



COMPARISON OF THE EFFECTIVENESS OF DUAL ANTIPLATELET AND MONO ANTIPLATELET AS NON-EMBOLIC ISCHEMIC STROKE THERAPY

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KEYWORDS	ABSTRACT
ischemic stroke, dual antiplatelet, mono antiplatelet.	Stroke is a clinical syndrome of acute, focal neurological deficits associated with vascular injury of the central nervous system. Stroke is not a single disease but can be caused by various risk factors, processes, and disease mechanisms. Ischemic stroke is the most common stroke, about 80-90% of all strokes. Based on the 2018 Basic Health Research (Riskesmas) states that the prevalence of stroke that occurs in Indonesia is 10.9%, with the highest prevalence in the Riau Islands (12.9%) and the lowest in Papua (4.1%). This literature is written to compare the effectiveness of mono and dual antiplatelets as a non-embolic ischemic stroke therapy. The method in this study was a literature review that was searched using Pubmed, Google Scholar, Medline, Ebsco, Hindawi, Science Direct, and Cochrane, published in the last ten years. After obtaining the appropriate literature, the manuscript is written. Based on the results of the study, dual antiplatelet administration was more effective in preventing recurrent ischemic stroke and cardiovascular events in ischemic stroke patients when compared to mono antiplatelet. The recommended dual antiplatelet drugs are Clopidogrel and Aspirin. Based on the literature search, it can be concluded that dual antiplatelet administration is more effective in preventing recurrent ischemic stroke in stroke patients. However, some literature states that dual antiplatelet administration must still consider the potential increased risk of bleeding.

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INTRODUCTION

Stroke is an acute clinical syndrome, a focal neurological deficit associated with vascular injury (infarction, hemorrhage) of the central nervous system. Stroke is not a single disease but can be caused by various risk factors, disease processes, and mechanisms (Murphy & Werring, 2020). Ischemic stroke is the most common type of stroke, which is around 80-90% of all strokes (Johns Hopkins University, 2023). According to the World Health Organization (WHO), revealed that cerebrovascular events are the second cause of mortality and the third cause of morbidity where the brain is in a condition of lack of blood flow which results in cell death so that brain cells experience hypoxia which causes neurological deficits (Albay et al., 2020).

From 1990 to 2019, the burden (in terms of an absolute number of cases) increased substantially (70% increase in stroke incidence, 43.0% stroke-related deaths, 102.0% stroke prevalence, and 143.0% DALYs), with most of the global stroke burden (86.0% deaths and 89.0% DALYs) are in low and lower-middle-income countries (World Stroke Organization, 2022). The incidence of stroke in Asia is 116 to 483/100,000 per year (Suwanwela et al., 2016). Based on the 2018 Basic Health Research (Riskesmas), the prevalence of stroke that occurs in Indonesia is 10.9%, with the highest prevalence in Riau Islands (12.9%) and the lowest in Papua (4.1%) (Ministry of Health of the Republic of Indonesia, 2018).

Antiplatelet therapy is the mainstay for primary stroke prevention in patients with risk factors and for prevention of recurrent stroke after a Transient Ischemic Attack (TIA) or ischemic stroke. Two trials demonstrated a reduced risk of recurrent ischemic stroke with Aspirin and Clopidogrel in combination versus Aspirin monotherapy lasting 21 or 90 days (Grotta, 2018). Aspirin is an inhibitor of cyclooxygenase-1 (COX-1) and a modifier of the enzymatic activity of cyclooxygenase-2 (COX-2). Unlike other NSAIDs, which bind reversibly, aspirin binds to this enzyme irreversibly. Aspirin also blocks thromboxane A2 on platelets in an irreversible way, preventing platelet aggregation (Arif & Aggarwal, 2022). Clopidogrel is an irreversible inhibitor of the platelet adenosine diphosphate P2Y12 receptor. Inhibition of this receptor prevents downstream activation of the glycoprotein IIb/IIIa receptor complex, leading to reduced platelet aggregation. Clopidogrel is an inactive prodrug that requires enzymatic activation via various CYP enzymes, including CYP2C19 and CYP3A4, via a two-step bioactivation process (Beavers & Naqvi, 2022). Previous research stated that dual antiplatelets (Clopidogrel and Aspirin) were safer and more effective in reducing stroke recurrence and various vascular events in ischemic stroke patients when compared to mono antiplatelets (Ye et al., 2019).

The 2018 American Heart Association/ASA Guidelines for Management of Acute Ischemic Stroke recommend using dual antiplatelets in mild acute ischemic stroke and is known to have a variety of working mechanisms that can prevent stroke more effectively compared to mono antiplatelet. (Powers et al., 2018). To the best of our knowledge, there have been no studies in Indonesia that specifically discuss the effectiveness and safety of each researched antiplatelet agent. Therefore, it is expected that this literature review can summarize the findings from studies on mono and dual antiplatelet therapy. Based on the background description above, this study aims to compare the effectiveness of mono and dual antiplatelet as therapy for non-embolic ischemic stroke. The benefit of this research is that it can help update treatment guidelines for non-embolic ischemic stroke. Also, the results of this study can encourage further research in terms of developing new therapies for non-embolic ischemic stroke.

METHODS

The method used in this study is a traditional review. Evaluation of studies regarding dual and mono antiplatelet comparisons in the treatment of non-embolic ischemic stroke was searched through several literature sources, namely Pubmed, Google Scholar, Medline, Ebsco, Hindawi, Science Direct, and Cochrane. The literature search used the keywords ischemic stroke, dual antiplatelet, and mono antiplatelet, published within the last ten years. After finding a variety of appropriate literature, literature writing begins. The literature will be compiled according to a predetermined format, starting from the definition, epidemiology, mechanisms, risk factors, pathophysiology of ischemic stroke, and treatment of non-embolic ischemic stroke.

RESULTS AND DISCUSSION

Non-embolic Ischemic Stroke

Stroke is an acute clinical syndrome, a focal neurological deficit associated with vascular injury (infarction, hemorrhage) of the central nervous system. Stroke is not a single disease but can be caused by various risk factors, disease processes, and mechanisms (Murphy & Werring, 2020). A case-control study states that risk factors for ischemic stroke are divided into modifiable and non-modifiable factors. Modifiable risk factors are hypertension, diabetes mellitus, smoking, regular physical activity, excessive alcohol consumption, heart disease, stress, and psychosocial depression. Risk factors that cannot be modified include age, sex, race/ethnicity, and genetics (Boehme et al., 2017).

Disability-Adjusted Life-Years Lost (DALYs) states that stroke remains the number two cause of death and the third combined cause of death and disability in the world. The estimated global cost of stroke is over US\$721 billion. From 1990 to 2019, the burden (in terms of an absolute number of cases) increased substantially (70% increase in stroke incidence, 43.0% stroke death, 102.0% stroke prevalence, and 143.0% DALYs), with most of the global stroke burden (86.0% deaths and 89.0% DALYs) are in low and lower-middle-income countries (World Stroke Organization, 2022). The incidence of ischemic and hemorrhagic stroke has increased over the last decade to 85–94 per 100,000 but is much higher (1151–1216 per 100,000) in persons >75 years of age. In addition, 85% of all stroke deaths occur in low-income countries, accounting for 87% of stroke-related disability-adjusted life years (Murphy & Werring, 2020).

The incidence of stroke in Asia is 116 to 483/100,000 per year (Suwanwela et al., 2016). Based on an epidemiological study conducted by Murphy et al., the lowest stroke rates in Asia are in Japan (706.6/100,000 people) and Singapore (804.2/100,000 people), with lower rates also seen in Bangladesh and Bhutan. The highest rates are in Mongolia (4,409.8/100,000 people) and Indonesia (3,382.2/100,000 people), with high rates also seen in Myanmar, Laos, North Korea, and Cambodia. This is associated with the country's economic status, which significantly impacts health technology advancement (Venketasubramanian et al., 2017). Based on the 2018 Riskesdas, the prevalence of stroke in Indonesia is 10.9%, with the highest prevalence in the Riau Islands (12.9%) and the lowest in Papua (4.1%) (Ministry of Health of the Republic of Indonesia, 2018).

Ischemic stroke is the most common type of stroke (85%), which can be caused by Cerebral Small Vessel Disease (CSVD), cardioembolism, and extensive artery disease (atherosclerosis). The pathophysiology of ischemic stroke begins with inadequate blood supply to focal areas of brain tissue. The central core of the tissue progresses to death within minutes and is referred to as the area of infarction. Tissue in the surrounding area, known as the penumbra, does not die immediately and can recover with early reperfusion. More Adenosine Triphosphate (ATP) is consumed than is produced in the reduced blood flow area, causing decreased energy stores, ionic imbalances, and electrical disturbances. These changes increased Reactive Oxygen Species (ROS) and Nitric Oxide (NO). The pathophysiological cascade will lead to cell membrane damage, cell lysis, and cell death by necrosis or apoptosis. Microglia are immediately activated in the ischemic area and extend into the penumbra, peaking 48 to 72 hours later, persisting for several weeks and causing an increase in proinflammatory cytokines, including ROS, NO, interleukin-1 β , tumor necrosis factor-alpha, anti-inflammatory cytokines, and neurotrophic factor. The culmination of the complex ischemic cascade initiated by acute stroke is the loss of neurons and supporting structures (Kuriakose & Xiao, 2020; Shatri & Senst, 2023).

Mechanism of antiplatelet action

Antiplatelet therapy is the mainstay of therapy for primary stroke prevention in patients with risk factors and for prevention of recurrent stroke after a transient ischemic attack (TIA) or ischemic stroke. Two trials have conclusively demonstrated a reduction in the risk of recurrent ischemic stroke with the combination of aspirin and clopidogrel versus aspirin monotherapy, lasting 21 or 90 days. The 2018 American Heart Association/ASA guidelines for managing acute ischemic stroke provide recommendations IIa for dual antiplatelets in acute minor ischemic stroke (Grotta, 2018).

a. Aspirin

Aspirin, an acetate salicylate (acetylsalicylic acid), is classified among non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is an inhibitor of cyclooxygenase-1 (COX-1) and a modifier of the enzymatic activity of cyclooxygenase-2 (COX-2). Aspirin binds to this enzyme irreversibly, unlike other NSAIDs (ibuprofen/naproxen), which bind reversibly. Aspirin also blocks thromboxane

A2 on platelets in an irreversible way, preventing platelet aggregation (Arif & Aggarwal, 2022; Hackam & Spence, 2019). The mechanism of action of aspirin varies according to the dose. Low doses (usually 75 to 81 mg/day) can irreversibly acetylate serine 530 cyclooxygenase (COX)-1. This effect inhibits the formation of platelets from thromboxane A2, producing an antithrombotic effect. Moderate doses (650 mg to 4 g/day) inhibit COX-1 and COX-2, block prostaglandin (PG) production, and have analgesic and antipyretic effects (Abramson, 2023).

b. Clopidogrel

Clopidogrel is an irreversible inhibitor of the platelet adenosine diphosphate P2Y₁₂ receptor. Inhibition of this receptor prevents downstream activation of the glycoprotein IIb/IIIa receptor complex, leading to reduced platelet aggregation. Clopidogrel is an inactive prodrug that requires enzymatic activation via various CYP enzymes, including CYP2C19 and CYP3A4, via a two-step bioactivation process. Genetic polymorphisms to these enzymes may influence response to therapy. Typically, in normal metabolism, the drug has a bioavailability of 50%, with only 15% of the oral dose being active via esterase hydrolysis with CYP enzymes. Clopidogrel actively inhibits platelets for the lifetime of platelets (7 to 10 days). Platelet function can begin to return as new platelets are cycled, and a complete return of function is often seen within five days (Beavers & Naqvi, 2022).

Comparison of the Effectiveness of Dual and Mono Antiplatelets in the Treatment of Non-Embolic Ischemic Stroke

Ischemic stroke is when the brain loses blood flow, resulting in hypoxia of brain cells, causing cell death. This results in focal neurological deficits in the areas of the brain that are damaged (Albay et al., 2020). The effects of ischemic stroke itself can result in high morbidity and mortality. Most of the effects occur within the initial 48-72 hours after attack onset and on delayed recovery of neurologic function. Patients who experience acute stroke, neurological damage, and recurrent strokes at a later date are joint events with a poor prognosis, so adequate treatment is needed to overcome this. Antiplatelets are standard therapy for non-embolic ischemic stroke events (Hui et al., 2022; Ye et al., 2019).

The 2018 American Heart Association/ASA Guidelines for Management of Acute Ischemic Stroke recommend using dual antiplatelets in mild acute ischemic stroke. Dual antiplatelet is known to have a variety of working mechanisms so that it can prevent stroke more effectively compared to mono antiplatelet. Dual antiplatelets have a synergistic effect by inhibiting different platelet pathways for activation. Dual antiplatelet therapy of any combination drug with aspirin significantly reduces stroke recurrence, cardiovascular complications, and mortality (Powers et al., 2018).

The study by Albay et al. found that dual antiplatelets were more effective in reducing the risk of stroke recurrence and combined cardiovascular events such as acute coronary syndrome and heart-related death compared to monotherapy. The combination of Clopidogrel and Aspirin is a dual antiplatelet that is good for preventing recurrent strokes, cardiovascular events, and preventing death. The combination of Clopidogrel and Aspirin carries the highest risk of bleeding episodes. Another combination, namely Ticagrelor and Aspirin, has proven to be a promising drug in reducing recurrent stroke and other cardiovascular events. However, the drawback is its safety profile regarding significant bleeding events (Albay et al., 2020). The same study conducted by Wang et al. found that compared to mono antiplatelet, dual antiplatelet proved to be more effective in reducing the incidence of stroke recurrence and other vascular events but had a higher risk of causing bleeding. This is suspected to be due to the higher loading dose of Clopidogrel and the longer duration of treatment for dual antiplatelets (Wang et al., 2018).

The study conducted by Trifan et al . found that the treatment of mild and moderate acute non-embolic ischemic stroke patients using dual antiplatelets was proven to reduce the risk of stroke recurrence, composite stroke, and death. The side effect of dual antiplatelet is increasing the risk of severe hemorrhagic complications, which is influenced by the length of treatment and the type of agent used. Short-term (≤ 30 days) treatment with aspirin and clopidogrel combination started within three days of attack onset may reduce the risk of stroke recurrence and death from any cause without increasing the risk of significant bleeding. The combination of Aspirin and Ticagrelor for 30 days or other dual antiplatelets for >30 days after stroke is indeed effective for reducing the risk of stroke recurrence and combined events but significantly increases the risk of significant bleeding (Trifan et al., 2021). A study with similar results was conducted by Lin et al . to compare mono antiplatelet and dual antiplatelet in patients with ischemic stroke with evidence of extensive artery atherosclerosis at 21 days. The pooled results show that compared to mono antiplatelet, dual antiplatelet is significantly more effective in reducing ischemic stroke recurrence without causing an increase in bleeding (Lin et al., 2022).

The study conducted by Brown et al . found that dual antiplatelet is more effective than mono antiplatelet for preventing recurrent ischemic stroke and severe cardiovascular events in mild to severe ischemic stroke patients. The use of dual antiplatelet at the initial onset after a mild ischemic stroke must still consider the potential increased risk of bleeding. The use of dual antiplatelets for long-term secondary prevention is no better than mono antiplatelets, given the risk of significantly increasing major bleeding (Brown et al., 2021). The same study conducted by Yang et al. showed that the combination of Aspirin and Clopidogrel was more effective in treating ischemic stroke than mono antiplatelet. However, the risk of bleeding would be relatively higher in treatment lasting more than one month (Yang et al., 2021).

Another study conducted by Wong et al . states that using dual antiplatelets at the start of treatment is effective in reducing the risk of stroke recurrence and other vascular events when compared with mono antiplatelets (Wong et al., 2013). The same study conducted by Su et al . showed that using dual antiplatelet is more effective in dealing with ischemic stroke events even though it affects a greater risk of bleeding. The choice of dual antiplatelet must still consider the daily side effects in clinical practice (Su et al., 2015).

CONCLUSION

Ischemic stroke is a condition in which the brain loses blood flow, resulting in hypoxia of brain cells, causing cell death which can affect high morbidity and mortality rates so that adequate treatment is needed. Antiplatelet is a drug indicated to treat nonembolic ischemic stroke. Based on the literature review conducted, the recommended dual antiplatelet drugs are Clopidogrel and Aspirin. The use of dual antiplatelets has shown to be more effective in treating non-embolic ischemic strokes compared to mono antiplatelets. However, the risk of bleeding must be taken into consideration.

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