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Impact of Cyp2c19 Allele 17 Mutase on Clopidogrel Hyper-Responsiveness in Indonesian Patients with Ischemic Stroke

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Abstract

BACKGROUND: Ischemic stroke dominated up to 76% of the 101.5 million stroke cases globally. One of the treatments for stroke is secondary prevention by administering antiplatelet. Clopidogrel is an add-on antiplatelet to the dual antiplatelet therapy (DAPT) regimen. In its metabolism, clopidogrel can show the nature of resistance and bleeding risk. Studies on resistance have been widely put forward but not with the bleeding. The study of the bleeding risk to Asian races focused only on East Asian races.

AIM: The objective of the study is to determine the bleeding risk in the Indonesian population and the correlation with the polymorphism of CYP2C19 allele 17.

METHODS: There were 112 participants in this study. About 45.5% showed a normal response to clopidogrel, but 40.2% had a bleeding risk. All participants (100.0%) had mutations in CYP2C19 allele 17, with 47.3% being intermediate metabolizers.

RESULTS: The bleeding risk was significantly correlated with clopidogrel (p: 0.02). The Indonesian population has a high bleeding risk from the clopidogrel administration.

CONCLUSION: Compared to DAPT administration, clopidogrel can be a monotherapy for secondary stroke prevention.

Introduction

In 2019, the American Heart Association and American Stroke Association (AHA/ASA) stated that the prevalence of stroke reached 101.5 million people globally, 76% of whom were ischemic strokes. Mortality and morbidity reached 6.6 million people and were the highest cause (13.9%) of disability compared to other diseases [1], [2].

Based on the recommendations of AHA/ASA 2021, stroke management included secondary prevention was by administering anti-platelet drugs, one of which was clopidogrel [3]. Clopidogrel administration was widely used for its effectiveness and better safety than other anti-platelets. The administration of clopidogrel had a high on-treatment platelet reactivity (HTPR) issue, 16.83–50%, and bleeding risk, 8.8% [4], [5]. Several studies had shown that the genetic mutation CYP2C19 was responsible for HTPR (alleles *2 and *3) and the bleeding risk (allele *17) [6], [7]. Clopidogrel was not used as a first drug choice (alternative) for secondary prevention but as an add-on to dual antiplatelet therapy (DAPT), given during the first 21–90 dayd [8], [9]. Another study, the trial study CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) showed that clopidogrel could be a secondary prevention monotherapy [10].

The widely stated data were resistance-related and rarely discussed the safety of drug use based on bleeding risk. Various studies had shown an increased bleeding risk, especially for East Asian races, but studies on South-east Asian races, especially Indonesians, were still challenging to find [11], [12]. For this reason, the researchers examined the bleeding risk of clopidogrel administration in the Indonesian population correlated with the genetic mutation CYP2C19 allele *17.

Materials and Methods

A cross-sectional study was conducted at the University of Indonesia Hospital (RSUI) and Cipto Mangunkusumo Hospital (RSCM) in Indonesia. Inclusion criteria were ischemic stroke patients in 2020–2021, either primary or recurrent, who had clopidogrel administration. At this stage, there were 128 participants. The researchers excluded those who missed the follow-up or did not complete examinations; thus, 112 participants. The bleeding risk in this study using the *VerifyNow* level had a P2Y12 Reaction Unit (PRU) value. *VerifyNow* (VN) results classified bleeding risk as PRU <95. The CYP2C19 polymorphism was evaluated using a TaqMan hydrolysis probe, followed by a sequence detection system software analysis.

Data were analyzed by evaluating the correlation between the risk factors and the bleeding risk. The study employed descriptive statistics. The researchers calculated the direct effect using chi-square. The researchers employed SPSS 26 for the statistical examination and considered a significant result if the p-value <0.05.

Ethics statement

The Ethics Committee approved this research of the Faculty of Medicine, University of Indonesia – Cipto Mangunkusumo Hospital, approval number KET-658/UN2/F1/ETIK/PPM.00.02/2020. This research also followed Declaration of Helsinki guidelines. All participants give their informed consent through written informed consent form.

Results

Table 1 showed the study participants' clinical data, laboratory, and radiological examination results.

Table 2 showed the results of the examination of the bleeding risk of clopidogrel administration using VerifyNow. In this study, 45 participants (40.2%) had bleeding risk.

This study conducted a CYP2C19 examination of *17 alleles based on genotypes which then determined the phenotype (Table 3). The study showed that all participants had mutations (100.0%) and were dominated by intermediate metabolizer.

The correlation between bleeding risk and various prognostic variables is shown in Table 4. A significant correlation was obtained in hemoglobin (Hb) values.

Table 1: The characteristics of the research participants

	n (%)	Mean (±SD)/Median (min-max)
Gender		
Male	66 (58.9)	-
Female	46 (41.1)	
Age (years old)		57.1 (±10.6)/57.5 (25–80)
>57	57 (50.9)	
≤57	55 (49.1)	
BMI (kg/m^2)		24.9 (±4.7)/24.3 (15.6–45.8)
>25	48 (42.9)	
≤25	64 (57.1)	
Hemoglobin (g/dL)		13.8 (±1.6)/13.9 (7.9–18.4)
≤13.9	57 (50.9)	
>13.9	55 (49.1)	
HbA1c (%)		6.5 (±2.3)/5.7 (4.0–15.0)
≥6.5	37 (33.0)	
<6.5	75 (67.0)	
HDL (mg/dL)		52.2 (±14.9)/52.2 (22–102)
≥60	32 (28.6)	
<60	80 (71.4)	
LDL (mg/dL)		127.0 (±40.6)/125 (38–269)
≥100	86 (76.8)	
<100	26 (23.2)	
USG fatty liver		
Yes	60 (53.6)	-
No	52 (46.4)	

Hb: Hemoglobin; BMI: Body mass index; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; USG: Ultrasonography

Table 2: The clopidogrel resistance results

VerifyNow	n (%)	Mean (±SD)/Median (min-max)
Total participants		115.2 (±71.3)/105.5 (1–273)
Bleeding risk (<95 PRU)	45 (40.2)	49.2 (±31.2)/56.0 (1.0–93.0)
Normal (95–208 PRU)	51 (45.5)	132.9 (±27.4)/134.0 (97.0–195.0)
No response (>208 PRU)	16 (14.3)	244.5 (±18.8)/241.5 (216.0–273.0)

Table 3: The genetic variation of the research participants

Phenotype	Genotypes	
	Wildtype	Mutation
	n = 0 (%)	n = 112
Rapid metabolizer	0 (0.0)	19 (17.0)
Intermediate metabolizer	0 (0.0)	53 (47.3)
Poor metabolizer	0 (0.0)	40 (35.7)

Table 4: Correlation between prognostic variables to bleeding risk

	Bleeding (%)	Non-bleeding (%)	p	OR (95% CI)
Gender				
Man	16 (34.8)	30 (65.2)	0.33†	0.68 (0.31–1.48)
Woman	29 (43.9)	37 (56.1)		
Age (years old)				
>57	20 (35.1)	37 (64.9)	0.263†	0.65 (0.30–1.39)
≤57	25 (45.5)	30 (54.5)		
BMI (kg/m^2)				
<25	20 (41.7)	28 (58.3)	0.78†	1.11 (0.52–2.39)
≤25	25 (39.1)	39 (60.9)		
Hemoglobin (g/dL)				
<13.9	17 (29.8)	40 (70.2)	0.02†‡	0.41 (0.19–0.89)
≥13.9	28 (50.9)	27 (49.1)		
HbA1c (%)				
≥6.5	15 (40.5)	22 (59.5)	0.96†	1.02 (0.4 6–2.28)
<6.5	30 (40.0)	45 (60.0)		
HDL (mg/dL)				
≥60	13 (40.6)	19 (59.4)	0.95†	1.03 (0.45–2.37)
<60	32 (40.0)	48 (60.0)		
LDL (mg/dL)				
≥100	32 (37.2)	54 (62.8)	0.24†	0.59 (0.25–1.44)
<100	13 (50.0)	13 (50.0)		
USG fatty liver				
Yes	26 (43.3)	34 (56.7)	0.46†	1.38 (0.62–2.84)
Not	19 (36.5)	33 (63.5)		
CYP2C19*17 genotype				
Wildtype	0 (0.0)	0 (0.0)	-	-
Mutation	45 (40.2)	67 (59.8)		
CYP2C19*17 phenotype				
Rapid Metabolizer	9 (47.4)	10 (52.6)	0.44†	1.65 (−)
Intermediate Metabolizer	18 (34.0)	35 (66.0)		
Poor Metabolizer	18 (45.0)	22 (55.0)		

Hb: Hemoglobin, BMI: Body mass index, HbA1c: Hemoglobin A1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein, USG: ultrasonography. †Chi-square, ‡p < 0.05.

Discussion

This study showed that ischemic stroke was dominated by men, with 58.9%. Similar findings were established by Virani *et al*. and Chang *et al*. that the incidence of ischemic stroke was higher in males and increased with age [13], [14].

This study's BMI, ≤25 kg/m^2, dominated up to 57.1%. Whitlock *et al*., Shiozawa *et al*., and Mitchell *et al*. obtained different result that the incidence of ischemic stroke increased in BMI >28 kg/m^2 [15], [16], [17]. The contradiction was due to the difference in BMI in Indonesia, ranging from 23 to 4 kg/m^2 [18].

In this study, participants with Hb levels ≤13.9 g/dL reached 50.9%,it was not significantly different from studies by Panwar *et al*. and Furlan *et al*., with 46.6% and 40.6%, respectively [19], [20]. Anemia might increase the bleeding risk with Hb <13 g/dL in men and Hb <12 g/dL in women [21].

CYP2C19 was one of the platelet receptors that play a significant role in clopidogrel active metabolism. CYP3C19 had several alleles, such as *2, *3, and *17. Mutations that occurred in alleles *2 and *3 were referred to as Loss-Of-Function (LOF) conditions that significantly caused Major Adverse Coronary Events (MACE) (HR: 2.3, p: 0.013) and ischemic risk (p: 0.013) [6], [7].

HbA1C levels, <6.5%, reached 67.0% in this study. This study found no significant correlation between HbA1C levels and bleeding risk. There were different results from the study of Nguyen *et al*. [22]. Studies conducted by Lemesle *et al*. showed that diabetic conditions significantly correlate to the risk of recitation [23].

The condition of dyslipidemia in this study was shown with LDL levels of ≥100 mg/dL in 76.8% of participants. Pol *et al*. showed a significant correlation between bleeding risk and lipoproteins from HDL, namely, polypoprotein A1 (ApoA1), and lipoproteins from LDL, namely, apolipoprotein B (ApoB) [24].

Radiological examination in this study was in the form of an ultrasound examination to diagnose the occurrence of fatty liver. This study found that 53.6% of patients had fatty liver conditions. These results were not different from the study of Xu *et al*., which found that 68.9% of the participants had the same condition and had an increased risk of stroke by 16% [25]. Not only the increased risk of stroke but also the condition of the fatty liver can cause an imbalance in the body's hemostasis through an increase in mean platelet volume (MPV). The increase that occurred could cause two conditions in the form of clotting or bleeding [26].

Data related to clopidogrel metabolism were more commonly found against the Caucasian races that tend to be resistant and the African-American with a tendency to have a high bleeding risk [27]. One study showed that the increased mutation of CYP2C19 allele *17 in blacks was more frequent than in whites [27]. Data related to the bleeding risk, especially in the Indonesian population, were scarce; even data in the South-east Asian region were difficult to find.

The Asian region that had numerous studies was the East Asia region. In this population, the bleeding risk due to antiplatelets was found to be relatively high compared to Caucasians, resulting in the emergence of the term East Asian Paradox [28]. The term indicated that antiplatelet management needed to be adjusted therapy. Not only did it have a bleeding risk, but overall outcomes such as repeated strokes to death could occur [28].

This study showed that the number of participants with a bleeding risk reached 40.2%. The number differed from the participants with a normal response (45.5%), while the amount of clopidogrel resistance was minimal (14.3%). The study found that all participants had mutations in the *17 (100.0%) allele. Those results contradicted the majority of studies. One such study by Gurbel *et al*. showed the number of mutations obtained in 21% Caucasian, 17% African-American, and 20% Asian-American races [29].

Based on the clopidogrel management consensus in the East Asian race, the duration of the clopidogrel administration was somewhat different compared to the world consensus. Long-term clopidogrel could last for 12–24 months, but the East Asian race consensus suggested giving it in a short-term manner of 1–12 months [28]. Other data, namely, the CHANCE and POINT studies, provided clopidogrel with 21 days and 90 days, respectively [8], [9]. These studies had shown that the clopidogrel administration needed to be adjusted to Indonesia's population, which can be done by adjusting the duration and dosage.

Although the bleeding risk in Asian races was relatively high in line with genetic results, various studies agreed not to make genetic examinations routine. A genetic examination could be suggested in patients with high-risk profiles such as anemia, old age, chronic kidney disease conditions, acute myocardial infarction (AMI), previous bleeding history, or a complex PCI history [28].

Conclusions

This study found that the responsiveness of clopidogrel in the Indonesian population is excellent. Even therapy administration needs to be focused on the very high bleeding risk. Compared to the administration of DAPT as secondary prevention, monotherapy therapy in the Indonesian population had an equally good possible outcome. In addition, further research related to minimum inhibitory concentration (MIC) to

make adjustments to drug doses.

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