolving toward acute respiratory failure. In adults, Acetylsalicylic Acid (ASA) is widely employed at low doses for primary and secondary prevention of cardiovascular diseases (CVD). Apart their anti-thrombotic effect, low ASA doses also exert an anti-inflammatory action. So, when these are assumed for CVD prevention, could prevent both inflammatory reaction and pro-coagulant tendency of Coronavirus-2019 (COVID-19) infection. In addition, some patients receiving ASA are simultaneously treated with Statins, to correct dyslipidemia. But, for their pleiotropic effects, Statins can also be useful to antagonist pulmonary thrombo-inflammation induced by COVID-19. Thus ASA, with or without Statins, employed for CVD prevention, could be useful to avoid or minimize inflammatory reaction and thrombotic complications of COVID-19. But, further studies performed in a wide range are requested to validate this hypothesis.

Keywords
SARS-CoV-2, interstitial pneumonia, acetylsalicylic acid, statins, inflammation, thromboembolism

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Introduction
The recent pandemic Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) may cause some thromboembolic complications1 and bilateral interstitial pneumonia (Figure 1), until acute respiratory distress. Alveolar inflammation caused by the hyper-production of pro-inflammatory cytokines (cytokines’ storm) and interleukins triggers thrombosis and increased coagulation. Multisystemic endothelitis associated with microthrombi formation often complicates the Coronavirus Disease-2019 (COVID-19) course and may be responsible for multi-organ dysfunctions, pulmonary embolism (Figure 2), significant injury in the respiratory tract with high mortality rate.2,3

Acetylsalicylic Acid
It is known that Acetylsalicylic Acid (ASA) at high doses (650 mg to 1 g/day) has anti-thrombotic, anti-pyretic, anti-inflammatory and anti-viral activities4-6 while, at low doses (75 to 325 mg/day), has an anti-inflammatory and anti-thrombotic effect, that can act on pro-coagulant and thromboembolic respiratory events induced by COVID-19.7

The efficacy of low doses of ASA (also called Aspirin) as antithrombotic agent has been demonstrated in several trials that evidenced the non-superiority of higher doses compared to lower doses.8 Traditionally, the anti-inflammatory dose of Aspirin in humans is 1 gr. (high dose). But, at low doses, Aspirin is able to dampen acute inflammatory response by triggering 15-epi-lipoxin A4. In turn, this compound acts by inhibiting leukocyte/endothelial attachments.9 In addition, low-dose Aspirin reduced vascular inflammation in mice, decreased macrophage foam cell content and increased the stability of atherosclerotic plaque.10

Thus, low ASA doses are commonly employed for primary and secondary prevention of thrombosis against cardiovascular

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But, the potential benefits are offset by potential harms of bleeding when ASA is employed as anti-thrombotic drug for primary CVD prevention. On the contrary, when ASA is used in patients previously suffering for an acute ischemic event (secondary prevention), the benefits outweigh the potential harms. So, the use of ASA in the primary prevention of CVD is not approved, even its beneficial effects on the mortality were pointed out. On the contrary, its employment for secondary prevention is widely used.

In this review, we hypothesized that low doses of ASA, already assumed for its anti-inflammatory and anti-thrombotic effects on CVD and/or its complications (atherogenic plaques), are also useful for weaken the thrombotic complications induced by COVID-19.

**Mechanisms of Action of COVID-19**

COVID-19 causes an inflammatory state prevalently located in the cells of pulmonary alveoli. In turn, the infection of alveolar, endothelial cells leads to activation and dysfunction of the endothelium. At the beginning coronavirus enters in the cells through ACE2 receptor by the S spike protein. Subsequently, the endothelial dysfunction favors the shift of the hemostatic balance toward the pro-coagulation starting the pro-thrombotic process. That happens by triggering complex molecular events that leads to inflammation by cytokines’ over-production (cytokine storm). In turn, the condition is responsible for the platelet’s activation, with increased levels of von Willebrand Factor and Factor VIII.

In addition, the increased levels of glycoproteins contribute to thrombin generation and fibrin clot formation. Consequently, an increased thrombotic risk happens, that favors arterial thrombotic events, such as acute myocardial infarction, ischemic stroke and peripheral arterial disease.

**Anti-Thrombotic ASA Effects**

Antithrombotic effect of ASA is due to the inhibition of platelets’ function by acetylation of the COX-1 at the functionally important amino acid serine 529. On the other hand, the COX-1 acetylation inhibits TXA-2, a stimulator of platelet reactivity. This inhibition results in anti-thrombotic effect, able to prevent thrombosis on the arterial walls. Most intensively, ASA is employed against arterial thrombosis, while it is not commonly used in venous thrombosis. Nevertheless concerning this topic, some trials (WARFASA, ASPIRE and a recent meta-analysis) evidenced that ASA also reduces venous thrombosis without significantly increasing the risk of bleeding. Really, the most common pro-coagulative event happening in COVID-19 is venous thromboembolism (VTE), while arterial thrombosis seems to have a minor incidence. Some reports also referred on microangiopathies, characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ damage, such as neurological, renal and cardiac dysfunction. It must be also added that pro-coagulation in COVID-19 patients is evidenced by the laboratory findings, showing a thrombocytopenia and an increased D-dimer levels.

In Figure 3, the mechanism through COVID-19 induces both arterial and venous thrombosis are illustrated.
Conclusive Remarks

Contrarily to the multiple effects (anti-inflammatory, analgesic, anti-pyretic anti-thrombotic and antiviral action against DNA and RNA viruses) obtained with high ASA doses, low doses have antithrombotic and anti-inflammatory effects only. Consequently, adult individuals receiving low ASA doses and nowadays affected by SARS-CoV-2, could be protected against possible inflammatory and thrombotic complications. To confirm this hypothesis, a retrospective, observational study performed by the Researchers of the Maryland University (US) demonstrated that hospitalized COVID-19 patients who were taking a daily low-dose Aspirin in secondary prevention for CVD had a significantly lower risk of inflammatory and coagulative events compared to those not taking Aspirin. Concerning that, in the near future, the RECOVERY II (Randomized Evaluation of COVID-19 thERapY II) trial will be performed to test the effectiveness of low dose Aspirin as anti-inflammatory and antithrombotic drug in the treatment of patients with COVID-19.

Furthermore, Hydroxy-Methyl-Glutaryl-Coenzyme A reductases (Statins) are other drugs frequently employed in CVD patients, to reduce dyslipidemia. Nevertheless, they also could supply some beneficial effects against the complications of COVID-19. These favorable effects depend on their pleiotropic actions, such as anti-thrombotic, anti-inflammatory, anti-oxidative effects and improvement of endothelial dysfunction. Moreover, Statins also induce the upregulation of Angiotensin-Converting Enzyme (ACE)-2 receptor, used for cellular entry of the coronavirus. These beneficial results were confirmed by a recent, retrospective study. But in this case, the higher severity of COVID-19 patients due to the CV comorbidities and treated with statin therapy, frustrated the supposed favorable effects.

Nevertheless, these observations on Aspirin at low doses (with or without Statins) about the favorable effects on the complications of COVID-19 could be confirmed by further studies performed in a wide range.

Abbreviations

SARS-CoV-2, Severe Acute Respiratory Syndrome-Coronavirus-2; COVID-19, Coronavirus Disease-2019; ASA, Acetylsalicylic Acid; RNA, Ribo Nucleic Acid; DNA, DeossiNucleic Acid; CVD, Cardio-Vascular Disease; ACE 2, Angiotensin Converting Enzyme-2; VTE, Venous Thrombo Embolism; COX-1, Cyclooxygenase-1; TXA-2, ThromboXAn-2; WARFASA, WARFarin and AcetylSalicylic Acid; ASPIRE, ASpirin to Prevent Recurrent Venous Embolism.

Authors’ Note

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