Comparison of effectiveness of aspirin, clopidogrel and cilostazol monotherapy treatment in ischaemic stroke

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Abstract. Stroke is the third most common cause of disability and the second most common cause of death globally. Between 1990 and 2019, its prevalence increased by 70%. The prevalence of stroke increased from 7% in 2013 to 10.9% in 2018 in Indonesia. Because antiplatelet medication does not improve platelet aggregation, ischemic stroke patients have significant death and disability rates. The efficacy of cilostazol, clopidogrel, and aspirin in ischemic stroke patients is compared in this study. 205 patients who satisfied the inclusion criteria from 919 stroke cases at RSUD Margono Soekarjo in 2023 were the subjects of a cross-sectional retrospective design using purposive sampling. The Kruskal-Wallis test and mean difference tests were used to examine the results of the therapy. Outperforming aspirin and cilostazol, clopidogrel (75 mg) were the most widely used medication (38.6%) and produced the best results, considerably enhancing PT (1 s), APTT (0.872 s), and lowering leukocytes (2.956) and platelets (3.035). Significant variations in leukocyte (p=0.045) and platelet (p=0.040) levels were found using statistical tests. When it came to enhancing coagulation markers and lowering inflammation, clopidogrel proved to be a more effective therapy option for ischemic stroke.

1 Introduction

Stroke is a global health problem because it is the leading cause of disability in adults and the second leading cause of death after heart disease [1]. The global prevalence of stroke increased by 70% from 1990 to 2019, with the mortality rate reaching 43% in developing countries [2] [1].

Stroke in Indonesia is the first cause of disability and the third cause of death [3]. The prevalence of stroke continued to increase from 2013 by 7% to 10.9% in 2018 [1]. The most common type of stroke in Indonesia is ischemic stroke at 81.2% [4]. The prevalence of ischemic stroke patients in Central Java increased by 14.9%, especially at Prof. Dr. Margono Soekarjo Purwokerto Hospital in 2023 as many as 919 patients.

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Ischemic stroke occurs due to blockage of the blood vessels of the brain by thrombus and embolism leading to a decrease in platelet aggregation resulting in cerebral artery occlusion [5]. One of the main therapies for ischemic stroke to restore platelet aggregation back to normal is antiplatelets. Antiplatelets work by inhibiting platelet aggregation and preventing the formation of thrombus in the arteries [6]. Increased use of ineffective antiplatelets is considered a major cause of global morbidity and mortality, especially increased intracranial bleeding and gastrointestinal bleeding [7].

Ischaemic strokes have a high risk of recurrent events, with incidence rates reaching 14-15% within the first year after the attack. Aspirin, clopidogrel and cilostazole are the most commonly used antiplatelets for the treatment of thrombus and embolism [5]. Aspirin and clopidogrel have been shown to be effective, but both also carry the risk of side effects such as gastrointestinal bleeding. Cilostazol, on the other hand, may offer an alternative with a better safety profile in some cases [7]. A study showed that the use of cilostazol as monotherapy has better effectiveness than aspirin in preventing recurrent stroke. This study reported that cilostazol can reduce the incidence of recurrent stroke with an odds ratio of 0.66, showing a significant benefit compared to aspirin and other antiplatelet drugs.

A study stated that there was no difference in effectiveness between the three in increasing phrothrombine time (PT) and Activated Partial Thromboplastin Time (APTT) levels to normal [8]. According to several studies conducted previously regarding the effectiveness of these three in reducing platelet aggregation, it has not been found definitively [7], [9]. This study aims to determine the effectiveness of single therapy of aspirin, clopidogrel and cilostazole on prothrombine time (PT), Activated thromboplastine time (APTT), Leukocytes and Platelets.

2 Methods

2.1 Study Design

The research is descriptive quantitative research. The data taken were cross-sectional retrospective then analyzed quantitatively and the data was presented descriptively. Quantitative data (secondary data) was obtained from data on the use of aspilet, clopidogrel and cilostazole for the period January 2023-December 2023 at the Pharmaceutical Installation of Prof. Dr. Margono Soekarjo Hospital. Health Research Ethics Committee of Prof. Dr. Margono Soekarjo Hospital with license number 420/04103.

2.2 Sample and Data Collection

Sampling was carried out by non-probability sampling technique by means of purposive sampling that met the inclution and exclusion criteria. The inclusion criteria include ischemic stroke patients with the age of ≥18 years, have clear and legible medical record data including patient identity, drug use profile, patients undergoing laboratory examinations of PT, APTT, leukocytes and platelets. The exclution criteria include ischaemic stroke patients with a history of comorbidities and receiving combination antiplatelet therapy. The population in this study was 919 patients and the sample obtained was 205 patients.

Data collection was carried out by filling out a research instrument sheet containing patient identity, drug dosage and laboratory therapy results (PT, APTT, leukocytes and platelets). The data were then tested statistically to see the normality of the data, then univariate tests were carried out to see the distribution of age, gender, profile of antiplatelet therapy use and the average score of laboratory therapy results to see differences in

effectiveness. The results of the normality test obtained were found to be not normally distributed so that the *One-Way Annova* test could not be used. Instead, non-parametric *Kruskall-Wallis* test was performed to see the difference between the three therapies.

2.3 Measures

2.3.1 Dependent Variable

Differences in the results of laboratory examinations of PT, APTT, leukocytes and platelets at the Inpatient Installation of Prof. Dr. Margono Soekarjo Hospital

2.3.2 Independent Variable

The use of aspirin, clopidogrel, and cilostazole therapy in acute ischemic stroke patients in the Inpatient Installation of Prof. Dr. Margono Soekarjo Hospital.

2.3.3 Inclution Criteria

Inclusion criteria included ischaemic stroke patients aged ≥18 years who received aspirin 80 mg, clopidogrel 75 mg and cilostazol 100 mg therapy, patients who underwent laboratory examination of PT, APTT, leukocytes and platelets and had clear medical record data.

2.3.4 Exclution Criteria

Ischaemic stroke patients with a history of comorbidities and receiving combination antiplatelet therapy

3 Results and Discussion

3.1 Patient Characteristics

The characteristics of the patients are presented in Table 1. Of the 205 patients, by gender, 123 patients (60%) were male and 82 patients (40%) were female. Based on age characteristics, most of them were experienced in the age range of 46-65 years, namely 130 patients (63.4%), then the age range > 65 years consisted of 60 patients (29.3%), the age range of 26-45 years consisted of 10 patients (4.9%) and the lowest in the age range of 18-25 years as many as 5 patients (2.4%).

Women tend to have a lower risk of stroke because they have the hormone estrogen which can provide neuroprotective effects. Estrogen can inhibit the apoptosis pathway through modulation of the expression of proteins involved in cell death, such as Bcl-2 (the anti-apoptosis) and Bax (the pro-apoptosis). Increased ratio of Bcl-2/Bax, estrogen may reduce nerve cell death [10]. This is in line with a study entitled Sex-Biased Autophagy As A Potential Mechanism Mediating Sex Differences In Isschemic Stroke Outcome explains that women experience neuroprotective effects related to the hormone estrogen which can stimulate neurogenesis as well as increase synaptic plasticity before menopause and tend to have a lower risk of stroke [11].

In contrast to the beneficial effects of estrogen, clinical and preclinical studies have shown that the male hormone testosterone contributes to increased susceptibility to cerebral ischemia associated with increased blood pressure, LDL levels and pro-inflammatory

activation that accelerates the process of atherosclerosis [12]. In addition to being influenced by hormones, unhealthy lifestyle behaviors such as smoking, alcohol consumption, high cholesterol, coronary artery disease, and peripheral artery disease are also risk factors for men's tendency to suffer from ischemic stroke compared to women [13].

Table 1. Characteristics of Ischemic Stroke Patients at Prof. Dr. Margono Soekarjo Hospital

Patient Characteristics	Category	Frequency (f)	Percent (%)
Gender	Man	123	60
	Woman	82	40
Age	18-25	5	2.4
	26-45	10	4.9
	46-65	130	63.4
	>65	60	29.3

The high incidence of stroke in old age is related to degenerative theories that cause changes in the structure and function of blood vessels such as lumen diameter, wall thickness, wall strength and endothelial function underlying atherosclerosis [14]. As we age, blood vessels tend to harden easily and cause the heart to work harder. Blood vessels become inelastic, especially the endothelial part that thickens the intima, resulting in narrowing of the lumen of blood vessels and having an impact on decreased blood flow. Narrowing of blood vessels is one of the causes of hypertension and causes ischemic stroke [15].

3.2 Profile Of Use of Aspirin, Clopidogrel and Cilostazole Monotherapy in Ischemic Stroke Patients

Pattern of use of single therapy of aspirin, clopidogrel and cilostazole given to ischemic stroke patients the number and percentage of ischemic stroke patients in the inpatient unit of Prof. Dr. Margono Soekarjo Hospital in 2023 who received single therapy with aspirin, clopidogrel and cilostazole can be seen in table 2.

In table 2. showed the use of single therapy of Aspirin 80 mg in 64 patients (31.2%), Clopidogrel 75 mg in 79 patients (38.6%) and Cilostazole 100 mg in 62 patients (30.2%) with the same frequency of administration 1 time during 3 days of treatment. The results of this study show that clopidogrel 75 mg is the most widely used single therapeutic option. This is associated with minimal gastrointestinal bleeding effects compared to aspirin. Gastrointestinal bleeding was 0.52% at clopidogrel administration and 0.77% at cilostazole [16].

Antiplatelet It is given with the aim of inhibiting platelet aggregation based on the role of platelets in the development of pathological thrombus in the incidence of endothelial injury [17]. The high use of clopidogrel therapy in ischemic stroke patients is also due to the consideration of minimal side effects compared to aspirin. Aspirin can cause ulceration because it is not ionized and accumulates in the cells of the gastric mucosa and changes the cell permeability due to the acidic atmosphere [18]. In addition, the high amount of single use of clopidogrel was associated with a lower risk of recurrent stroke than acetosal [19].

Table 2. Profile of the Use of Single Therapy of Aspirin, Clopidogrel and Cilostazole in Ischemic Stroke Patients at Prof. Dr. Margono Soekarjo Hospital

Antiplatelet Therapy	Dose (mg)	Frequency (f)	Percent (%)
Aspirin	80	64	31.2
Clopidogrel	75	79	38.6
Cilostazol	100	62	30.2

3.3 Effectiveness of Single Therapy of Aspirin, Clopidogrel and Cilostazole

Table 3 is the results of the comparative effectiveness test between aspirin, clopidogrel and cilostazole seen from the difference in the mean parameters of Prothrombine Time (PT), Active Thromboplastin Time (APTT), leukocytes and platelets. Differential tests were performed to determine the difference between the aspirin, clopidogrel and cilostazole groups. Since the data are not normally distributed, the *One-Way Annova* analysis cannot be used, instead a non-parametric analysis is used *Kruskall-Wallis test.*

Table 3. Comparison of the therapeutic effectiveness of aspirin, clopidogrel and cilostazole

Test Parameters	Average increase difference value (Δ)			p-value
	Aspirin	Clopidogrel	Cilostazol	
PT	0,967	1,00	0,911	0,420
APTT	0,851	0,872	0,798	0,888

Table 3. Showing a comparison of effectiveness between aspirin, clopidogrel and cilostazole in prolonging Prothrombine Time (PT) and Activated Thromboplastine Time (APTT). The results of this study showed the difference in the average increase in the highest Prothrombin Time (PT) value, namely in the administration of clopidogrel therapy, which was for 1 second, while in the lowest therapy, namely in the administration of cilostazole with an average increase difference of 0,911 seconds. The results of the *Kruskall-Wallis* test obtained a value of p=0,420. The highest prothrombin activation time extension was at clopidogrel for 0,872 seconds while the lowest prothrombin activation time extension was at cilostazole for 0,798 seconds. The results of the comparison test with *Kruskall-Wallis* test were obtained p=0,888. This suggests that there was no significant difference between the use of aspirin, clopidogrel and cilostazol monotherapy.

Table 4. Showing a comparison of the effectiveness between aspirin, clopidogrel and cilostazole in reducing lecocyte and platelet levels in ischemic stroke patients at Prof. Dr. Margono Soekarjo Hospital showed the highest decrease, namely in clopidogrel as many as 2.956 cells/mm^3 and the smallest difference was in the administration of aspirin, which was 2.327 cells/mm^3. The test results using *Kruskal-Wallis* analysis produced a value of *p=0,045*. The comparison of the difference in platelet values decreased highest in clopidogrel administration of 3.035 cells/mm^3, while the lowest decrease in cilostazole administration was 2.254 cells/mm^3 with *p=0,040.*

Table 4. Comparison ff the Therapeutic Effectiveness of Aspirin, Clopidogrel and Cilostazole

Test Parameters	Average decrease difference value (Δ)			P value
	Aspirin	Clopidogrel	Cilostazol	
Leukosit	2.327	2.956	2.674	0,045
Platelet	3.023	3.035	2.254	0,040

3.4 Protrombin Time (PT)

This study showed that there was a prolongation of Prothrombine Time (PT) after administration of aspirin, clopidogrel or cilostazol therapy. However, the increase was not significant. The prolongation of PT is related to the mechanism of action of aspirin, clopidogrel and cilostazol. Aspirin has antithrombotic effects related to genetic polymorphisms that can mutate factor XIII [20]. The mechanism of action of clopidogrel in prolonging prothrombin time where clopidogrel activates ADP-induced platelet aggregation mediated by the P2Y12 enzyme to increase platelet cAMP [21].

While the mechanism of action of cilostazol in extending prothrombin time where cilostazol inhibits phosphodiesterase III so that it can extend prothrombin time so as to prevent coagulation in the blood capillary wall [22]. A study using clopidogrel can extend PT before and after therapy. The results of the examination before therapy were 9,46 seconds elongated to 11,38 seconds after clopidogrel therapy [8], [23]. Similar to clopidogrel, the use of aspirin can prolong prothrombin time for 0.07 seconds after therapy [20].

The results of this study are in line with research conducted at Dr Sardjito Hospital Yogyakarta which states that there is no significant difference between the administration of Clopidogrel aspirin and DLBS1033 on changes in PT values with a p-value of 0,709 [24]. This also supports research that has been conducted at the Bekasi Regency Hospital and Dr Wahidin Sudirohusodo Hospital which states that there is no difference between the administration of 75 mg clopidogrel therapy either single or combined with 80 mg aspirin with a value of p=0,396 and p=0,384. The results of the examination before therapy 9,46 seconds, lengthened to 11,38 seconds after clopidogrel therapy [8],[23]. Similar to clopidogrel, the use of aspirin can extend prothrombin time for 0,07 seconds after therapy [20].

Low Prothrombin Time (PT) values indicate high fibrinogen levels. Fibrinogen plays an important role in platelet plug formation and increases blood coagulability. High blood coagulability can increase the risk of thrombus formation and inhibit the haemostasis process [25]. Meanwhile, high prothrombin time (PT) may indicate low fibrinogen levels. Fibrinogen plays an important role in platelet plug formation. Low fibrinogen levels can inhibit thrombus formation and reduce the risk of thrombosis, but can increase bleeding [26].

3.5 Active Thromboplastin Time (APTT)

These results are in accordance with research conducted at Dr Wahidin Sudirohusodo Makassar Hospital related to Comparison of the Effectiveness of the Use of Antiplatelet Drugs Clopidogrel and the Combination of Clopidogrel with Aspilet in Ischaemic Stroke Patients, stating that the use of clopidogrel can extend APTT before and after therapy. The results of the examination before therapy were 21,30 seconds which lengthened to 24,46 seconds after clopidogrel therapy [8]. Similar to clopidogrel, the use of aspirin 80 mg can extend APTT for 1.46 seconds after therapy [20].

Partial Thromboplastin Time Extension (APTT) is associated with the performance of aspirin, clopidogrel and cilostazole. Aspirin is able to prolong the Time of Activated Partial Thromboplastin (APTT) blocking the formation of COX platelets, leading to a decrease in TXA2 synthesis [20]. Clopidogrel activates ADP-induced platelet aggregation mediated by the P2Y12 enzyme against platelet cAMP increase which can prolong thromboplastin activation time [27]. Cilostazole prolongs APTT by inhibiting phosphodiesterase III which is vasodilating and antiplatelet so that it can prolong Activated Partial Thromboplastin Time (APTT) so that it can prevent coagulation of blood capillary walls [28].

A study stated that the use of clopidogrel can prolong APTT before and after therapy. The result of the pre-therapy examination, which was 21,30 seconds, was extended to 24,46

seconds after clopidogrel therapy [8]. Similar to clopidogrel, the use of aspirin 80 mg can prolong APTT for 1,46 seconds after administration of therapy [20].

3.6 Leukocyte

The decrease in leukocyte levels after the administration of therapy is closely related to its activity as an antiplatelet. The decrease in leukocytes administered by cilostazole is related to its activity as a phosphodiesterase III inhibitor with antiplatelet, vasodilator and antiproliferative effects found in smooth muscle cells that inhibit the proliferation and inhibition of leukocyte adhesion on the endothelium so as to provide an anti-inflammatory effect, reducing the effect of cholesterol levels that cause atherosclerosis so that it can reduce the risk of thrombus formation [7].

Clopidogrel has an indirect activity in lowering leukocytes in attacking inflammation. Clopidogrel works by inhibiting the adenosine diphosphate (ADP) pathway at the P2Y12 receptor in platelets, thereby disrupting the activation of the GPIIb/IIIa complex and reducing platelet aggregation [29]. Adenosine essentially induces an anti-inflammatory phenotype characterized by a decreased ability to release metastatic inflammatory mediators [30]. This is in accordance with studies related to the inhibition of P2Y12 by clopidogrel in a mouse model of abdominal sepsis or lipopolysaccharide-induced inflammation (LPS) has been shown to reduce the levels of pro-inflammatory mediators in plasma, especially IL-6, TNFα, CCL4 (MIP-1β) and IL-1β [31].

A National Library of Medicine study states that the mechanism of action of aspirin in lowering leukocyte values at the cellular level by inhibiting the over-expressed proinflammatory COX-2 enzyme in liver cells can lead to thickening of the lumen wall [32]. This suggests that aspirin at levels used in cardiac protection can be anti-inflammatory [30]. This is in accordance with research conducted by Nelson et al which states that clopidogrel can reduce the average (SD) leukocyte count by 7,23 (1.97) x109/L [33]. The decrease in leukocytes on clopidogrel therapy is in accordance with research entitled Retrospective cohort study of the effect of clopidogrel on the incidence and severity of CAP in a large Medicaid database shows that the decrease in leukocytes on clopidogrel therapy is due to activation of platelets expressing cell surface receptors and the release of molecules that can strengthen the immune response [34].

3.7 Platelet

These results are in accordance with a study entitled The effect of clopidogrel on platelet activity in patients with and without type-2 diabetes mellitus: a comparative study states that the use of clopidogrel can reduce platelets in patients with type 2 diabetes mellitus better than the administration of a 100 mg dose of ASA but both have no significant difference with a value of p=0,370 [35].

Platelet decline after administration of aspirin, clopidogrel and cilostazole may be closely related to the response to anti-inflammatory effects. In clopidogrel its active metabolite selectively inhibits ADP binding to the P2Y12 receptor, thereby inhibiting the activation of the GPIIb/IIIa complex and reducing platelet aggregation in the blood, clopidogrel significantly decreases the level of P-selectin expression, especially in patients with relatively high platelet activity [36]. P2Y12 synthesis activity on adenosine diphosphate (ADP) receptors by activating platelet aggregation stimulated by ADP receptors which can attenuate platelet expression and release inflammatory cytokines thereby reducing P-selectin expression in inflammatory reactions [37].

Meanwhile, Cilostazole has activity on phosphodiesterase III inhibitors with antiplatelet, vasodilator and antiproliferative effects found in vascular smooth muscle cells that prevent

platelet attachment to the endothelium so that it provides an anti-inflammatory effect [7]. A study from the American Society Of Hematology states that the decrease in tombocytes by aspirin related to its activity inhibits platelet aggregation through inhibition of A2 platelet synthesis [38].

These results are in accordance with a study entitled The effect of clopidogrel on platelet activity in patients with and without type-2 diabetes mellitus: a comparative study states that the use of clopidogrel can reduce platelets in patients with type 2 diabetes mellitus better than the administration of a 100 mg dose of ASA but both have no significant difference with a value of p=0,37 [35].

This study is a retrospective study so that it has limitations in sampling and is not able to see the patient's condition directly and side effects after the use of therapy cannot be monitored. Further research may be needed regarding the effectiveness and side effects after administration of the therapy.

4 Conclusion and Suggestion

The results showed that the most single therapy used clopidogrel 75 mg as many as 79 patients (38.6%) and the least Cilostazol 62 patients (30.2%). The highest prothrombin time (PT) lengthening measurement was clopidogrel (1 Δ/sec) and the lowest was cilostazol (0.911 Δ/sec) with p=0.420. Thromboplastin activation time (APTT) prolongation was highest with clopidogrel (0.872 Δ/sec) and lowest with cilostazol (0,798 Δ/sec) with p=0,888. The highest decrease in leucocyte and platelet levels was cilostazol (2,956 (Δ)/cells/mm3 and 3,035 (Δ)/cells/mm3), significant differences between the three therapies with p=0,045 and p=0,040. Thrombosis and embolism in ischaemic stroke are better using clopidogrel monotherapy. In addition, clopidogrel has minimal side effects of GI and intracranial bleeding compared to other antiplatelets. This allows clopidogrel to be used as a therapeutic option for the long-term treatment of ischaemic stroke patients with embolism or thrombosis as well as the success of therapy.

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