Aspirin and Clopidogrel Resistance in Filipino Patients with Recurrent Noncardioembolic Ischemic Strokes in a Tertiary Hospital: A Cross-Sectional Study

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ABSTRACT

Background

Antiplatelet resistance is one factor that contributes to stroke recurrence among patients with noncardioembolic ischemic strokes.

Objectives

This paper aims to describe the prevalence of aspirin and clopidogrel resistance, along with frequency of statin, NSAID and proton pump inhibitor use among our cohort of stroke patients. Method. This is a single-center cross-sectional review that included all adult patients with recurrent noncardioembolic ischemic stroke admitted in a tertiary hospital between January 2019 and June 2023.

Results

A total of 1,374 patients were admitted for ischemic stroke from January 2019 to June 2023. Among these, 155 (11.28%) were recurrent noncardioembolic ischemic strokes. Prevalence of aspirin and clopidogrel resistance were 25% and 32.7%, respectively. Clinical profiles of those in the resistant group were comparable with those in the nonresistant group. None of the patients taking aspirin had concomitant use of nonsteroidal antiinflammatory drugs. Only 2 of the patients who were resistant to clopidogrel were on proton pump inhibitors. More than half of the patients both in the resistant and the nonresistant groups were on statin. The study had a small sample size and hence it was not enough to establish causal relationship between factors and antiplatelet resistance.

Conclusion

More patients were resistant to clopidogrel than to aspirin. Further studies with a bigger sample size are recommended to explore factors that contribute to antiplatelet resistance in Filipino patients.

INTRODUCTION

Stroke remains to be a leading cause of disability worldwide and one of the top three leading causes of mortality in the Philippines[1,2]. Ischemic strokes comprise 85% of total stroke cases. Guidelines on management of ischemic strokes include secondary prevention using antiplatelets for noncardioembolic ischemic strokes[3]. Despite adequate therapeutic management and lifestyle modification for secondary stroke prevention, recurrence of stroke still occurs. Stroke recurrence is defined as a new ischemic event occurring at least 28 days after an incident event. Stroke recurrence rate ranged from 5.7% to 51.3%, with most

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frequent recurrence seen in large artery atherosclerosis and cardioembolic strokes[4]. In one study by Jamora, et al. (2017), the risk of recurrent stroke was 7.9% for the first year and the risk of recurrent stroke while taking aspirin was 17.8%[5].

Antiplatelet resistance is one factor that contributes to stroke recurrence among patients with acute noncardioembolic ischemic strokes. Aspirin resistance is defined as inhibition of COX-1 of greater than 40U as measured objectively by the aspirin response monitoring test tests given that the patient is compliant to intake of aspirin for at least 5 days[6]. Clopidogrel resistance is defined as measurement of platelet aggregation curve showing high platelet reactivity of equal to or more than 46U, posing high thrombotic risk determined objectively by the clopidogrel response monitoring test by impedance platelet aggregometry, given that the patient is compliant in taking clopidogrel for at least 5 days[7]. Prevalence of aspirin and clopidogrel resistance showed a wide range of 3-65% and 8-56% respectively in previous studies[8,9,10]. Resistance with aspirin combined with clopidogrel also varied from 1.8% to 35% according to the meta-analysis of Lim, et al. (2020)[10].

The purpose of this paper is to report the prevalence of aspirin and clopidogrel resistance among Filipino patients with recurrent noncardioembolic ischemic stroke in a tertiary hospital.

METHODS

Study Design, Site and Participants

This is a single-center cross-sectional review that included all adult patients with recurrent noncardioembolic ischemic stroke between January 2019 and June 2023. The study site is a 600-bed tertiary hospital. The hospital admits 30 to 50 cases of acute ischemic stroke per month.

The medical records were reviewed by the authors and all patients with incomplete clinical data were excluded from this study.

Study Variables

The following information were retrieved from the patients' medical records: age and sex of patient, risk factors including hypertension, atrial fibrillation, diabetes mellitus (DMT2), current smoker or alcohol drinker, hypercholesterolemia, hypertriglyceridemia and glycohemoglobin (hba1c). We recorded the blood thinner the patient is being maintained on- aspirin or clopidogrel monotherapy, dual therapy and anticoagulant and their respective doses. Aspirin and clopidogrel resistance was determined using the Rosche Multiplate Analyzer. The Multiplate Analyzer is a semiautomated device, well standardized, easy and reliable to use, with results available within 10 minutes from the testing process. It correlates well with the gold standard light transmission aggregometry (LTA). We recorded the values and indicated if the patient is resistant or nonresistant to the given antiplatelet. We also recorded if the patient has concomitant use of proton pump inhibitor (PPI), nonsteroidal anti-inflammatory drugs (NSAIDs) and statins.

Data Analysis

We calculated for the frequencies and percentages of each variable. We calculated for the prevalence of the prevalence of aspirin or clopidogrel resistance among those whom response monitoring assays were requested.

Informed consent of the patients included in the database was obtained. The study was approved by the Institutional Ethics Review Committee.

Results

We had a total of 1,374 patients admitted for ischemic stroke from January 2019 to June 2023. Among these, 155 (11.28%) were recurrent noncardioembolic ischemic strokes. Demographics and clinical profile of the patients are seen in Table 1. Mean age was 65 +/- 13 years with a range of 32 to 96 years. There were 87 males (56.13%) and 63 females (40.65%).

Table 1. Demographics and Clinical Profile of patients with recurrent noncardioembolic ischemic strokes.

	n (%)
Recurrent Stroke	155 (11.28%)
Age in years (mean +/- SD)	65 +/- 13 (32-96)
Male	87 (56.13%)
Risk factors	
Hypertension	133 (85.81%)
Diabetes Mellitus	74 (47.74%)
Current Smoker	10 (6.45%)
Alcohol	4 (2.58%)
Hypercholesterolemia	43 (27.74%)
Hypertriglyceridemia	30 (19.35%)
Elevated LDL	56 (36.13%)
Elevated HBA1C	36 (23.23%)
Antiplatelet Therapy	
Aspirin Monotherapy	50 (32.36%)
Clopidogrel monotherapy	47 (30.32%)
Aspirin and Clopidogrel DAPT	4 (2.58%)
Aspirin and Cilostazol DAPT	2 (1.29%)
Clopidogrel and Cilostazol DAPT	6 (3.87%)
Antiplatelet Resistance	
Aspirin resistance (n=36)	9 (25%)
Clopidogrel resistance (n=49)	16 (32.67%)

Among those with recurrent strokes, 133 (85.81%) had hypertension, 74 (47.74%) had DMT2, 4 (2.58%) had atrial fibrillation, 10 (6.45%) were current smokers and 4 were alcoholic beverage drinkers (2.58%). Forty-three (27.74%) of the patients had hypercholesterolemia, 30 (19.35%) had hypertriglyceridemia, 56 (36.13%) had elevated LDL and 36 (23.23%) had uncontrolled DMT2. Fifty (32.26%) of the patients with recurrent noncardioembolic ischemic strokes were maintained on monotherapy with Aspirin 80 mg or 100 mg once daily and 47 (30.32%) were on clopidogrel 75 mg once daily. Four (2.58%) were on dual antiplatelet therapy (DAPT) with Aspirin 80 mg once daily and clopidogrel 75 mg once daily while 2 (1.29%) were on aspirin and cilostazol and 6 (3.87%) were on clopidogrel and cilostazol.

Aspirin response monitoring assays were requested in 36 of the subjects with recurrent stroke on aspirin and among these, 9 (25%) showed to be resistant to aspirin- 8 were on 80mg dosage of aspirin once a day and 1 was on 160 mg dose once a day. For the nonresistant group, 19 were on 80 mg dose while 7 were on 100 mg dose. None of the patients were on nonsteroidal anti-inflammatory drugs.

As for clopidogrel response monitoring assay, 49 subjects were tested- 16

Table 2. Clinical Profile of Aspirin Resistant and Nonresistant.

	Aspirin Resistant	Aspirin Nonresistant
No of patients tested (n=36)	9 (25%)	27 (75%)
Age in years (mean +/- SD)	56.7 +/- 20.1	66.2 +/- 12.7
Male	5 (55.6%)	16 (59%)
Dosage		
80mg/day	8 (88.9%)	19 (70.4%)
100mg/day	0 (0%)	7 (26.0%)
160mg/day	1 (11.1%)	1 (3.7%)
Risk factors		
Hypertension	9 (100%)	25 (92.6%)
Diabetes Mellitus	3 (33.3%)	11 (40.7%)
Current Smoker	2 (22.2%)	3 (11.1%)
Alcohol	1 (11.1%)	2 (7.4%)
Hypercholesterolemia	1 (11.1%)	7 (25.9%)
Hypertriglyceridemia	2 (22.2%)	6 (22.2%)
Elevated LDL	3 (33.3%)	9 (33.3%)
Elevated HbA1C	3 (33.3%)	4 (14.8%)
NSAID* use	0 (0%)	0 (0%)

**Nonsteroidal anti-inflammatory drugs*

Table 3. Clinical Profile of Clopidogrel Resistant and Nonresistant.

	Clopidogrel Resistant	Clopidogrel Nonresistant
No of patients tested (n=49)	16 (32.7%)	33 (67.35%)
Age in years (mean +/- SD)	68.8 +/- 12.9	69.9 +/- 13.3
Male	9 (56.3%)	15 (45.5%)
Risk factors		
Hypertension	13 (81.3%)	32 (97%)
Diabetes Mellitus	10 (62.5%)	19 (57.6%)
Current Smoker	1 (6.3%)	0 (0.0%)
Alcohol	1 (6.3%)	0 (0.0%)
Hypercholesterolemia	5 (31.3%)	6 (18.2%)
Hypertriglyceridemia	4 (25%)	4 (12.1%)
Elevated LDL	7 (43.8%)	9 (27.3%)
ElevateHbA1C	3 (18.8%)	9 (27.3%)
*PPI use	2 (12.5%)	5 (15.2%)
Statin use	9 (56.3%)	25 (75.8%)

**Protein-pump inhibitor*

(32.7%) showed to be resistant. Only two were on proton pump inhibitors (PPIs)-particularly esomeprazole and pantoprazole. More than half (56.3%) and three-fourths (75.8%) were on statins in the resistant and the nonresistant group, respectively (Table 3).

The percentage of recurrent noncardioembolic ischemic strokes in this study was 11.28%. This is comparable with the reported risk of stroke recurrence which ranges from 10% to as high as 40% by 10 years based on previous studies[11-13]. One

important factor for noncardioembolic ischemic stroke recurrence is antiplatelet treatment failure. Data on aspirin and clopidogrel resistance showed a prevalence of 5-65% and 4-30%, respectively, depending on cutoff values and population tested[8-10,14]. Based on the study by Lev, et al. (2006), among patients with coronary artery disease, approximately 20-30% of patients given antiplatelet treatment show high platelet reactivity[15].

Various methods of acquiring aspirin and clopidogrel response assays are available. The one used in the institution is the Rosche Multiplate Analyzer, which is a semiautomated device, well standardized, easy and reliable to use. It correlates well with the gold standard light transmission aggregometry (LTA) and is able to detect the effect of different antiplatelet agents - (i) the cyclooxygenase-1 inhibitor aspirin; (ii) the ADP receptor antagonists clopidogrel, prasugrel, and ticagrelor; and (iii) GPIIb/IIIa inhibitors[16].

Studies on prevalence of aspirin resistance using platelet function analyzer (PFA) among stroke patients showed a prevalence ranging from 0-37%[17-22]. In our study, the prevalence was 25%. This percentage is higher than in Navarro, et al. (2007) which showed 10.4% but is comparable with the study by Gengo, et al. (2006) which showed aspirin resistance rate of 29% among 62 post stroke patients[14,23]. Previous studies have shown that aspirin resistance is more common in women and the elderly[18,24], but this was not seen in our study. Only 4 out of the 9 nonresponders were women and the mean age was 56 years old - which is younger than the majority of the subjects in general.

Aspirin is an antiplatelet that acts by interfering with the biosynthesis of cyclic protanoids, thromboxane A2 (TXA2), prostacyclin and other prostaglandins. Aspirin inhibits the prostaglandin (PG) H-synthase/ COX irreversibly, thereby inhibiting platelet aggregation. Aspirin resistance may be due to various factors including interference by other drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), insufficient suppression of COX-1, over- expression of COX-2 mRNA, erythrocyte induced platelet activation, genetic polymorphism of enzymes like cyclooxygenase 1 and 2 (COX-1 and COX-2) or thromboxane A2 synthase[25]. Furthermore, non-thromboxane-dependent platelet activation or platelet overproduction in situations of inflammation or infection may also contribute to aspirin resistance[26,27]. There are studies that strongly suggest that aspirin resistance is dose-dependent. Aspirin doses of less than 160mg/day were shown to be less effective in preventing stroke than doses of 160mg or more[28,29]. Most of the patients who were resistant to aspirin were on 80 mg dose and 1 was on 160 mg dose. Nineteen of the patients in the nonresistant group were likewise on 80mg dosage of aspirin and seven were on 100 mg dose. A causal relationship between the dosage and resistance could not be established.

As for clopidogrel response monitoring assay, the prevalence of resistance was 32.7% in our study. Although the same technique of determining response to clopidogrel was used- the Multiple Analyzer, this prevalence was higher than the study by Gabriel, et al. (2014) which showed a prevalence of only 15%[30]. Clopidogrel is a prodrug that irreversibly inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor, thereby inhibiting platelet aggregation. Since clopidogrel is a prodrug, it has to be effectively metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The action of clopidogrel on platelets is then expected to be effective throughout the lifespan of the platelets (about 7 to 10 days). CYP450 enzymes may be polymorphic or affected by metabolism of other drugs in some individuals, hence not all individuals will have adequate platelet inhibition with clopidogrel [31]. Resistance to clopidogrel may occur despite compliance to intake of clopidogrel. Just like aspirin, response to clopidogrel may be affected by drug-to-drug interaction. Concomitant use of the proton pump

inhibitors (PPIs), specifically omeprazole, has been shown to significantly increase the odds of clopidogrel resistance by 9.83. We were not able to establish any causal relationship between the use of PPIs and clopidogrel resistance because of the small sample size. Aside from PPIs, statins like atorvastatin, simvastatin and fluvastatin have been shown to suppress the antiplatelet activity of clopidogrel by 90% by competing with clopidogrel for conversion to its active form by CYP3A4[32,33]. However, more than half of the patients both in the resistant and the nonresistant groups were on statin. Other reasons for clopidogrel resistance may be attributable to variable absorption of the prodrug or clearance of the metabolite and the amount of CYP3A4 activity[34].

There are several limitations of this study. One is that this study focused only on the prevalence of aspirin and clopidogrel resistance among patients with recurrent noncardioembolic ischemic strokes, it does not include patients maintained on aspirin or clopidogrel for primary prevention or for cardiovascular indications. Second, determination of association of risk factors that contribute to aspirin and clopidogrel resistance is already beyond the scope of this study. Lastly, given that the sample size of our study is small, the effect of concomitant use of PPIs, NSAIDs and statins on the resistance could not be established.

CONCLUSION AND RECOMMENDATIONS

Prevalence of aspirin and clopidogrel resistance among patients with recurrent noncardioembolic ischemic strokes based on our study are 25% and 32.7%, respectively. More patients were resistant to clopidogrel than to aspirin. None of our patients who were on aspirin had intake of NSAIDs and we also did not find any correlation between the use of statins and PPIs and clopidogrel resistance. Further studies with a bigger sample size are recommended to explore these factors that contribute to antiplatelet resistance in Filipino patients.

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