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Review

The role of acetylsalicylic acid in the prevention of thrombosis and its effect on the outcome of patients with COVID-19

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Summary

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, was marked by a high incidence of thrombotic complications contributing to poor outcomes, particularly in hospitalized patients. Acetylsalicylic acid (ASA), known for its antiplatelet and anti-inflammatory properties, has been widely investigated for its potential role in mitigating thrombotic events associated with COVID-19. This review explores the pathophysiological mechanisms linking SARS-CoV-2 infection with thrombosis and highlights the rationale for ASA use in this context. We analyze relevant clinical and observational studies, meta-analyses, and the results of the RECOVERY trial, which offer varying degrees of evidence regarding ASA effectiveness. While several retrospective studies suggest a reduction in thrombotic events, mechanical ventilation, and mortality among patients receiving low-dose ASA, randomized trials report mixed results, including a modest reduction in hospitalization duration, but no significant impact on overall mortality. Adverse events such as increased bleeding risk must also be considered. This review underscores the importance of individualized risk assessment and the need for further randomized controlled trials to determine the precise role of ASA in COVID-19 management.

Key words: acetylsalicylic acid, COVID-19, thrombosis, anticoagulation, inflammation, RECOVERY trial

Introduction

After two years of the COVID-19 pandemic caused by the SARS-CoV-2 virus from the perspective of clinicians and after experience with patients in Covid units, we could assume that the highest percentage of fatal outcomes occurred due to thromboses, pulmonary, cerebral, coronary or systemic [1].

What we did not know at the very beginning of the epidemic, we can now analyze with certainty. Science has not wasted time, it has studied the effects of the virus, and presented the results of the study implemented in the current recommendations for the treatment of outpatients and hospital patients.

COVID-19 and thrombosis

Bearing in mind the results of the research, it is completely justified that the basis of the treatment of hospitalized patients was the prevention of thrombosis. Both experimental and clinical studies have proven the enormous thrombogenic potential of SARS and MERS Co viruses. Overexpression of a significant number of genes involved in the regulation of the coagulation cascade (eg, fibrinogen, factors II, III, VII, X, XI, XII, serine proteinase inhibitors [SERPIN]) and platelet aggregation (eg, TBXAS, TLR9) has been described in SARS-CoV-1 infected peripheral blood mononuclear cells. Also, an excess of microvascular thrombi was observed in the lung tissue of MERS-CoV-infected mice transgenic for human dipeptidyl peptidase 4 (DPP4) [1, 2].

In addition to these changes, changes in laboratory markers of increased risk of thrombosis in patients with SARS-CoV-1 and MERS-CoV have been described. Also, the presence of antiphospholipid antibodies (eg, anticardiolipin IgA, anti-β2-glycoprotein I IgA and IgG) has been described in the serum of patients with COVID, which may contribute to an increased risk of venous and arterial thrombosis [2].

Direct viral injury of the myocardium, systemic overactivation of the cascade inflammatory reaction, as well as virus-induced destabilization of the atherosclerotic plaque and micro-macrovascular thrombosis have been proposed as possible mechanisms leading to the cardiovascular manifestations of COVID-19 [1, 2].

COVID-19 and acetylsalicylic acid

„Where is thrombosis, there is also acetylsalicylic acid“, one could say. Numerous studies analyzed the use of ASA in the prevention of thrombogenic incidents in patients with COVID-19. Given the increased exposure to Tromboxane A2, the use of ASA in the early stages of the disease is fully justified. Scientific curiosity leads us through numerous clinical and laboratory analyzes of this current topic. We will try to analyze only some of them that confirm or show its impotence in the prevention of thrombotic events in patients with COVID-19 [2].

From infection to thrombosis, a complex cascade of mutual reactions of proinflammatory and prothrombotic factors occurs leading to arterial and venous thrombosis, and also organic and multiorgan damage [2].

Can small doses of ASA interrupt this vascular undesirable chain reaction? (Figure 1). The answer is given by numerous clinical studies.

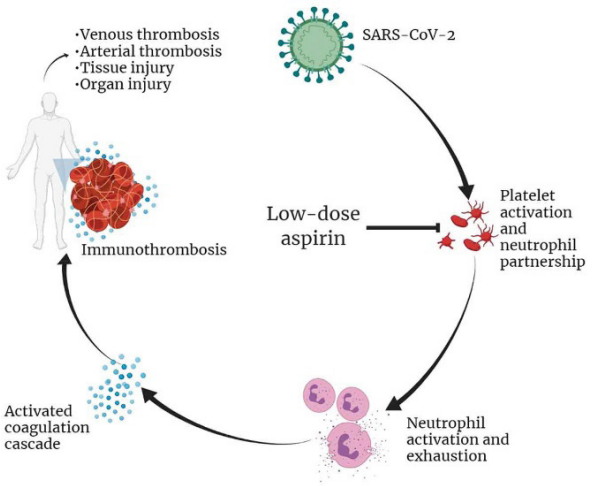

Figure 1. Potential role of early introduction of ASA in the reduction of thromboinflammatory incidents in SARS-CoV-2 virus

Clinical worsening in COVID-19 is associated with inflammation, coagulopathy and endothelopathy. ASA can potentially influence the pathogenesis of COVID-19 through its anti-inflammatory, anti-aggregation and anticoagulant properties, as well as due to its pleiotropic effect on endothelial function [1, 2].

During COVID-19, low-dose ASA was used effectively for secondary prevention of CVD, prevention of venous thromboembolism after hip or knee replacement, and prevention of preeclampsia. Prehospital administration of low-dose ASA may be associated

with a reduced risk of admission to intensive care, mechanical ventilation, while the impact on mortality is still debatable [2, 3].

Many authors recommend the use of low-dose ASA for the primary prevention of arterial thromboembolism in patients aged 40–70 years who have high ASCVD or intermediate ASCVD risk with a risk "enhancer" such as a family history of premature cardiovascular disease, who have a low risk of bleeding [3].

Additional randomized clinical trials are needed to determine the protective role of ASA in COVID-19-related acute lung injury, in patients without previous CV disease, with vascular thrombosis, without previous CV disease and mortality.

What do the studies tell us?

In numerous meta analyses, prospective and retrospective studies, it is difficult to single out the most important ones.

In retrospective cohort study conducted among patients with confirmed COVID-19 at Mansoura University Quarantine Hospital, Egypt, among hospitalized and home-treated patients from September to December 2020 in Mansoura Governorate, Egypt patients were divided into three groups. One group of patients treated practically at home were on ASA (81-162 mg orally per day), the second group of hospital treated patients received Enoxaparin and low doses of ASA and the third group of patients received only Enoxaparin. Enoxaparin doses were received according to the severity of the clinical picture and d dimer values. Depending on the clinical picture, patients were treated with Hydrochloroquine, Ivermectin or Remdesivir along with glucocorticoids according to the severity of the clinical picture. The primary outcome was the occurrence of thrombosis such as deep vein thrombosis DVT, pulmonary embolism, peripheral artery occlusion, ischemic stroke, myocardial infarction with ST elevation or intestinal thrombosis, and the need for mechanical ventilation. The results showed that the use of low doses of ASA could reduce the incidence of thromboembolism associated with COVID-19, but the use of ASA and enoxaparin showed promising results in reducing thrombotic events and the need for mechanical ventilation [4].

Through a systematic literature search of PubMed, Scopus, Embase and Clinicaltrials, a meta-analysis was performed of six studies that included 13,993 patients. ((Chow et al., 2021; Liu et al., 2021; Meizlish et al., 2021; Merzon et al., 2021; Osborne et al., 2021; Yuan et al., 2021). The primary outcome was the analysis of mortality. The focus was on low doses of ASA (75-325mg /24h) in patients with COVID-19, for at least seven days during the illness. The meta-analysis showed that the use of low doses of AKA was independently associated with reduced mortality [RR 0.46 (95% CI 0.35–0.61), $P < 0.001$; $I2 = 36.2\%$, $P = 0.155$]. Subgroup analysis on hospital use of low-dose ASA also showed a significant reduction in mortality [RR 0.39 (95% CI 0.16– 0.96), $P < 0.001$; $I 2 = 47.0\%$, $P = 0.170$] [5].

In the absence of randomized controlled clinical trials, the best evidence for the early use of ASA comes from the recently published large retrospective Osborne I study that analyzed outcomes in US veterans with COVID-19. The use of ASA was associated with a statistically and clinically significant reduction in overall mortality of over 50% after 15 and 30 days, reducing the odds of death by more than half. This study supports the use of ASA for the primary prevention of thrombosis in patients with COVID-19 [6].

A randomized study (Randomized Evaluation of COVID-19 Therapy, RECOVERY Trial or RECOVERY) is a large clinical trial of possible treatments for people in the United Kingdom admitted to hospital with severe COVID-19 infection. The study examined seven different drugs, including ASA, and their effect on the clinical picture and outcome of

patients. There was no evidence that treatment with ASA reduced mortality in 7541 patients who were on 150 mg of ASA. Patients who received ASA had a slightly shorter duration of hospitalization, and for every 1000 patients treated with ASA, approximately six patients experienced major bleeding and almost the same number of patients experienced a thromboembolic event. The modest, nonsignificant reduction in thrombotic events associated with low-dose ASA treatment is likely explained by the fact that the vast majority (626 of 735) of these outcomes were episodes of pulmonary embolism, occurring despite concomitant (inadequate?) anticoagulant therapy, with only 80 presumed atherothrombotic events (49 in the usual care group and 31 in the ASA group). As expected, ASA therapy significantly increased major bleeding (although intracranial bleeding was numerically less), mainly gastrointestinal. Cytoprotective therapy (eg, proton pump inhibitors) was not mentioned among concomitant treatments or co-medications required by the protocol, even though enrolled patients had at least four risks [7].

Data from a retrospective study in Bangladesh that is flawed due to a small sample (11 patients) proved the absolute effectiveness of 75 mg ASA on the occurrence of complications and death in patients with COVID-19 [8].

Conclusion

At the very beginning of the COVID-19 pandemic, unknown to us, the use of ASA was widespread, without even proving its effectiveness.

The author personally advocates the use of ASA in the prevention of thrombotic events in patients suffering from COVID-19, but with the importance and reference to the severity of the clinical picture, associated risk factors and without diminishing the importance of other additive therapy.

Taking into account all the mechanisms of the action of ASA on the endothelium injured by the COVID-19 virus, it remains for science to investigate all its potential benefits in the prevention of thrombotic incidents, which ultimately, to the greatest extent, affect the death outcome of this group of patients.

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Uloga acetilsalicilne kiseline u prevenciji tromboze i njen uticaj na ishod liječenja pacijenata sa COVID-19

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Pandemiju COVID-19, izazvanu virusom SARS-CoV-2, pratio je visok stepen trombotičnih komplikacija koje su značajno doprinijele nepovoljnim ishodima, naročito kod hospitalizovanih pacijenata. Acetilsalicilna kiselina (ASK), poznata po svojim antiagregacionim i antiinflamatornim svojstvima, intenzivno je ispitivana kao potencijalna terapija u prevenciji trombotičnih događaja kod oboljelih od COVID-19. Ovaj pregled prikazuje patofiziološke mehanizme koji povezuju infekciju SARS-CoV-2 sa trombozom i analizira opravdanost primjene ASK u tom kontekstu. Obrađene su relevantne kliničke i opservacione studije, meta-analize i rezultati RECOVERY studije, koje pružaju različite nivoe dokaza o efikasnosti ASK. Dok neke retrospektivne studije ukazuju na smanjenje trombotičnih incidenata, potrebe za mehaničkom ventilacijom i mortaliteta kod pacijenata koji su primali male doze ASK, randomizovane studije pokazuju ograničene efekte – poput blagog skraćenja boravka u bolnici, ali bez značajnog uticaja na ukupni mortalitet. Neželjeni efekti, kao što je povećan rizik od krvarenja, takođe se moraju uzeti u obzir. Zaključno, naglašava se značaj individualne procjene rizika i potreba za daljim randomizovanim kontrolisanim studijama kako bi se precizno odredila uloga ASK u liječenju COVID-19.

Ključne riječi: acetilsalicilna kiselina, COVID-19, tromboza, antikoagulacija, inflamacija, RECOVERY studija