Original Article
Pak Armed Forces Med J 2018; 68 (6): 1744-48

TRENDS IN PRESCRIBING ANTIPLATELET DRUGS FOR SECONDARY PREVENTION OF NON-CARDIOEMBOLIC ISCHEMIC STROKE

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ABSTRACT

Objective: To determine the trends of physicians and neurologists in prescribing anti-platelet agents for secondary prevention of non-cardio embolic stroke after 3 months of stroke.
Study Design: A descriptive study.
Place and Duration of Study: Combined Military Hospital (CMH) Lahore over a period of four months.
Material and Methods: Patients suffering from old (≥3 months) non-cardio embolic stroke, taking anti-platelet agents for secondary prevention and visiting CMH Lahore neurology clinic. Information about their stroke and treatment was obtained from their previous investigations and medical prescriptions.
Results: A total of 60 patients met the inclusion criteria of the study; 36 (60%) were taking a combination of clopidogrel 75mg plus Aspirin 75 mg and 12 (20%) received Aspirin 75 mg daily while 12 (20%) were getting other regimens.
Conclusion: Combination of clopidogrel 75mg plus Aspirin 75 mg was the most common anti-platelet regimen prescribed for secondary prevention of non-cardio embolic stroke in our study population.

Keywords: Anti-platelet agents, Non-cardio embolic stroke, Secondary prevention of stroke

INTRODUCTION

Stroke is abrupt onset of a neurologic deficit attributedto a focal cerebral vascular cause. It is second leading cause of death in the world[1]. Theannual incidence of stroke in Pakistan is estimatedto be 250/100,000, which means 350,000 new cases per year[2]. A community based survey in a slum of Karachi suggested a 21.8% prevalence of stroke[3]. Ischemic stroke accounts for 80% of strokes and among the ischemic strokes 20-30% result from cardioembolism, 14-40% from atherothrombosis and 15-30% from small penetrating artery disease resulting inlacunar infarcts[4]. Atheroma is the most common arterial disorder and atheromatous plaques most commonly form at the origin of internal carotid arteries, origin of basilar artery and proximal parts of middle, posterior and anterior cerebral arteries[5]. Hemodynamic stresses may cause endothelial trauma and ulceration of atheromatous plaques at these sites. Damaged endothelium activates platelets which release thromboxane A2 and adenosine diphosphate (ADP) which may propagate the process leading to formation of a thrombus. The thrombus may obstruct the arterial lumenor it mayembolize to occlude a distal artery. Such emboli may fragment and vanish or occlude the distal artery leading to infarction in its territory. Primary prevention of stroke is defined as decreasing the risk of stroke by reducing its' modifiable risk factors (table-I)[6]. It is also suggested that an angiotensin-converting enzyme (ACE) inhibitor may decrease risk of stroke regardless of initial hypertensive status[7]. Secondary preventionof stroke is defined as measures to prevent a recurrent stroke after first stroke ortransient ischemic attack (TIA). Recurrence risk after TIA or ischemic stroke ranges from 5 to 20% per year with the highest risk in the first few weeks particularly in patients with carotid stenosis[8]. Secondary prevention depends on control of vascular risk factors, antithrombotic therapy and vascular surgery. Antiplatelet therapy is the mainstay of secondary stroke prevention. Antiplatelet drugs decrease platelet

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Received: 18 Sep 2017; revised received: 16 Jan 2018; accepted: 18 Jan 2018

aggregation and prevent thrombus formation. Aspirin inhibits platelet cyclooxygenase and thromboxane A2 and has been the most widely used antiplatelet agent. Dipyridamole is an inhibitor of phosphodiesterase. It reduces the risk of stroke by the same amount as aspirin. Its' main adverse effects are headache and hypotension induced by peripheral vasodilatation. Ticlopidine and clopidogrel block platelet activation by ADP and are considered to be marginally more effective than aspirin. Clopidogrel is preferred over ticlopidine because the later may produce neutropenia. Newer antiplateletagents such as triflusal and cilostazol are also potentially effective in the secondary prevention of ischemic stroke. Dual antiplatelet therapy (DAPT) is considered to be superior to aspirin alone in secondary stroke prevention but some studies have suggested an increased risk of cerebral hemorrhage with this regimen[9]. When carotid doppler studies and angiography reveal a surgically accessible high-grade stenosis (70-99%) on the side of infarction or TIA, carotid endarterectomy or angioplasty and stenting may reduce risk of ipsilateral carotid stroke. Physicians must try to identify TIAs, atrial fibrillation and carotid artery stenosis and encourage their patients to reduce their risk factors of stroke such as hypertension, diabetes mellitus and smoking. The main purpose of this study was to determine trends of physicians and neurologists in our set up in prescribing antiplatelet agents for secondary prevention of non-cardio embolic stroke after 3 months of stroke.

Table-I: Modifiable Risk factors for stroke.

Hypertension (BP>140 mmHg systolic or 90 mmHg diastolic)
Diabetes mellitus
Cigarette smoking
Dyslipidemia (High total Cholesterol, Low HDL cholesterol(<40mg/dl)
Obesity (Especially abdominal)
Physical inactivity
Asymptomatic Carotid stenosis (>60%)

Table-II: Oral antiplatelet agents and their combinations available in Pakistan.

Aspirin 75 mg (Asp-75)
Aspirin 150 mg (Asp-150)
Aspirin 300 mg (Dispirin)
Clopidogrel 75 mg (Clo-75)
Combination of Clopidogrel 75 mg plus Aspirin 75 mg (CloAsp-75)
Combination of Clopidogrel 75 mg plus Aspirin 150 mg (CloAsp-150)
Ticlopidin (Ticlid 250 mg)
Dipyridamole (Persantin 25mg, 100 mg)
Prasugrel (Eficlot 5mg, 10 mg)

MATERIAL AND METHODS

This descriptive and observational study was conducted at neurology clinic of Combined Military Hospital (CMH) Lahore from 01 Mar 2016 to 30 Jun 2016. Patients suffering from TIAs or ischemic stroke for ≥6 months, taking antiplatelet drugs and presenting consecutively to the Neurology clinic of CMH Lahore were included in this study. Information about their drugs was obtained from their old medical prescriptions. Patients suffering from cardio-embolic stroke and those who were taking anticoagulants were not included in the study. Patients who could not produce their old medical record and prescriptions were also excluded from the study. A detailed history was taken from the patients at their presentation and physical examination was done. Their past medical record was reviewed and the patients were inquired

regarding their compliance of drugs mentioned in their prescriptions. Table-II shows antiplatelet drugs available in Pakistan[10]. The different commercial brands of aspirin (Asp), clopidogrel (Clo) and their combinations (CloAsp) were identified. Data was analyzed using SPSS version 18 and descriptive statistics were used to describe the results.

RESULTS

A total of 60 patients, 36 (60%) males, 24 (40%) females were included in this study. Their ages ranged from 52 to 81 years; mean age 70 years (SD ± 5.98). The duration of their stroke was 6 to 24 months; mean 11 months (SD ± 5.25). Figure shows the frequencies of different antiplatelet drug regimens prescribed to our study population. Combination of clopidogrel 75 mg plus Aspirin 75 mg (CloAsp-75) was the most common antiplatelet regimen taken by the majority of our patients. Dipyradamole and Ticlopidine were not prescribed to any patient in our set up.

DISCUSSION

Ischemic stroke is the most common formof cerebrovascular disease and the patients surviving it are at increased risk of a recurrent stroke which may be more devastating than the first stroke. According to Jamieson *et al* 29% of all strokes in the United States are recurrent strokes thus emphasizing the importance of prevention of a recurrent stroke after a TIA or among survivors of a first ischemic stroke[11]. Early studies indicated that antiplatelet drugs significantly reduce risk of recurrent stroke among patients with a prior TIA or stroke[12]. Antiplatelet therapy now has become one of the main strategies to prevent recurrent at herothromboticis chemic strokes. Low-dose aspirin (75–162 mgdaily), clopidogrel 75 mg daily and aspirin (50 mg) plus dipyridamole (400 mg) daily can be used for long term prevention of TIAs and recurrent ischemic strokes. Low-dose aspirin (75–162 mg daily) is considered as effective as higher daily doses. It has the most extensive evidence regarding its benefits in secondary prevention of stroke. The combination of antiplatelet agents for secondary prevention of ischemic stroke has always remained a matter of debate. A combination of dipyridamole and aspirin may further reduce the risk of stroke than aspirin alone. An earlier meta-analysis by Thijs *et al* showed that a combination of aspirin and dipyridamole was better than either drug alone for secondary prevention of stroke[13]. This observation was corroborated later on by meta-analysis of Malloy *et al* which also showed that aspirin plus dipyridamole was more protective than aspirin alone for preventing recurrent stroke[14]. A combination of clopidogrel and aspirin is considered to be superior to either drug alone for prevention of recurrent stroke but some studies caution about an increased risk of cerebral hemorrhage with this combination.

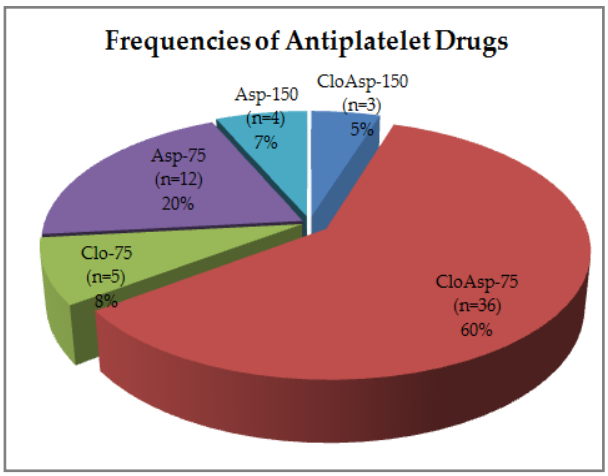

Figure: Frequency of antiplatelet drug regimens prescribed for secondary prevention of ischemic stroke in our study population (n=60).

Wang *et al* have reported that adding clopidogrel to aspirin in a large population of Chinese patients demonstrated a reduction in stroke recurrence during first 90 days after aTIA or minor stroke with no increase in cerebral bleed[15]. Nevertheless, American Heart Association/ American Stroke Association issued guideline for healthcare professionals in 2014 stressing that combination of aspirin and clopidogrel may be considered within 24 hours of a minor ischemic stroke or TIA and be continued for 21 days. This combination increases the risk of hemorrhage relative to either agent alone if continued for 2 to

3 years. Hence, this regimen is not recommended for routine long-term secondary prevention of ischemic stroke[16]. A systematic review and meta-analysis by Gouya *et al* suggested that combination of clopidogrel 75mg and low dose aspirin (75-100mg) compared with aspirin alone decreases risk of recurrent stroke without increasing risk of intracranial hemorrhage[17]. Zhang *et al* analysed eight randomized controlled trials and concluded that compared to monotherapy, short term (≤3 months) combination of aspirin with clopidogrel is more effective for prevention of recurrent stroke without increasing risk of hemorrhage. Long-term (≥1 year) combi-nation therapy does not reduce risk of recurrent stroke and is associated with increased risk of major bleed[18]. A meta-analysis of 14 trials by Elmariah *et al* suggested that compared toshort duration (≤6 months) clopidogrel plus aspirin or aspirin alone, extended duration clopidogrel plus aspirin was not associated with a difference in mortality as compared to aspirin alone[19]. Pan *et al* suggest that a combination of Clopidogrel and aspirin may reduce stroke risk out weighing the potential risk of increased bleeding especially within the first 2 weeks compared with aspirin alone in patients with TIA or minor stroke[20]. The combination of aspirin and clopidogrel may be superior to aspirin alone in prevention of recurrent ischemic stroke. However, it may increase the risk of cerebral bleed in some patients. This regimen should be avoided in patients who are at a high risk of bleeding. Our study was focused on determining the trends of our physicians and neurologists in prescribing antiplatelet agents for secondary prevention of non-cardio embolic stroke after 3 months of stroke. We found that majority of our patients (>60%) were prescribed dual antiplatelet therapy, mainly a combination of Clopidogrel 75 mg plus aspirin 75mg, for long term secondary prevention of stroke. No similar data was found to compare with our study.

CONCLUSION

The most common anti-platelet regimen employed by majority of our physicians for secondary prevention of ischemic stroke is a combination of clopidogrel plus low dose Aspirin. Although this combination may remain controversial, it mayconfer some benefit over aspirin alone. It appears that majority of our physicians consider the benefits of Clopidogrel plus low dose Aspirin out weigh its' potential risks for prevention of recurrent ischemic stroke in majority of their patients.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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