Comparison of antihypertensive therapy on the outcomes of COVID-19 patients: literature review

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Abstract

COVID-19 which caused atypical pneumonia outbreaks are caused by coronavirus, which WHO later named this virus as SARS-CoV-2. The severity of COVID-19 patients is associated with the comorbidities. The comorbidity that most commonly accompanies COVID-19 in Indonesia is hypertension, approximately 50.3%. It can significantly heightens the risk of death by 4.53 times and substantially delays the clearance of the SARS-CoV-2. Currently, the effect of antihypertensive drugs on COVID-19 patients is still being debated. This review aims to determine the comparison between the use of five antihypertensive drugs on the clinical outcomes of COVID-19 patients. There are differences in the results between each antihypertensive agent on the outcomes of COVID-19 patients. Beta-blocker has the potential to reduce SARS-CoV-2 entry receptors by downregulating ACE-2 and have protective mechanisms including the reduction of anti-inflammatory cytokine. Meanwhile, the use of RAAS inhibitors comes with pros and cons. There is a potential risk of increasing the likelihood of SARS-CoV-2 infection due to their ability to upregulate ACE-2 receptors. However, ACE-2 may protect against more severe complications of COVID-19 infection by limiting the effects of angiotensin II on the heart and blood vessels. However, ACE-2 may protect against more severe complications of COVID-19 infection by limiting the effects of angiotensin II on the heart and blood vessels. As for Calcium Channel Blocker (CCB) could inhibit SARS-CoV-2 replication. Whereas diuretic has not yet been proven because only a few samples of the use of thiazide therapy are available.

Keywords: COVID-19; SARS-CoV-2; hypertension; antihypertensive drugs

1. Introduction

COVID-19 is a disease that was first discovered in a group of cases in Wuhan, Hubei Province, China, which caused pneumonia and then spread rapidly and resulted in an epidemic throughout China [1]. This case of atypical pneumonia outbreak was caused by the corona virus, which WHO later named this virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is the agent that causes Corona Virus Disease-19 (COVID-19). So, it was recorded that Asia was the first continent to become the source of the outbreak [2]. This outbreak was first declared by World Health Organization (WHO) as a pandemic on March 11, 2020. It has spread globally and as of April 14, 2020 it was reported that there were around 1,844,683 cases confirmed positive and 117,021 people died in at least 213 countries [3]. The severity of COVID-19 in patients is associated with the presence or absence of comorbidities in each individual. The comorbidity that

most commonly accompanies COVID-19 in Indonesia is hypertension, affecting approximately 50.3%, followed by diabetes mellitus at 36.7% and heart disease with a percentage of 17.5% [5]. Various studies have stated that hypertension, as a comorbidity of COVID-19, is associated with increased mortality due to COVID-19. Hypertension can increase the risk of death by 4.53 times [6]. Hypertension also correlates with the severity of COVID-19. It was explained that clearance of the SARS-CoV-2 virus is more likely to be delayed in COVID-19 patients with hypertension as at least one comorbidity, compared to patients without comorbidities. This suggests that hypertension as a comorbidity can worsen outcomes and lengthen the recovery time [5].

Currently, the effect of antihypertensive drugs on COVID-19 patients is still being debated. The use of renin-angiotensin-aldosterone system (RAAS) inhibitors, which has generated both pros and cons in COVID-19 patients related to the drug's mechanism of action, is attributed to the fact that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can upregulate ACE2. ACE2 is the receptor utilized by SARS-CoV-2 to enter the host cell, potentially leading to an increased risk of infection [7]. There is comparative research regarding the comparison of non-ACEI antihypertensive drugs with ACEI, stated that among those infected with COVID-19, patients taking ACEI/ARBs were not associated with a higher risk of developing severe infection. Instead, ACEI/ARB exposure was associated with a lower risk of death compared with non-ACEI/ARB antihypertensive drugs [8]. As for the use of diuretic drugs, based on the information we have, there is no documentation regarding the impact of diuretics on the prognosis of COVID-19, especially in terms of mortality or severity. Giving diuretics to individuals with COVID-19 can provide positive and negative results [9]. Additionally, a meta-regression analysis incorporating random effects revealed that the correlation between calcium channel blocker (CCB) use and reduced mortality among individuals with hypertension showed a lack of statistical significance, as well as remaining unaffected by age [10]. Whereas, Beta-adrenergic blockers emerge as potential drug candidates for COVID-19 patients. Firstly, their mechanism can reduce the penetration of the SARS-CoV-2 virus into cells. Additionally, these blockers may lower the risk of complications such as ARDS, septic shock, and respiratory failure in severe cases [11]. Therefore, the objective of this article is to comparison between the use of five antihypertensive drugs on the clinical outcomes of COVID-19 patients.

2. Pathophysiology of hypertension

Mechanism of hypertension is through the formation of Angiotensin II from Angiotensin I by ACE. ACE plays an important physiological role in regulating blood pressure. Blood contains angiotensinogen which is produced in the liver. Furthermore, the hormone renin, produced by the kidneys, converts angiotensinogen into angiotensin I. Subsequently, ACE found in the lungs converts angiotensin I into angiotensin II. Angiotensin II has a key role in raising blood pressure through two main actions. The first action is to increase the secretion of antidiuretic hormone (ADH) and thirst. ADH is produced in the hypothalamus (pituitary gland) and acts on the kidneys to regulate urine osmolality and volume. With increasing ADH, minimal urine is excreted outside the body (antidiuresis), so it becomes concentrated and has a high osmolality. To dilute it, the volume of extracellular fluid will be increased by withdrawing fluid from the intracellular part. As a result, blood volume increases which will ultimately increase blood pressure. The second action is to stimulate the secretion of aldosterone from the adrenal cortex. Aldosterone is a steroid hormone that has an important role in the kidneys. The role of aldosterone in regulating extracellular fluid volume involves reducing the excretion of NaCl (salt). Aldosterone facilitates the reabsorption of salt from the renal tubules. When the NaCl concentration rises, it will be diluted again by increasing the volume of extracellular fluid

which in turn will increase blood volume and pressure [12].

3. Pathophysiology of COVID-19

3.1. Mechanism of invasion of SARS-CoV-2 into host cells

Coronaviruses belong to a group of single-stranded RNA viruses that infect various mammalian species. Coronaviruses belong to a group of single-stranded RNA viruses that infect various mammalian species. They are divided into four generations based on their genome structure. The life cycle of a virus and its host consists of five steps: attachment, penetration, biosynthesis, maturation, and release. Once viruses bind to host receptors, they enter the cell via endocytosis or membrane fusion (penetration). When the viral content successfully enters, the viral RNA enters the nucleus for replication. Coronaviruses consist of four structural proteins; spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The spike protein consists of a transmembrane trimetric glycoprotein that protrudes from the surface, which determines host diversity and tropism. Spike consists of two functional subunits, namely the S1 subunit is responsible for binding to the host cell receptor while the S2 subunit is for the fusion of the virus and cell membrane. The functional receptor for SARS-CoV is ACE-2. This receptor is highly expressed in the lung, heart, ileum, kidney, and bladder. In the lungs, ACE-2 is most expressed in lung epithelial cells [13].

3.2. Host response to SARS-CoV-2

ACE-2 receptor is highly expressed on the apical side of lung epithelial cells in the alveolar space. This is consistent with the fact that initial lung injury in COVID-19 is often seen in the distal airways. Epithelial cells, alveolar macrophages, and dendritic cells are the three main components of innate immunity in the airway. Dendritic cells and macrophages function as innate immune cells to fight viruses until adaptive immunity is involved. Dendritic cells and macrophages can phagocytose apoptotic cells infected by viruses. SARS-CoV can also bind to the dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN) in addition to ACE-2. These antigen-presenting cells migrate to the lymph nodes to present viral antigens to T cells. CD4+ and CD8+ T cells play crucial roles. CD4+ T cells stimulate B cells, promoting the production of virus-specific antibodies, while CD8+ T cells possess the capability to eliminate virus-infected cells. Patients with severe disease are reported to have increased plasma concentrations of proinflammatory cytokines, including interleukins (IL-6, IL-10), granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumor necrosis factor. The more severe the inflammation, the higher the IL-6 levels [13].

4. Relationship between antihypertensive therapy in COVID-19 patients

4.1. Beta-blocker

Beta-blockers have the potential to reduce SARS-CoV-2 entry receptors by downregulating ACE-2. Therefore, Beta-blockers can reduce mortality rates by reducing the severity of disease in respiratory failure, ARDS and septic shock conditions. The mechanism of action of beta-blockers is to inhibit sympathetic

activation so that it can reduce renin released by juxtaglomerular cells in the kidney. This reduction in renin release can reduce activity in both arms and can reduce ACE-2 receptors. In addition, it can also reduce angiotensin II levels because of this mechanism. Therefore, beta-blockers have two useful mechanisms in reducing mortality rates in ARDS, septic shock, and respiratory failure [11].

Beta-blockers exhibit potential protective mechanisms, notably in reducing interleukin-6 (IL-6), pro-inflammatory cytokines, and hypercoagulable states [14]. This mechanism suggests that beta-blockers may contribute to managing immune system effects associated with resistance to SARS-CoV-2, specifically addressing cytokine storm (CS) and sympathetic storm (SS). Notably, beta-blockers such as propranolol, metoprolol, and labetalol have shown effectiveness in managing SS by mitigating autonomic and sympathetic dysregulation, as reported in patients with thalamic injury [15]. In this context, the anti-inflammatory and regulatory effects of beta-blockers may offer a systematic approach to modulating immune responses and addressing related complications in the context of SARS-CoV-2 resistance.

4.2. RAAS inhibitor (ACEI and ARB)

The use of antihypertensive drugs such as Angiotensin Converting Enzyme (ACEI) and Angiotensin Receptor Blocker (ARB) comes with pros and cons. This is attributed to the fact that ACEI and ARB can increase the regulation of ACE-2, which is the receptor utilized by SARS-CoV-2 to infect host cells. Therefore, it is said that there is a possibility that antihypertensive treatment using this group could potentially increase the risk of SARS-CoV-2 infection. However, on the other hand, cardiopulmonary disease is associated with decreased ACE-2 activity. By limiting the effects of angiotensin II on the heart and blood vessels, ACE-2 may protect against more severe complications of COVID-19 infection. Experimentally increased ACE-2 expression may provide potential pulmonary and cardiovascular protective effects [16]. The mechanism of action of ACE-2 is by reducing the RAAS and acting as a deactivator of angiotensin II which is an active peptide that can cause vasoconstriction, pro-fibrosis, pro-inflammatory action, stimulate aldosterone secretion by binding to the AT1 receptor and converting it to angiotensin 1-7. It is an active peptide that has properties opposite to Angiotensin II, can induce vasodilation and exhibits anti-fibrosis and anti-inflammatory properties [17].

ACEI has a target action on ACE-1 with the mechanism of preventing the conversion of angiotensin I to angiotensin II, while ARB works on angiotensin II which is converted from angiotensin I by ACE-1. ACE-1 is homologous to ACE-2, the target receptor of both SARS-CoV-2 and SARS-CoV, playing a crucial role in host infection. ACE-2 is a receptor that is widely expressed on vascular and lung endothelium, especially on type 2 alveolar endothelium and epithelial cells. SARS-CoV and SARS-CoV-2 will bind ACE-2 and then activate Transmembrane Serine Protease-2 (TMPRSS2), which is generally found in the lungs. ACE-1 and ACE-2 will each break down the angiotensin peptide. ACE-1 breaks down the histidine and leucine dipeptides from Angiotensin I which then converts them into Angiotensin II and can cause vasoconstriction, bronchoconstriction, increased vascular permeability, inflammation and fibrosis as well as the risk of ARDS via the Angiotensin II type 1 receptor (AT1R) [18].

4.3. Calcium channel blocker (CCB)

An *in vitro* study found that all Calcium Channel Blocker (CCB) agents could inhibit SARS-CoV-2 replication, among which benidipine HCl, amlodipine besylate, cilnidipine, and nicardipine HCl showed more significant inhibitory effects. CCBs inhibit SARS-CoV-2 in a dose-dependent manner without causing strong cytotoxic effects. Analysis of its mode of action reveals that it can block the entry of intracellular calcium. When intracellular calcium levels are blocked, the inflammatory response is also reduced. Furthermore, this

mechanism can impair the calcium-dependent cellular pathway of viral entry, consequently inhibiting viral replication. The effect of CCB which can inhibit virus replication can reduce the severity and mortality rate in COVID-19 patients [19].

4.4. Diuretic

Based on research related to the effect of antihypertensive drugs, one of the effects of thiazide use in elderly COVID-19 patients before being hospitalized is associated with an increase in clinical indices related to infection and inflammation, including CRP, lymphocyte count, and procalcitonin. These clinical indices improved significantly towards normal levels in the elderly, except for blood clot biomarkers [20]. An observational study discussing the relationship of antihypertensive therapy to the risk of severity of COVID-19 in hospitalized patients with comorbidities also showed that the use of antihypertensive therapy did not increase the severity of COVID-19. It is said that thiazides can reduce the expression of the ACE-2 receptor, which means they can potentially reduce the entry of SARS-CoV-2 [21]. However, research regarding the effect of thiazides on improving outcomes from COVID-19 has not yet been proven because only a few samples of the use of thiazide therapy are available.

5. Conclusion

In conclusion, beta-blocker have the potential to reduce SARS-CoV-2 entry receptors by downregulating ACE-2 and have protective mechanisms including the reduction anti-inflammatory cytokine. Meanwhile, the using RAAS inhibitors, there are pros and cons regarding this. There is a potential possibility of increasing the risk of SARS-CoV-2 infection because can increase the regulation of ACE-2. However, ACE-2 may protect against more severe complications of COVID-19 infection by limiting the effects of angiotensin II on the heart and blood vessels. As for CCB could inhibit SARS-CoV-2 replication. Whereas diuretic has not yet been proven because only a few samples of the use of thiazide therapy are available.

This study only relied on a review of several studies that may not be represent the entire study. Therefore, further validation is necessary to determine the effect of each antihypertensive agent on the outcome of COVID-19 patients.

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