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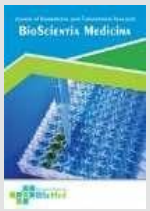

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The Effectiveness of Antiplatelet Therapy in COVID-19 Patients: A Narrative Literature Review

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A B S T R A C T

Coagulopathy is a feature of severe COVID-19 disease and contributes to an increased risk of thromboembolic complications and death. This literature review aimed to describe the effectiveness of antiplatelet therapy in COVID-19 patients. There is an inverse relationship between the likelihood of COVID-19 infection, duration of illness and death, and use of antiplatelets for primary prevention. A study showed that COVID-19 patients who did not receive antiplatelet drugs had three times the risk of dying with antiplatelet drugs. This study shows the strong effect of antiplatelet drugs on reducing the mortality rate of COVID-19 patients. Another study showed that COVID-19 patients who received antiplatelet drugs had 1.18 times the risk of dying than those without antiplatelet drugs. This study shows that antiplatelet therapy does not affect the reduction in mortality in patients hospitalized with COVID-19. In conclusion, the effectiveness of antiplatelet administration in COVID-19 patients is still unclear, so further research is needed.

1. Introduction

COVID-19 mainly spreads through respiratory droplets with an incubation period between 1-14 days, generally 3-7 days.[1,2] The clinical spectrum of COVID-19 varies from asymptomatic to symptomatic, with symptoms of fever, cough, shortness of breath, headache, sore throat, and rhinorrhea. Some patients may experience gastrointestinal manifestations such as nausea and diarrhea. Patients may experience severe clinical manifestations, including severe pneumonia, sepsis, septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS). Patients who are over 65 years old, smoke, and have comorbid diseases such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and

malignancy have a higher risk of experiencing a more severe degree of disease and higher mortality if infected with COVID-19.

Although dominated by respiratory manifestations, recent evidence shows that patients with severe COVID-19 often have coagulation disorders similar to other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) and microangiopathic thrombosis. These complications are associated with a significant increase in mortality. The hyperinflammation that occurs in COVID-19 causes increased activation of the coagulation cascade and excessive thrombin production. Coagulation disorders in COVID-19 cause a prothrombotic state which increases the risk of thrombosis and venous and arterial thromboembolism.[1,2]

Coagulopathy is a feature of severe COVID-19 disease and contributes to an increased risk of thromboembolic complications and death. Platelets are cell fragments without nuclei derived from megakaryocytes that may become hyperactive in the pathological mechanism of COVID-19. Antiplatelet agents, such as aspirin and P2Y12 inhibitors, have been proposed as a potential treatment strategy for COVID-19 patients based on their mechanisms, namely antithrombotic and anti-inflammation.[3] This literature review aimed to describe the effectiveness of antiplatelet therapy in COVID-19 patients.

Pathogenesis of COVID-19

According to WHO, COVID-19 is an infectious disease caused by a newly discovered coronavirus. The new virus that causes COVID-19 is now known as severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2.[4] Coronavirus is a ribonucleic acid (RNA) virus with a particle size of 120-160 ηm. This virus initially caused infection in animals, namely bats, and camels.

The virus can pass through mucous membranes, especially the nasal and laryngeal mucosa, then enter the lungs through the respiratory tract. Furthermore, the virus will attack target organs that express angiotensin-converting enzyme-2 (ACE-2), such as the lungs, heart, renal system, and gastrointestinal tract. The S protein in SARS-Cov2 facilitates the entry of the coronavirus into target cells. Viral entry depends on the ability of the virus to bind to ACE-2, an extracellular membrane receptor expressed on epithelial cells and depends on priming S protein into cellular proteases. The S protein in SARS-CoV-2 and SARS-CoV has an almost identical three-dimensional structure in the receptor-binding domain. The S protein in SARS-CoV has a strong binding affinity with ACE2 in humans.[5]

The incubation period for COVID-19 lasts between 3-14 days and is characterized by leukocyte and lymphocyte levels that are still normal or slightly decreased. Subsequently, the virus began to spread through the bloodstream, mainly to organs expressing ACE-2, and the patient began to experience mild symptoms. Four to seven days after the initial symptoms, the patient's condition began to deteriorate, marked by the onset of shortness of breath, decreased lymphocytes, and worsening of the lesions in the lungs. If this phase is not resolved, acute respiratory distress syndrome (ARDS) can occur *with* sepsis and other complications.[5]

The innate immune system can detect viral RNA through RIG-I-like receptors, NOD-like receptors, and toll-like receptors. This will further stimulate interferon (IFN) production, as well as trigger the emergence of antiviral effectors such as CD8+ cells, natural killer (NK) cells, and macrophages. Infections from other betacoronavirus, namely SARS-CoV and MERS-CoV, are characterized by rapid viral replication and delayed IFN production, especially by dendritic cells, macrophages, and respiratory epithelial cells, which are then followed by increased levels of proinflammatory cytokines as the disease progresses.

COVID-19-related cytokine storm

The immune response as a result of exposure to the virus, the immune response seems to be responsible for the clinical experience of sufferers of COVID-19. Patients with mild or asymptomatic

clinical conditions have good immunity. On the other hand, it has been proven from various studies around the world that in patients with severe COVID-19, complex immunopathogenesis occurs, which involves many inflammatory mediators. The normal condition of the body will respond to exposure to the SARS-CoV-2 virus, starting with lysing infected cells by natural killer cells (NK) as innate immunity and CD8+ cytotoxic T cells as adaptive immunity. Infection from a virus is capable of producing an exaggerated immune reaction in the host. In some cases, there is a reaction known collectively as a cytokine storm.[5]

Cytokine storm is an event of excessive inflammatory reaction in which cytokine production occurs rapidly and in large quantities in response to an infection. In relation to COVID-19, it was found that there was a delay in the secretion of cytokines and chemokines by innate immune cells due to blockade by viral non-structural proteins. Furthermore, this causes a surge in proinflammatory cytokines and chemokines (IL-6, TNF-α, IL-8, MCP-1, IL-1 β, CCL2, CCL5, and interferon) through macrophage and lymphocyte activation. The release of these cytokines triggers the activation of adaptive immune cells such as T cells, neutrophils, and NK cells, along with the continued production of proinflammatory cytokines. This rapid surge of proinflammatory cytokines triggers inflammatory infiltration by the lung tissue, which causes lung damage to the epithelium and endothelium. This damage can result in the occurrence of ARDS and multiorgan failure, which can cause death in a short time.[5,6]

Mechanisms of thrombosis in COVID-19

COVID-19 disease caused by infection with SARS CoV-2 is a complex syndrome that mainly affects the respiratory tract, which can cause acute respiratory distress, but it can also cause damage to various physiological systems, such as the hemostatic system. Early studies reported an overall incidence of thromboembolic complications admitted to hospital in patients with COVID-19 ranging from 7–46%, with rates higher in critically ill patients requiring intensive care units (ICU).[7]

Angiotensin-converting enzyme-2 (ACE2) is the main receptor for SARS-CoV-2. ACE2 is widely expressed in alveolar epithelial cells of the lungs, especially type II alveolar cells. In addition, ACE-2 is also found in the heart, vascular endothelium, kidneys, and gastrointestinal tract, so multiorgan manifestations can occur in COVID-19 infection. The coronavirus genome consists of 4 main proteins, namely spike (S), nucleocapsid (N), membrane (M), and envelope (E). Infection occurs when the S protein binds to the ACE2 receptor. SARS-CoV-2 aggregation in the lungs causes disruption of alveolar epithelial and endothelial cells, together with the infiltration of inflammatory cells, causing the emergence of proinflammatory cytokines (IL1, IL-6, and TNF-α, and others).

In severe COVID-19 patients, this immune response can be exaggerated and cause a systemic cytokine storm that triggers systemic inflammatory response syndrome (SIRS). The excessive systemic inflammatory response can lead to systemic endothelial injury (endotheliopathy) and a hypercoagulable state that increases the risk of systemic macro thrombosis and micro thrombosis. Manifestations of macro thrombosis can be venous thromboembolism (e.g., deep vein thrombosis and pulmonary embolism) or arterial thromboembolism (e.g., stroke). Microthrombosis plays a role in the process of ARDS and multiorgan failure.[8]

COVID-19-associated hypoxia can lead to vasoconstriction and reduced blood flow which contribute to endothelial injury. Hypoxia can also shift the basic antithrombotic and anti-inflammatory phenotype in the endothelium to a procoagulant and proinflammatory phenotype. Endothelial injury triggers the release of ultra-large von Willebrand factor (ULVWF), which plays a role in the process of hemostasis. ULVWF acts as a bridge between endothelial injury and platelet activation. ULVWF triggers platelet aggregation and initiation of

thrombogenesis in the microvasculature, which can lead to the formation of microthrombi. Circulating monocytes, neutrophils, platelets, and microparticles attach to activated endothelium, together with tissue factor (TF), and the formation of neutrophil extracellular traps (NETs) initiate the coagulation cascade, resulting in the production of large amounts of thrombin and leading to a hypercoagulable state.[8]

Virchow's triad is the basis for understanding thrombosis, which includes endothelial injury, blood flow stasis, and hypercoagulation. Thrombosis and thromboembolism that occur in COVID-19 follow the concept of Virchow's triad. Endothelial injury in COVID-19 can occur through the mechanism of direct invasion of SARS-CoV-2 into endothelial cells, which causes cell injury or as a result of an inflammatory response by proinflammatory cytokines. Blood flow stasis can be caused by immobilization in hospitalized patients. The hypercoagulable state is exacerbated by prothrombotic factors such as increased ULVWF, factor VIII, fibrinogen, NETs, and thrombotic microparticles. The main causes of death from COVID-19 are ARDS and progressive respiratory failure. The mechanism of ARDS and respiratory failure in COVID-19 is not only caused by inflammatory factors. Microthrombosis has an important role in this. Primary viral infection causes alveolar injury and the production of significant proinflammatory cytokines in COVID-19 patients. Activation and recruitment of mononuclear cells and neutrophils lead to increased damage to lung tissue and vascular endothelium. Hypoxic conditions, endothelial injury, and a sustained inflammatory response promote a procoagulant state that can lead to pulmonary vascular micro thrombosis, leading to ARDS and respiratory failure.[8]

Several studies conducted using the RCT method found that the incidence of thrombotic events when using prophylactic anticoagulants ranged from 2.1% in moderately ill and 10.4% in critically ill patients. The majority of thrombotic events are venous thromboembolism, especially pulmonary embolism, and deep vein thrombosis, although thrombosis can also occur in arteries.[7] A COVID-19-induced hypercoagulable state exhibits clinical and laboratory partial overlap with coagulopathy caused by sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulation (DIC). This condition may be termed COVID-19-associated coagulopathy (CAC). CAC is characterized by dysregulation of coagulation parameters, such as increased D-dimer and prolonged prothrombin time, whereas the platelet count is only slightly reduced. The exact mechanism of CAC is still under investigation and appears to be very complex due to the specific pathophysiological environment created by SARS-CoV-2 infection, which is influenced by a multitude of mediators.[7]

Although platelets are thought to play an important role in COVID-19-associated hypercoagulability, evaluation of randomized trials of COVID-19 therapy did not demonstrate a clear benefit of aspirin as standard thromboprophylaxis in hospitalized patients with COVID-19. However, other antiplatelet drugs, such as P2Y12 inhibitors, may have more potent platelet inhibitory properties and have been associated with certain anti-inflammatory effects.[9]

Inflammatory processes in the alveoli of the lungs also cause pulmonary tissue edema and intravascular coagulopathy. The intravascular thrombotic pathway leads to microvascular and macrovascular thrombotic complications due to strong local and systemic cytokine production. Platelets are activated and interact with neutrophils. The process of neutrophil extracellular trap (NET) can also stimulate thrombin production and fibrin deposition. Excess fibrin deposition and cessation of fibrinolysis lead to intravascular thrombosis leading to thromboembolic complications.[10]

Activation of platelets not only promotes thrombosis but can also mediate inflammation. Therefore, antiplatelet therapy may be beneficial in COVID-19. However, it is unclear whether current antiplatelet agents can be anti-inflammatory by reducing platelet activation or through other mechanisms. This is of particular concern because aspirin or P2Y12 inhibitors, both of which inhibit

autocrine activation of platelets, appear to be effective in COVID-19. The coagulopathy in COVID-19 is characterized by high blood fibrinogen levels. Conceptually, glycoprotein IIb/IIIa inhibitors (such as abciximab, eptifibatide, or tirofiban) could be more effective because they directly interfere with platelet aggregation via fibrinogen bridges. P-selectin inhibition is interesting because it targets both activated platelets and the endothelium, thereby potentially providing more effective protection against microvascular thrombosis.[11]

Mechanism of action of antiplatelet drugs

Antiplatelets can be classified based on their mechanism of action as follows; platelet aggregation inhibitors such as aspirin and cyclooxygenase inhibitors; oral thienopyridines such as clopidogrel, ticagrelor, ticlopidine, and prasugrel; platelet glycoprotein inhibitors such as abciximab, eptifibatide, and tirofiban; and protease-activated receptor-1 antagonists such as vorapaxar.[12]

Aspirin, the most commonly used oral antiplatelet drug, works by irreversibly inhibiting the activity of the cyclooxygenase (COX) enzyme in the prostaglandin H_2 synthesis pathway (PGH_2). These prostaglandins are precursors of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2). Thromboxane A_2 works by inducing platelet aggregation and vasoconstriction, and COX-1 mediates its production, while PGI_2 acts by inhibiting platelet aggregation and induces vasodilation, and is mediated by COX-2. Low-dose aspirin (75-150 mg) can induce complete or nearly complete inhibition of COX-1, thereby inhibiting TXA_2 production, while larger doses are required to inhibit COX-2.[12]

Oral thienopyridines selectively inhibit adenosine diphosphate (ADP)-induced platelet aggregation. These drugs are converted into active drugs with the help of the liver's CYP450 system, which can irreversibly inhibit platelet P2Y12 receptors. Prasugrel is the most potent drug, has a rapid onset of action, and is superior to clopidogrel in patients undergoing coronary stenting. Ticlopidine has fallen out of favor because of its bone marrow toxicity. Cangrelor is a reversible intravenous P2Y12 receptor antagonist with a rapid onset of action.[13]

Platelet glycoprotein inhibitors work by inhibiting the glycoprotein IIb/IIIa (GpIIb-IIIa) receptors on platelets, thereby reducing platelet aggregation, and are most commonly used in ACS. This drug is available only in intravenous form and thus is used as short-term therapy. Dipyridamole has antiplatelet and vasodilating properties and inhibits platelet cyclic nucleotide phosphodiesterase. This enzyme is responsible for the degradation of adenosine monophosphate (AMP) to 5'AMP, which enhances the intra-platelet accumulation of cyclic AMP and inhibits platelet aggregation. It also blocks the uptake of adenosine by platelets, which also increases cyclic AMP. Cilostazol has also been reported to have vasodilatory, antiplatelet, and antiproliferative effects by reducing smooth muscle cell hyperproliferation and intimal hyperplasia after endothelial injury.[14]

The effectiveness of using antiplatelet drugs in reducing mortality in COVID-19 patients

A retrospective cohort study conducted by Chow et al. revealed that patients who received aspirin within 24 hours of hospital admission experienced reduced rates of need for mechanical ventilation in the intensive care unit and reduced in-hospital mortality.[15] There were no significant differences in bleeding side effects between patients who received aspirin and those who did not. Meanwhile, the results of a study conducted by Abu-Jamous et al. found that COVID-19 patients who did not receive antiplatelet drugs had a 10-fold risk of death compared to those who took antiplatelet drugs.[16] This study shows the strong effect of using antiplatelet drugs on reducing the mortality rate of COVID-19 patients. This study provides an important piece of evidence regarding the relationship between comorbidities and the use of antiplatelet drugs.

Research conducted by Benson et al. also showed that COVID-19 patients who did not receive antiplatelet drugs had 2 times the risk of dying than those with antiplatelet drugs.[17] This study showed

statistically significant results and the effect of antiplatelet drugs on reducing the death rate of COVID-19 patients. Another study stated that COVID-19 patients who received antiplatelet drugs had a risk of dying 3.8 times compared to those without antiplatelet drugs.[18]

There appears to be an inverse relationship between the likelihood of COVID-19 infection, duration of illness and death, and the use of aspirin (an antiplatelet) for primary prevention. A study showed that COVID-19 patients who did not receive antiplatelet drugs had three times the risk of dying with antiplatelet drugs.[18] This study shows the strong effect of antiplatelet drugs on reducing the mortality rate of COVID-19 patients. Prospective evaluation is needed to assess this correlation and its implications for patient care.

Yuan et al. in 2021, in their research, also stated that COVID-19 patients who did not receive antiplatelet drugs had a risk of dying 1.94 times compared to those with antiplatelet drugs.[19] This study showed results that were not statistically significant despite the effect of antiplatelet drugs on reducing the death rate of COVID-19 patients. Collectively, the investigators suggest that prehospital use of antiplatelets (low-dose aspirin) is associated with the clinical outcome of patients with CAD who are hospitalized with COVID-19 infection.

Contradictory results were found in a study conducted by Corrochano et al. in 2022 which showed that COVID-19 patients who received antiplatelet drugs had a risk of dying 1.18 times compared to those without antiplatelet drugs.[20] This study shows that antiplatelet therapy does not affect the reduction in mortality in patients hospitalized with COVID-19. However, this study showed that patients receiving antithrombotic therapy admitted to the ICU were lower than patients who were not treated with antithrombotic therapy prior to hospitalization.

2. Conclusion

The effectiveness of antiplatelet administration in COVID-19 patients is still unclear, so further research is needed.

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