

Conference Paper

Use of Clopidogrel in Ischemic Stroke Patients

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ORCIDFirasti AN Sumadi: <https://orcid.org/0000-0002-5406-9340>**Abstract.**

Stroke is a clinical condition that develops rapidly and is caused by focal (diffused) brain injuries or damage accompanied by symptoms that can occur for 24 hours, and it can lead to death. Clopidogrel is an antiplatelet drug used to prevent stroke by reducing the ability of blood to clot. This study aimed to examine the usage pattern of clopidogrel in ischemic stroke patients at Sidoarjo Public Hospital during the period of January – December 2020. This study was observational and retrospective. The data were analyzed descriptively. Monotherapy of clopidogrel was registered in all patients (100%) with a dosage of 1 x 75 mg delivered orally. The use of clopidogrel with other antiplatelet drugs was 1 x 80 mg ASA delivered orally and 1 x 75 mg clopidogrel given orally for 1 patient.

Corresponding Author: Firasti AN Sumadi; email: firasti@umm.ac.id**Keywords:** clopidogrel, antiplatelet, ischemic stroke

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1. INTRODUCTION

Stroke are clinical signs that develop rapidly due to focal (or global) brain dysfunction, with symptoms lasting 24 hours or more, and can lead to death [1]. Stroke is a disease that affects the arteries leading to and within the brain. When the blood vessels that carry oxygen and nutrients to the brain are blocked due to plaque or ruptured blood vessels. Then the brain can't get the blood (and oxygen) it needs, so the brain and brain cells die, and a stroke occurs [2].

Stroke is the second leading cause of death and the third leading cause of disability. Globally, 70% of stroke cases and 87% of deaths due to stroke occur in low- and middle-income countries [1]. Nationally, the prevalence of stroke in Indonesia in 2018 based on a doctor's diagnosis in the population aged more than 15 years was 10.9%, or an estimated 2,120,362 people. The provinces of East Kalimantan (14.7%) and DI Yogyakarta (14.6%) are the provinces with the highest prevalence of stroke in Indonesia. Meanwhile, Papua (4.1%) and North Maluku (4.6%) have the lowest stroke prevalence compared to other provinces [3].

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Strokes are classified as ischemic stroke and hemorrhagic stroke. Ischemic stroke is a major part of all stroke events with a percentage reaching 87% of cases. An ischemic stroke (infarction or blockage) is a stroke caused by plaque or blood clots. The formation of a thrombus or embolism can cause a blockage to form, resulting in decreased blood flow to the brain. Ischemic stroke consists of thrombotic ischemic stroke and embolic ischemic stroke [4]. A Hemorrhagic (bleeding) stroke is a stroke that occurs due to the rupture of a blood vessel in the brain. A ruptured blood vessel will cause blood to leak out into the brain. This situation will disrupt the process of supplying oxygen and nutrients to the brain. The incidence percentage for this type of stroke is about 13% of cases. A Hemorrhagic stroke consists of intracerebral hemorrhage and subarachnoid hemorrhage [4].

Therapies for Ischemic Stroke that can be given are Thrombolytics, Antiplatelets, Anti-coagulants, Neuroprotectants, Antihypertensives, and Antihyperlipidemias [5]. Based on the results of the CHANCE trial, the American Heart Association recommends that antiplatelet therapy such as clopidogrel and ASA be started within the first 24 hours after symptom onset. One of the therapies for Ischemic Stroke patients is the use of Antiplatelet. Antiplatelet therapy is of paramount importance as antithrombotic therapy for secondary prevention of ischemic stroke and should be used in noncardiembolic strokes. Antiplatelet agents can be used in all patients who have had an acute ischemic stroke and should receive long-term antithrombotic therapy for secondary prevention. Antiplatelets that are often used are ASA, ASA-Dipyridamole, and Clopidogrel [6]. Clopidogrel is an antiplatelet drug that has been widely used. The usual therapeutic dose is 75 mg. Clopidogrel is rapidly absorbed and reaches peak plasma levels after 45 minutes of administration. The advantage of Clopidogrel when compared to ASA is that Clopidogrel has a longer half-life of 2 hours while ASA has a half-life of 30-40 minutes. Meanwhile, when compared with Dipyridamol, Clopidogrel has a higher bioavailability of 85% whereas Dipyridamole has a bioavailability of 37-66% [7].

Clopidogrel is a thienopyridine compound that has an active metabolite that selectively inhibits the binding of adenosine diphosphate to the platelet receptor P2Y₁₂ and adenosine following diphosphate-mediated activation of the glycoprotein (GP) IIb/IIIa complex, thereby inhibiting platelet aggregation [8].

Side effects of Clopidogrel such as abdominal pain, bleeding disorders (including gastrointestinal), diarrhea, and dyspepsia [9].

2. RESEARCH METHODS

This research was conducted at the Inpatient Installation of the Sidoarjo Hospital starting from March 20 to April 6, 2021. This research is a descriptive study with the data collection method carried out retrospectively based on RMK records at the Sidoarjo Hospital for the period January - December 2020. This descriptive study is intended to describe the pattern of clopidogrel use in ischemic stroke patients.

The population of this study was inpatients diagnosed with ischemic stroke who received

Clopidogrel therapy at the Sidoarjo Hospital in the period January-December 2020 and the population was 27 patients. From 27 patients, a sample of 24 Ischemic Stroke patients received Clopidogrel therapy. Samples that met the inclusion criteria were 24 patients.

3. RESULTS

3.1. Patient Demographic Data

In the period January to December 2020, out of a total of 24 patients, the most common age of Ischemic Stroke sufferers was at the age of 61-70 years as many as 13 patients (54%). The distribution of Ischemic Stroke patients by gender is more in men than women. From the results of the study, it was found that the male sex was 15 patients (62%) and the female sex was 9 patients (38%). Classification of Ischemic Stroke is divided into those included in the classification, namely 1 patient thrombotic CVA (4%), 1 patient embolic CVA (4%), and 22 patients (92%).

3.2. Clopidogrel Single Therapeutic Use Pattern

Table 1 shows the pattern of Clopidogrel uses in 24 Ischemic Stroke patients with Clopidogrel therapy at the Inpatient Installation of the Sidoarjo Hospital for the period January to December 2020.

TABLE 1: Clopidogrel Single Use Pattern.

Medicine name	Dose	Number of Patients	Percentage (%)
Clopidogrel	(1x75 mg) <i>po</i>	24	100
Total		24	100

3.3. The Pattern Of Using Clopidogrel switching (switch) with other antiplatelets in ischemic stroke patients

Table 2 shows the pattern of using Clopidogrel as a substitute (Switch) with other antiplatelets from 24 Ischemic Stroke patients with Clopidogrel therapy at the Inpatient Installation of Sidoarjo Hospital for the period January - December 2020

TABLE 2: The pattern of use of Clopidogrel alternation (Switch) with other Antiplatelet.

Initial Therapy	Switch Therapy	Amount	Percentage (%)
ASA (1x80mg) <i>po</i>	Clopidogrel (1x75mg) <i>po</i>	1	100
Total		1	100

3.4. Duration of Use of Clopidogrel

The longest duration of use of clopidogrel was in the range of 4-6 days in as many as 15 patients (63%), followed by a range of >6 days in 5 patients (20%), a range of 1-3 days with 4 patients (17%).

3.5. Drug therapy other than clopidogrel in ischemic stroke patients

Table 3 shows drug therapy other than Clopidogrel from 24 Ischemic Stroke patients with Clopidogrel therapy at the Inpatient Installation of the Sidoarjo Hospital for the period January - December 2020. Neuroprotectant therapy is used to prevent irreversible injury to potentially viable neurons in ischemic areas. One of the actions of neuroprotective agents is aimed at the early prevention of ischemic injury [10]. The most widely used neuroprotectant was Citicoline with a dose of 3x500mg iv in as many as 19 patients (59%).

3.6. Length of Hospital Admission

Length of Hospital Admission (MRS) in Ischemic Stroke patients at Sidoarjo Hospital is divided into two categories, namely patients with MRS 1-10 days as many as 21 patients (87%), and as many as 3 patients (17%) more than 10 days

TABLE 3: Drug therapy other than clopidogrel in ischemic stroke patients.

Class Therapy	Drug Class	Drug Regimen	Dose	Number* Patients	Group Percentage (%)	
Neuro-protectant		Citicoline	(3x250mg) iv	4	63	
			(3x500mg) iv	19		
		Piracetam	(4X3g) iv	8		
		Piracetam	(2X3g) iv	1		
		Total		32		
Antiplatelet		ASA	(1x80mg) po	1	2	
		Total		1		
Antihypertensive	CCB	Amlodipine	(1x5mg) po	2	21	
			(2x5mg) po	1		
			(1x10mg) po	2		
	ARB	Nicardipine	(0.5µg/kg/BW) iv	1		
		Candesartan	(1x8mg) po	3		
		Beta Blockers	Bisoprolol	(1x2.5mg)po		2
			Total			11
Antidyslipidemia	statins	Atorvastatin	(1x20mg) po	6	14	
			(1x80mg) po	1		
		Total		7		
Total				51	100	

Note: * One patient can receive more than one therapy

3.7. Conditions Out of Hospital (KRS)

There are several conditions of patients when they leave the hospital, including patients recovering and patients going home with improved conditions. From the results of RMK data for Ischemic Stroke patients at the Inpatient Installation of RSUD Sidoarjo, 24 samples were obtained, namely 30% KRS with recovered conditions in as many as 7 patients and the remaining 70% in as many as 17 patients with improved conditions. No patient with KRS condition died.

4. DISCUSSION

Age is the main risk factor for stroke that cannot be modified, the risk factor for stroke will increase after the age of 55 years. Approximately three-quarters of stroke incidents occur in people 65 years of age. The increase in the frequency of stroke along with increasing age is related to the aging process, where all organs of the body experience a decline in function, including the blood vessels of the brain. Blood vessels become

inelastic, especially the thickened endothelium, resulting in narrower blood vessel lumens and the impact will be a decrease in cerebral blood flow [11]. Gender is an irreversible risk factor for ischemic stroke. Fekadu et al., 2019 showed men have a higher percentage than women. This can be caused by lifestyles such as smoking and alcohol which are more often consumed by men. Smoking and consuming alcohol too often can increase the risk of ischemic stroke [12].

Thrombotic CVA occurs when blood flows through the arteries, leaving plaques that stick to the inner walls of the arteries. Over time, these plaques can enlarge so that they narrow or clog arteries and stop blood flow to the brain, causing blockages that cause the brain to lack the blood supply. CVA An embolism occurs when a blood clot forms in a part of the body (usually the heart), it can travel through a blood vessel to the brain. When a blood clot is in a blood vessel channel in a small part of the brain, it can cause the blood clot to get stuck in a blood vessel, resulting in a blockage and stopping the flow of blood entering the brain, causing a lack of blood supply [13]. CVA Infarction is a stroke caused by plaque or blood clots. The formation of a thrombus or embolism can cause a blockage to form, resulting in decreased blood flow to the brain. An ischemic stroke consists of thrombotic ischemic stroke and embolic ischemic stroke [4]. CVA Infarction is a stroke caused by plaque or blood clots. The formation of a thrombus or embolism can cause a blockage to form, resulting in decreased blood flow to the brain. An ischemic stroke consists of thrombotic ischemic stroke and embolic ischemic stroke [4]. CVA Infarction is a stroke caused by plaque or blood clots. The formation of a thrombus or embolism can cause a blockage to form, resulting in decreased blood flow to the brain. An ischemic stroke consists of thrombotic ischemic stroke and embolic ischemic stroke [4].

Clopidogrel therapy was only given alone to Ischemic Stroke patients at Sidoarjo Hospital based on medical record data for all patients. The administration of Clopidogrel alone has the benefit of a lower risk of gastrointestinal (GI) bleeding compared to the administration of combination antiplatelet therapy. The results of research conducted by A/L Rajendram et al., 2015 showed that gastrointestinal bleeding was the most common side effect of antiplatelet therapy. Combination therapy may increase the risk of gastrointestinal bleeding in patients [14]. Switching from ASA to clopidogrel because clopidogrel has the same safety profile as ASA in patients at high risk for recurrent ischemic events but noted lower rates of gastrointestinal and intracranial bleeding. A study conducted by Paciaroni et al., 2019 compared the administration of Clopidogrel and ASA alone. The results demonstrated a lower risk of major adverse cardiovascular or cerebrovascular events, recurrent stroke, and bleeding events compared with ASA.

These findings support the clinical benefit of single antiplatelet therapy with clopidogrel versus ASA for secondary prevention in patients with recent ischemic stroke [15].

The duration of the use of a combination or single antiplatelet can be given for 21 days. Time for 21 days is the time that can be used to maximize the effectiveness of therapy in Ischemic Stroke and minimize the risk of bleeding (gastrointestinal) [16]. Antiplatelet therapy as secondary prevention of Ischemic Stroke can be given for up to 33 months. However, if the patient has a high ischemic risk, the patient can be given a combination of antiplatelet therapy. In some patients, this can mean lifelong treatment [17]. The most widely used antihypertensive therapy is the CCB (Calcium Channel Blocker) group, especially Amlodipine. Amlodipine reduces the risk of total cardiovascular events by 10%, and the risk of death by 5% compared to non-CCB antihypertensive therapy. CCB is one of the widely accepted antihypertensive groups and has advantages over other antihypertensive agents for stroke prevention [18].

The most widely used antidyslipidemic therapy in this study was atorvastatin 1x20 mg po in 6 patients (86%). Statin therapy is recommended for all Ischemic Stroke patients, regardless of baseline cholesterol level, to reduce stroke recurrence. Statin therapy has been shown to reduce the risk of stroke by approximately 30% in patients with coronary artery disease and elevated plasma lipids [6]. The length of treatment is highly dependent on changes in the patient's condition. Ischemic stroke patients with complex comorbid diagnoses will undergo longer treatment than uncomplicated stroke patients. The results of research by Göz et al., 2017 aim to determine the factors that affect LOS (*Length of Stay*) in acute stroke patients. The results showed that the average length of hospitalization was 7 days (range: 5-13 days). Patients with infarction, hemorrhage, aphasia, infection, atrial fibrillation, and a history of smoking had a significantly longer LOS. LOS was also longer when patients received physiotherapy. The Presence of infection and level of functional disability are factors for LOS [19].

5. CONCLUSION

1. Clopidogrel was used alone in all patients (100%) at a dose (1x75mg) po.
2. The switch pattern of using Clopidogrel with other antiplatelet drugs, namely ASA (1x80mg) po Clopidogrel (1x75mg) PO in 1 patient.

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