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Prevalence of Aspirin Resistance in Patients with Ischemic Stroke at a Tertiary Care Center in North India

Authors
Singh S Laxmi[1], Atam Virendra[2], Verma Rajesh[3], Kumar Ashutosh[4], Singh Jyotsana[5], Atam Isha[6]
[1]Senior Resident, Department of Medicine King Georges Medical University Lucknow
Email: *neeraj.kgmu@gmail.com*
[2]Professor, Department of Medicine King Georges Medical University Lucknow
Email: *v_atam@yahoo.com*
[3]Professor, Department of Neurology King Georges Medical University Lucknow
Email: *drrajeshverma32@yahoo.com*
[4]Professor Department of Pathology King Georges Medical University Lucknow
Email: *ashutosh45kumar@gmail.com*
[5]MBBS Student, Sarojini Naidu Medical College Agra
Email: *drjoylax2013@gmail.com*
[6]MBBS Student, King Georges Medical University Lucknow
Email: *aquashield95@gmail.com*
Corresponding Author
Dr.Laxmi Shankar Singh
Senior Resident, Department of Medicine King Georges Medical University Lucknow, UP 226003

ABSTRACT
Background: *Ischemic strokes are one of the leading causes of morbidity and mortality now days. Problem increases further if stroke is recurrent. Therefore alongside of acute stroke management, secondary prophylaxis is veryimportant. As for as drugs are concerned aspirin is the most common drug used for the secondary prophylaxis. Despite of these various measures there are recurrences in many patients. Many factors have been held responsiblefor causing such recurrences and aspirin resistance is one of them.*
Aim*: The aim of this study was to assess the prevalence of aspirin resistance in patients with ischemic stroke.*
Material and Method: *This study was conducted in the ischemic stroke patients admitted to the Department of Medicine, King George's Medical University, Lucknow over a period of One year. The study comprised of 76 consecutive patients of ischemic stroke admitted in our wards. All patients with ischemic stroke (acute/recurrent) received standard treatment with non-enteric coated Aspirin 150 mg per day (supervised) at least for 7 days after which study for platelet function to assess aspirin resistance was performed.*
Result: *Prevalence of Aspirin resistance in our study was found to be 23.7% and this was more prevalent among elderly patients.*
Conclusion: *Based on results of this study we concluded that aspirin resistance does exist. However in absence of any standard definition and gold standard tests exact prevalence and its role in stroke recurrence is still a matter of research.*

Introduction

Aspirin reduces the activation of platelets by irreversibly acetylating cyclooxygenase-1, and thereby reduces thromboxane A2 produced by platelets.[1-5]The inhibition of COX-1 is rapid, dose-independent, and permanent for the life of the platelets, because platelets are deficient in the synthetic machinery to transcribe new proteins. Studies suggest that platelet COX-1 activity recovers by about 10% per day because of new platelet formation after a single 325-mg dose of aspirin.[5]Aspirin also has dose-dependent anti-thrombotic effects on platelet function which is not related to its ability to inhibit platelet COX-1.[2]However; these mechanisms are much less important.[1, 2]In contrast, endothelial cells because of their capacity to generate new COX recover shortly after exposure to aspirin. Net effect is such that aspirin acts as an antithrombotic agent. Therefore Aspirin is used during treatment and prevention of ischemic heart disease and ischemic strokes. As per the American Heart Association (AHA) guidelines an initial dose of upto 325 mg aspirin should be given for treatment of most of the ischemic stroke patients within 24 to 48 hours after the onset. Aspirin to be given after 24hours for those who have received intravenous fibrinolysis.[6]similarly, the American College of Chest Physicians (ACCP) guidelines also advocates early (48hour) aspirin treatment at an initial dose of 160 to 325mg for persons with ischemic stroke or TIA[7]. Also both these guidelines recommended low dose aspirin 75-100 mg/day as initial antiplatelet agent to reduce the risk of recurrent stroke and other cardiovascular events for patients with non-cardio embolic ischemic stroke.[8]Howeverstudies have shown individual variations in response of platelets to aspirin. So the hypothesis is: the extent of platelet inhibition by this antiplatelet agent is somehow related to recurrence of ischemic strokes and therefore consistent level of platelet inhibition is required to deliver an effective therapy. Based on the studies done so far, possible causes for aspirin resistance includes the following factors: (1) Reduced bioavailability (e.g., poor compliance, decreased absorption or metabolism); (2) problem in binding to COX-1 (e.g., Concomitant NSAIDs administration); (3) Extra production of thromboxaneA2 (TXA2)from monocytes, macrophages and endothelial cells);(4) Increased sensitivity of platelets to collagenand adenosine di phosphate (ADP); (5) Rapid platelet turnover (such as in patients with coronary arterybypass surgery); (6) Genetic polymorphisms (e.g., polymorphisms of COX-1, COX-2); (7) tachyphylaxis; and (8) Causes other than atherosclerosis for cerebrovascular events which may not respond to antiplatelet agents such as vacuities.[9]Aspirin Resistance have been classified as either laboratory or clinical phenomenon.[10]Laboratory resistance is said to be present when antiplatelet agent fail to inhibit platelet TXA2 production and therefore platelet aggregation.[10] Clinical resistance has been defined as failure of aspirin to prevent clinical events and is also known as aspirin treatment failure. There are available numbers of test to assess platelet function and detect aspirin resistance. All these tests have got advantages and limitations

compared to each other. Light or optical aggregation study for platelet function is the traditional gold standard widely available and also correlates with clinical events. This test is based on the fact that Inhibition of platelet aggregation can be used to measure change in transmitted light intensity and therefore antiplatelet drug's efficacy. Multiple agonists in varying concentrations have been used to assess the aggregation response. In our study ADP was used as an agonist to assess response of aspirin by light transmission aggregometry (LTA).[11-14] Although it is not specific to the COX pathway, when administered in low concentrations (1–3 micromoles) it requires an active COX to induce platelet aggregation.[15-17]whereas at higher ADP concentrations (10–20 µM) aggregation goes via TxA2-independent pathwaysIt is moderate concentration of ADP (5 µM), which partially depends on thromboxane A2 synthesis but led to identify aspirin resistance in patients with reliable level of agreement.[17] This study was carried out to assess the prevalence of aspirin resistance in patients with ischemic stroke at a tertiary care center of north India. Simultaneously, we also tried to study association of various risk factors of stroke to the prevalence of aspirin resistance.

Material and Methods

This study was conducted on the ischemic stroke patients admitted to the Department of Medicine, King George's Medical University, and Lucknow over a period of One year. The study comprised of 76 consecutive patients of ischemic stroke admitted in our wards. During identification ischemic stroke patients are confused with few other congener cerebrovascular diseases, therefore both clinical assessment as well as imaging modality was used to select patients for this study. This included detailed clinical current and past history, examination as well as radiological investigations to rule out other diseases. Symptoms that are commonly associated with ischemic stroke include: Sudden onset numbness or weakness of the face, arm, or leg especially on one side of the body, mental confusion, trouble speaking or understanding, trouble walking, dizziness, loss of balance or coordination, trouble seeing in one or both eyes. Sudden severe headache with no known cause.Patient with any of these complains were considered for the study after confirmation of ischemic stroke on imaging modality either CT scan or MRI. Present study is a hospital based prospective observational study.

Inclusion Criteria

All ischemic stroke patients (new/recurrent) of age more than 30 years and admitted to medical wards of King George's Medical University, Lucknow with or without history of transient ischemic attacks were included in the study.

Exclusion Criteria

Patients with Age <30 years, Ischemic stroke patients with zone of ischemia > 50% of involved hemisphere, Ischemic stroke with haemorrhagic transformation, Cardio-embolic strokes, any contraindications to aspirin therapy,subarachnoid hemorrhage, intra cerebral hemorrhage, those who underwent thrombolysis, those who fell and

suffered head injury, patients with positive family history for stroke and patients with very low general condition at presentation were excluded from the study.

Assessment of Aspirin Resistance

There are yet no standardized approach to the diagnosis and also no proven effective treatments for aspirin resistance that improve outcome. Among various tests available we used principles of light transmission aggregometry with Chronolog aggegometer (USA), which measures change in light transmission upon addition of an agonist. The test is a labor intensive test with variable sensitivity and not so great specificity. However some of the researchers consider this test to be the gold standard. Each patient in study population were given non enteric coated aspirin formulations for at least 7 days along with other specific and supportive treatments before they are subjected to the test 0.9ml of patient's blood was collected in 3.8% sodium citrate tubes and was immediately transported to nearby pathology lab. Sample was checked for platelet counts, only samples with platelet count >100,000 were considered for further testing, as<100,000 platelet counts is not compatible with study of aggregation using optical method. Samples were then centrifuged to obtained platelet rich and platelet poor plasma. Platelet rich plasma was then subjected to the test for platelet function. ADP 5µmol was used as an agonist to induce platelet aggregation. Each test was carried out with one control and standard graphs were obtained at the end of the test. Graphs showing platelet aggregation of more than 70% after addition of ADP were considered to have aspirin resistance.[18-24] (Figure 1 and 2).

Statistical Analysis

The results are presented in mean ± SD (standard deviation) and percentage. Chi-square test was used to compare the dichotomous/categorical variables. The $P< 0.05$ was considered as significant. All the analysis was carried out by using SPSS (Statistical Product and Service Solutions) 15.0 versions.

Results

Age distribution of the patients shows wide variation and more than 2/3 of the patients were of age >60 years (72.4%, 55 patients), 22.4% (17) patients were between 50-60 years and 5.3% (4) patients were <50 years of age with mean age of 66.54±9.28.More than half, 57.9% (44) of the patients in our study were male, 36.8% (28) patients were diabetic and 34.2 %(26) patients were detected to have hypertension. 60.5% (46) patients in our study were having lacunar infarction as compared to 39.5% (30) patients of non-lacunar infarction. 7.9% (6) patients gave history of previous stroke /TIA. (Table1and 2) showing various demographical and biochemical parameters of the study population. Prevalence of Aspirin resistance in our study was 23.7%. Aspirin resistance was more prevalent among elderly patients: 34.5% patients with aspirin resistance were of age > 70 years. 27.3% (12) males as compared to 18.8% (6) females were having aspirin resistance; however, this difference

was statistically insignificant. (p=0.38) (Table 3). Patients with diabetic mellitus were having more prevalent aspirin resistance 35.7% as compared to that of 16.7% among non-diabetics (p=0.06). Whereas systolic and diastolic blood pressure values were almost identical in both, aspirin resistant and aspirin responsive group. Among various bio-chemical parameters studied HBA1C and fasting lipid profiles were having statistically significant association to aspirin resistant with p-values – 0.04 (HBAIC), 0.002 (Total cholesterol), 0.01 (triglycerides), 0.001 (High Density Lipoprotein), 0.01 (Low density lipoprotein), 0.02 (very low density lipoprotein) respectively. Non lacunar infarction were significantly associated with aspirin resistance (p=0.03).Also thehistory of previous stroke / TIA was significantly associated with occurrence of aspirin resistance (p=0.01). (Table 4)

Table-1

	No.(n=76)	**%**
Age in years		
<50	4	5.3
50-60	17	22.4
61-70	26	34.2
>70	29	38.2
Mean±SD	66.54±9.28	
Gender		
Male	44	57.9
Female	32	42.1
Diabetes		
Diabetic	28	36.8
Non-diabetic	48	63.2
Hypertension		
Hypertensive	26	34.2
Non-hypertensive	50	65.8
Type of infarction		
Lacunar	46	60.5
Nonlacunar	30	39.5
History of previous stroke/TIA		
Yes	6	7.9
No	70	92.1

Table-2

Parameters	Mean	SD	Min.	Max.
SBP	159.68	25.36	112.00	212.00
DBP	90.76	8.87	60.00	110.00
BMI	26.92	2.33	22.40	32.10
HB	11.92	1.99	8.10	16.10
TLC	11053.93	7127.93	1800.00	39400.00
PLATELETS	2.45	1.15	1.01	4.87
FASTING BS	127.80	49.41	65.00	414.00
PP BS	214.45	79.13	132.00	634.00
HbA1C	7.41	1.70	3.90	13.50
S. UREA	44.50	17.45	24.00	122.20
S.CREATININE	1.12	0.49	0.40	3.10
S. TG	150.39	28.21	92.00	288.00
S.T CHL	179.71	50.65	104.00	267.60
S. HDL	33.81	6.28	15.00	50.00
S. LDL	117.17	41.61	31.00	220.40
S. VLDL	26.44	7.79	5.00	58.00

Table-3

Age in years	No. of patients	%	Prevalence of aspiration resistance		Chi-square, p-value
			No.	%	
<50	4	5.3	1	25.0	3.20, 0.36
50-60	17	22.4	3	17.6	
61-70	26	34.2	4	15.4	
>70	29	38.2	10	34.5	

Table-4

Biochemical parameters	Aspiration resistance		p-value[1]
	Yes	No	
Hb	12.21±2.22	11.83±1.93	0.53
TLC	10572.67±8036.60	11203.29±6891.54	0.38

Platelets (in lacs)	2.58±1.11	2.41±1.17	0.62
Fasting BS	143.61±75.35	122.80±37.38	0.36
PPBS	228.41±115.13	210.11±64.85	0.93
HbA1C	8.27±2.11	7.13±1.47	0.04*
Serum urea	46.20±26.27	43.97±13.91	0.63
Serum creatinine	1.10±0.55	1.12±0.47	0.90
Total cholesterol	208.81±44.49	167.54±45.47	0.002*
TG	160.33±19.33	144.51±28.45	0.01*
HDL	29.33±3.54	35.20±6.31	0.001*
LDL	140.83±33.02	107.04±38.63	0.01*
VLDL	30.03±3.75	25.32±8.39	0.02*

Figure 1

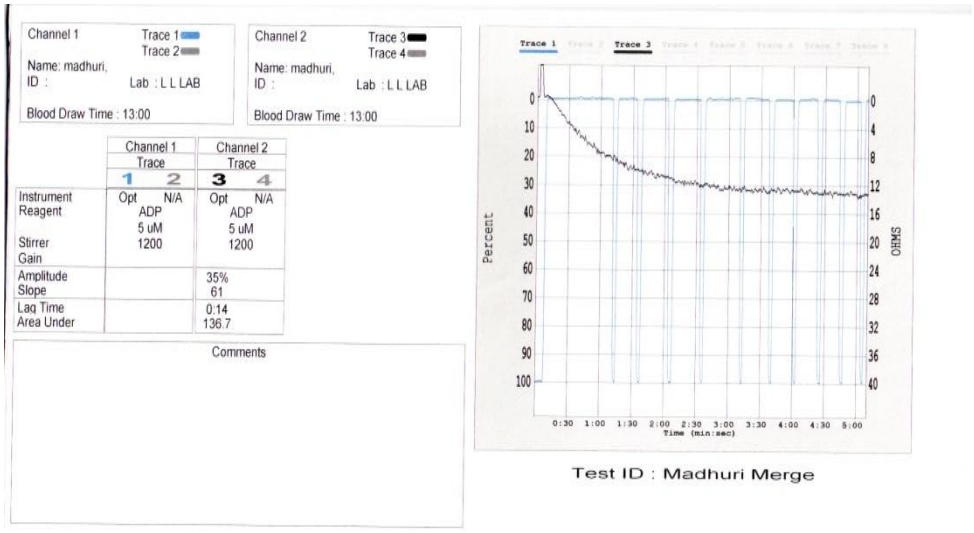
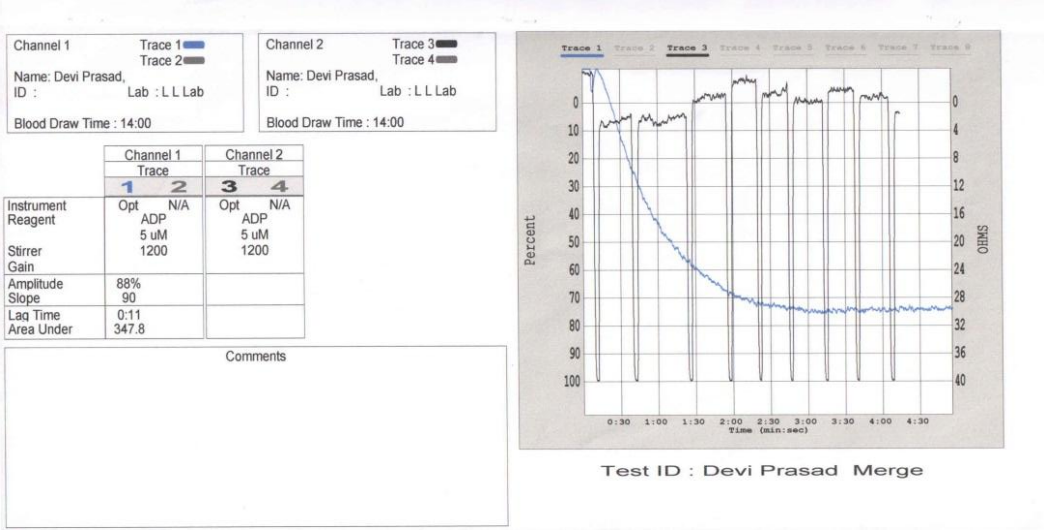


Figure 2



Discussion

The prevalence of aspirin resistance in our study was found to be 23.7%. However, prevalence of laboratory aspirin resistance in previous studies among ischemic stroke patients ranges from 5% to 78 %.[25]These variations may be due to small sample sizes, different types of population studied (different prevalence of patients confounders such as age, sex, origin and clinical condition), different level of compliance, different definition of aspirin resistance and different tests of platelet functions used. Few of observations of our study were in accordance to the studies done in the past whereas few were on the opposite bank.

Conclusion

The development of new cerebrovascular events despite aspirin use has created an interest in a possible resistance to the drug. Several definitions have been set and various laboratory testing modalities are available. This has led to a wide range of prevalence reports in different clinical entities. There are numbers of etiologic possibilities related to various demographic and biochemical, and other factors. This phenomenon may be clinically significant and treatment is at present limited to increasing the dose and adding upon another antiplatelet drug. So there is a need of further research to validate the existence, definition, gold standard diagnostic test and any promising treatment of aspirin resistance.

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