Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 144 (2020) 109975

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Should aspirin be used for prophylaxis of COVID-19-induced coagulopathy?

Background

The worldwide pandemic caused by the novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a new and lethal disease termed coronavirus disease 2019 (COVID-19). Data for early cases showed that the incidence of stroke among hospitalized patients with Covid-19 was approximately 5% [1]. Since then Covid-19 positive cases showed increasing number of new- onset cases of large-vessel ischemic stroke in patients younger than 50 years compared to the previous 12 months [2]. Recently, complete autopsy performed on 12 COVID-19 cases, revealed deep venous thrombosis in 58% in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients and diffuse alveolar damage was seen in 8 patients. This high incidence of thromboembolic events suggests an important role of COVID-19 induced coagulopathy. It was suggested that further studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19–related death, as well as possible therapeutic interventions to reduce it [3].

The reported diffuse alveolar hemorrhage (DAH) as a common finding from lung pathology in COVID-19 patients, raised safety concerns regarding the use of antiplatelet therapy on life-threatening bleeding complications among SARS-CoV-2 infected patients [4]. A link between NSAIDs and both respiratory and cardiovascular adverse effects lead to a recommendation to avoid using Aspirin and NSAIDs [5].

COVID-19 pandemic provides a unique opportunity to study the key questions concerning the preventive, therapeutic, or even aggravating effects of antiplatelet therapy on viral pneumonia based on real-world data. In this perspective, we aim to revise the recommendation of early use of aspirin in COVID-19 patients, as it may reduce the incidence of COVID-19 induced coagulopathy and may hinder the severe and critical deterioration resulting from cardiovascular, neurologic and vascular complications.

Mechanism of aspirin action

The antithrombotic action of aspirin has long been recognized. Aspirin inhibits platelet function through irreversible inhibition of cyclooxygenase (COX) activity. Low doses (typically 75–81 mg/day) are sufficient to irreversibly acetylate serine 530 of cyclooxygenase (COX)-1. This effect inhibits platelet generation of thromboxane A2, resulting in an antithrombotic effect. Intermediate doses (650 mg to 4 g/day) inhibit COX-1 and COX-2, blocking prostaglandin (PG) production, and have analgesic, anti- inflammatory and antipyretic effects [6].

Although aspirin is not commonly used in the guidelines for the treatment of SARS-CoV-2, it has been confirmed to have antiviral effect on multiple levels [7]. It inhibits virus replication by inhibiting prostaglandin E2 (PGE2) in macrophages and up regulation of type I interferon production [8]. Furthermore, under certain conditions, platelets play as a contributor of innate immune response, studies have found that in the lung injury model there is dynamic neutrophil and platelet aggregation; this could be reduced by aspirin and antithrombotic drugs [9].

Current evidence of use of aspirin in COVID-19 disease

On March 2020, scientists claimed that reasonable evidence exists of a link between NSAIDs and both respiratory and cardiovascular adverse effects in several settings. To avoid these plausible harms they stated that: regular NSAID use should probably not be recommended as the first line option for managing the symptoms of COVID-19 [5]. Two weeks later, they changed their advice on Ibuprofen to say that the drug can be used to treat patients with symptoms of COVID-19, although the evidence that prompted the revision has not been made public. The Commission on Human Medicines' expert working group on COVID-19 and WHO concluded that there is currently insufficient evidence to establish a link between use of ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs), and contracting or worsening symptoms of COVID-19 [10–12]. Only children and teenagers should not take aspirin due to the risk of it causing a life-threatening condition called Reye's syndrome [12].

A systematic review on acute viral respiratory infections or conditions commonly caused by respiratory viruses - but none specifically addressed COVID-19, SARS, or MERS- showed very low certainty evidence on mortality among adults and children. Effects of NSAIDs on the risk for ischemic and hemorrhagic stroke and myocardial infarction in adults with acute respiratory infections were unclear. Moderate to high certainty evidence showed little or no difference between Ibuprofen (as NSAID) and acetaminophen (paracetamol) among children with fever with regard to effects on death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding [13].

As mentioned earlier, it should be considered that COVID-19 besides having a high infection rate and mortality, it has serious complications such as heart injury that cannot be ignored. The occurrence of progressive inflammatory factor storm and coagulation dysfunction in severe and fatal cases points out a new direction for reducing the incidence of cardiovascular complications. In this regards, it is suggested that Aspirin has several effects of inhibiting virus replication, anticoagulant, anti- platelet aggregation, anti-inflammatory and hence anti-lung injury. The early use of aspirin in COVID-19 patients is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and reduce the incidence of cardiovascular complications [14].

A recent perspective on Antiplatelet Therapy Following Percutaneous Coronary Intervention (PCI) in Patients Complicated by COVID-19 added that, in addition to thrombosis and hemostasis, emerging evidence supports a putative role of platelets in host defense against infections, which add a greater layer of complexity in

https://doi.org/10.1016/j.mehy.2020.109975
Received 10 May 2020; Received in revised form 26 May 2020; Accepted 5 June 2020
Available online 08 June 2020
0306-9877/

evaluating the role of antiplatelet therapy in the setting of viral pneumonia. Early antiplatelet therapy may be beneficial due to their inhibitory effects on platelet activation and generation of neutrophil-platelet aggregates, key mechanisms in both thrombus formation and pulmonary neutrophil recruitment [15]. COVID-19 patients taking low dose aspirin for secondary prevention of cardiovascular disease should continue their treatment [16].

Even during pregnancy, when indicated, the continuous use of prophylactic aspirin in pregnant women during the COVID-19 pandemic is needed [17]. The combination of heparin (UFH or LMWH) plus aspirin during the course of pregnancy may increase live birth rate in women with persistent Antiphospholipid syndrome (aPL) [18].

Lastly, a described case of a 6-month-old infant admitted and diagnosed with classic Kawasaki disease (KD), who also screened positive for COVID-19 in the setting of fever and minimal respiratory symptoms. The patient was treated per treatment guidelines, with intravenous immunoglobulin (IVIG) and high-dose aspirin (ASA), and subsequently defervesced with resolution of her clinical symptoms [19]. This is an added value of aspirin use in COVID-19 complicated cases.

Limitations of aspirin use in SARS-CoV-2

Besides the usual side effects of aspirin, the drug irreversibly inhibits platelet cyclooxygenase, and its effect persists for the circulating life of platelets [7–10] days) making its use is controversial in COVID-19 patients. There are some concerns that the delay between SARS-CoV-2 test positivity and clinical deterioration is similar to the delay between the last aspirin intake and the end of its clinical effect [20].

Furthermore, aspirin is not indicated for the treatment of DIC, or other venous thromboembolic complication that might be associated with severe COVID-19, and may increase the bleeding risk in severely thrombocytopenic patients [21].

We suggest an approach for risk stratifying patients and determine the “no-harm criteria “of aspirin in SARS-CoV-2 patients based on Troponin and D-Dimer thresholds to identify patients who should use prophylactic doses of Aspirin with or without anticoagulation.

Conclusions

Given that many clinicians are already using aspirin and NSAIDs to treat viral infections including COVID-19 off-label, without recourse to robust evidence of safety or effectiveness, there is an urgent need for well-conducted, randomized clinical trials in this area. The results of such studies will help to guide clinical practice during this pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109975.

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