

Aspirin Resistance in Patients with Ischemic Stroke: Study at a Tertiary Care Teaching Hospital

¹Kumar Gourav Behera, ²Soumya Samal, ³Jayshree Swain, ⁴Jatindra Nath Mohanty*

¹Department of Cardiology, IMS and Sum hospital, SOA deemed to be University, Bhubaneswar, Odisha, India

²Department of Anaesthesiology, IMS and Sum hospital, SOA deemed to be University, Bhubaneswar, Odisha, India

³Department of Endocrinology, IMS and Sum hospital, SOA deemed to be University, Bhubaneswar, Odisha, India

⁴Medical Research Laboratory, IMS and Sum hospital, SOA deemed to be University, Bhubaneswar, Odisha, India

Corresponding Author

Jatindra Nath Mohanty, Assistant Professor, Medical Research Laboratory, IMS and Sum hospital, SOA deemed to be University, Bhubaneswar, Odisha, India

Mail ID- jatindranathmohanty@soa.ac.in

Abstract

Aspirin is utilized in ischemic stroke treatment. Notwithstanding, a few patients are not receptive to the antithrombotic activity of aspirin. In this way close by of intense stroke management, secondary prophylaxis is vital. As far as drugs are concerned aspirin is the most common drug used for the secondary prophylaxis. In spite of these different measures there are repeats in numerous patients. Numerous factors have been considered answerable for causing such repeats and aspirin resistance is one of them. The point of this investigation was to evaluate the prevalence of aspirin resistance in Ischemic Stroke patients. This study was conducted in the ischemic stroke patients admitted to the OPD at department of cardiology and Emergency medicine over a period of One year. The study comprised of 38 consecutive patients of ischemic stroke admitted in our wards. All patients with ischemic stroke received standard treatment with non-enteric coated Aspirin 150 mg per day at least for 7 days after which study for platelet function to assess aspirin resistance was performed. Prevalence of Aspirin resistance in our study was found to be 23.7% and this was more prevalent among elderly patients. In light of aftereffects of this investigation we reasoned that aspirin resistance exists. Anyway without any standard definition and best quality level tests accurate predominance and its part in stroke repeat is as yet a matter of examination.

Key words: Aspirin resistance, Ischemic stroke, Tertiary care teaching hospital, Cardiology

Introduction

Stroke is the quickly creating loss of brain functions because of unsettling influence in the blood supply to the cerebrum. It is the main source of grown-up inability in the United States and Europe as well as India. As of now, the subsequent driving reason for death positioning after coronary illness and before malignant growth is representing 10% of deaths overall^{1, 2}. Around 80–90% of strokes are brought about by ischemia, and the rest of hemorrhage³. Arterioarterial microthromboembolism is a significant etiological factor in the pathogenesis of

ischemic stroke. Platelet initiation in cerebrovascular illness is related with intermittent stroke and demise, and the restraint of platelet work by antiplatelet drugs including aspirin brings down the risk of ischemic stroke^{4,5}. Aspirin is a powerful antiplatelet agent, displaying its activity by irreversibly hindering platelet cyclooxygenase-1 enzyme, in this way forestalling production of thromboxane A2 (TXA2). It has been utilized in the essential and auxiliary avoidance of thromboembolic vascular occasions⁵⁻⁷. However, a few patients experience repetitive ischemic events despite ideal antiplatelet treatment. This has raised the likelihood that these patients might be impervious to aspirin and produced much interest in identification of such patients with laboratory tests of platelet function. Although numerous investigations have demonstrated aspirin resistance in cardiovascular disorders including coronary corridor infection^{8, 9}, metabolic condition¹⁰, and diabetes¹¹⁻¹³ by specific trial of aspirin resistance, there are still worries that these tests have not related intimately with resulting intermittent occasions, and have not dependably distinguished non-responders to antiplatelet treatment.¹⁴⁻¹⁶ Notwithstanding the absence of any standardized approach to deal with diagnosis, there is as of now no demonstrated viable treatment for aspirin resistance. In spite of the aspirin resistance has been shown as a potential risk factor for recurrent cardiovascular ischemic events, there is an absence of information corresponding aspirin resistance and risk of cerebrovascular ischemic events¹⁷. However, the greater part of authors agrees that aspirin resistance in stroke patients isn't exceptional^{18, 19}. So our aim of this study was to survey the predominance of aspirin resistance in patients with acute ischemic stroke in our hospital.

Material and Methods

The study was approved by the local ethics committee and all participants gave written informed consent before participating. This study was conducted on the ischemic stroke patients admitted to the OPD of Department of Emergency Medicine and Cardiology of IMS and Sum hospital, SOA deemed to be University over a period of One year. The study involved of 38 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 35 years and admitted to admitted to the OPD of Department of Emergency Medicine and Cardiology of IMS and Sum

hospital, SOA deemed to be University over a period of one year with or without history of transient ischemic attacks were included in the study.

Exclusion Criteria

Patients with Age <35 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 haemorrhage, 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 study

There are yet no normalized way to deal with the finding and furthermore no demonstrated successful medicines for ibuprofen obstruction that improve result. Among different tests accessible in our examination we gauges change in light endless supply of an agonist. The test is a work concentrated test with variable affectability and not very good particularity. Anyway a portion of the analysts believe this test to be the highest quality level. Every patient in investigation populace were given non enteric covered anti-inflammatory medicine details for at any rate 7 days alongside other explicit and strong medicines before they are exposed to the test 0.9ml of patient's blood was gathered in 3.8% sodium citrate tubes and was quickly moved to close pathology lab. Test was checked for platelet tallies, just examples with platelet tally >100,000 were considered for additional testing, as <100,000 platelet checks isn't viable with investigation of collection utilizing optical technique. Tests were then centrifuged to acquired platelet rich and platelet helpless plasma. Platelet rich plasma was then exposed to the test for platelet work. ADP 5µmol was utilized as an agonist to incite platelet accumulation. Each test was completed with one control and standard charts were acquired toward the finish of the test. Diagrams demonstrating platelet collection of over 70% after expansion of ADP were considered to have headache medicine opposition.¹⁸⁻²⁴

Statistical Analysis

The outcomes are introduced in mean ± SD (standard deviation) and rate. Chi-square test was utilized to compare the dichotomous/categorical factors. The P< 0.05 was considered as significant. All the examination was done by utilizing SPSS (Statistical Product and Service Solutions) 15.0 variants.

Results

Age distribution of the patients shows wide variation and more than 2/3 of the patients were of age >60 years (72.4%, 26 patients), 22.4% (8) patients were between 50-60 years and 5.3% (2) patients were <50 years of age with mean age of 66.54±9.28. More than half, 57.9% (22) of the patients in our study were male, 36.8% (14) patients were diabetic and 34.2 % (13) patients were detected to have hypertension. 60.5% (23) patients in our study were having lacunar infarction as compared to 39.5% (15) patients of non-lacunar infarction. 7.9% (3) patients gave history of previous stroke /TIA. (Table 1 and 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% (6) males as compared to 18.8% (3) females were having aspirin resistance; however, this difference was statistically insignificant. ($p=0.38$) (Table 3).

Table 1: Demographics details

	No.(n=7)	%
Age in years		
<50	2	5.3
50-60	8	22.4
61-70	13	34.2
>70	29	38.2
Mean $\pm$ SD	66.54 $\pm$ 9.28	
Gender		
Male	22	57.9
Female	16	42.1
Diabetes		
Diabetic	14	36.8
Non-diabetic	24	63.2
Hypertension		
Hypertensive	13	34.2
Non-hypertensive	25	65.8
Type of infarction		
Lacunar	23	60.5
Nonlacunar	15	39.5
History of previous stroke/TIA		
Yes	3	7.9
No	35	92.1

Table.2 : Biochemical parameters of the study population

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

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 pvalues – 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 the history of previous stroke / TIA was significantly associated with occurrence of aspirin resistance ($p=0.01$). (Table 4)

Table 3: Prevalence of aspiration resistance

Age in years	No. of patients	%	Prevalence of aspiration resistance		Chi-square, p-value
			No.	%	
<50	2	5.3	1	25.0	3.20, 0.36
50-60	8	22.4	3	17.6	
61-70	13	34.2	4	15.4	
>70	14	38.2	10	34.5	

Table 4: Aspirin resistance data with other biochemical test

Biochemical parameters	Aspirin 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*

Discussion

The pervasiveness of aspirin resistance in our investigation was discovered to be 23.7%. Notwithstanding, pervasiveness of research center aspirin resistance in past investigations among ischemic stroke patients goes from 5% to 78 %.²⁵ These varieties might be because of little example sizes, various kinds of populace contemplated (diverse pervasiveness of patients confounders, for example, age, sex, root and clinical condition), distinctive degree of consistence, distinctive meaning of aspirin resistance and various trial of platelet capacities utilized. Not many of perceptions of our examination were in understanding to the investigations done previously though few were on the contrary bank.

Aspirin resistance recommended expanded danger of mortality among our populace of ischemic stroke patients. Both inhospital and 2-year death rates were higher in aspirinresistant patients. Albeit moderately more established age and higher NIHSS scores in the anti-inflammatory medicine safe patients may have impacted the death rate, calculated relapse investigation demonstrated ibuprofen opposition as a free indicator of mortality in our associate. Aspirin resistance has been proposed to be autonomously connected with an

expanded danger of atherothrombotic vascular occasions in a wide scope of cardiovascular patients.²⁶⁻²⁹ Ibuprofen obstruction has been related with a four times expanded danger of antagonistic occasions among stable cardiovascular patients.^[29]

Aspirin resistance is related with an expanded danger of myocardial dead tissue and cardiovascular passing.^{26,27} The expanded danger of clinical occasions is relied upon to be also connected with headache medicine obstruction among ischemic stroke patients, given the regular hidden pathology of atherothrombosis. Grottemeyer et al.³⁰ followed up 180 post ischemic stroke patients more than 2 years and discovered 33% of the populace to be headache medicine safe with a ten times increment in clinical occasions (counting myocardial localized necrosis, vascular passing and stroke) among safe patients. Nonetheless, it ought to be remembered that there are worries that the headache medicine obstruction tests probably won't be corresponded intimately with ensuing repetitive occasions. A few creators even propose that distinguishing proof of Aspirin resistance based on these tests needs affectability and explicitness for recognizing thrombotic hazard, and is probably going to beartifactual.¹⁴ In addition, it is likewise conceivable that aspirin resistance and the noticed expansion in mortality are not related with a causal relationship. Patients with further developed phases of cerebrovascular sickness and higher rate of atherothrombosis have higher mortality hazard and might be bound to have hyper reactive platelets.

Conclusion

The improvement of new cerebrovascular occasions notwithstanding aspirin use has made an interest in a potential protection from the medication. A few definitions have been set and different research facility testing modalities are accessible. This has prompted a wide scope of pervasiveness reports in various clinical substances. There are quantities of etiologic prospects identified with different segment and biochemical, and different variables. This marvel might be clinically significant and treatment is at present restricted to expanding the portion and adding upon another antiplatelet drug. So there is a need of additional examination to approve the presence, definition, best quality level indicative test and any encouraging treatment of aspirin resistance.

Reference

1. Feigin VL (2005) Stroke epidemiology in the developing world. *Lancet* 365:2160–2161
2. Donnan GA, Fisher M, Macleod M, Davis SM (2008) Stroke. *Lancet* 371:1612–1623
3. Bogousslavsky J, Van Melle G, Regli F (1988) The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke* 19:1083–1092
4. Yip HK, Liou CW, Chang HW, Lan MY, Liu JS, Chen MC (2005) Link between platelet activity and outcomes after an ischemic stroke. *Cerebrovasc Dis* 20:120–128
5. Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324:71–86
6. Ridker PM, Manson JE, Buring JE, Goldhaber SZ, Hennekens CH (1991) The effect of chronic platelet inhibition with low-dose aspirin on atherosclerotic progression and

- acute thrombosis:clinical evidence from the Physicians' Health Study. *Am Heart J* 122:1588–1592
7. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2:349–360
8. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber AA, Gams E, Schrörr K, Hohlfeld T (2003) Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation* 108:542–547
9. Borna C, Lazarowski E, van Heusden C, Ohlin H, Erlinge D (2005) Resistance to aspirin is increased by ST-elevation myocardial infarction and correlates with adenosine diphosphate levels. *Thromb J* 3:10
10. Kahraman G, Sahin T, Kilic T, Baytugan NZ, Agacdiken A, Ural E, Ural D, Komsuoglu B (2007) The frequency of aspirin resistance and its risk factors in patients with metabolic syndrome. *Int J Cardiol* 115:391–396
11. Watala C, Pluta J, Golanski J, Rozalski M, Czyz M, Trojanowski Z, Drzewoski J (2005) Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med* 83:148–158
12. Anfossi G, Russo I, Trovati M (2008) Resistance to aspirin and thienopyridines in diabetes mellitus and metabolic syndrome. *Curr Vasc Pharmacol* 6:313–328
13. Fateh-Moghadam S, Pločinger U, Cabeza N, Htun P, Reuter T, Ersel S, Gawaz M, Dietz R, Bocksch W (2005) Prevalence of aspirin resistance in patients with type 2 diabetes. *Acta Diabetol* 42:99–103
14. Gorog DA, Sweeny JM, Fuster V (2009) Antiplatelet drug 'resistance'. Part 2: laboratory resistance to antiplatelet drugs—fact or artifact? *Nat Rev Cardiol* 6:365–373
15. Eikelboom JW, Emery J, Hankey GJ (2010) The use of platelet function assays may help to determine appropriate antiplatelet treatment options in a patient with recurrent stroke on baby aspirin: against. *Stroke* 41:2398–2399
16. Lev EI (2009) Aspirin resistance transient laboratory finding or important clinical entity? *J Am Coll Cardiol* 53:678–680
17. Bennett D, Yan B, Macgregor L, Eccleston D, Davis SM (2008) A pilot study of resistance to aspirin in stroke patients. *J Clin Neurosci* 15:1204–1209
18. Hohlfeld T, Weber AA, Junghans U, Schumacher M, Boucher M, Schrörr K, Siebler M (2007) Variable platelet response to aspirin in patients with ischemic stroke. *Cerebrovasc Dis* 24:43–50
19. Burke J, Kraft WK, Greenberg HE, Gleave M, Pitari GM, Van Buren S, Wagner JA, Waldman SA. Relationship of arachidonic acid concentration to cyclooxygenase-dependent human platelet aggregation. *J Clin Pharmacol* 2003;43:983–989.
20. Harrison P, Segal H, Blasbery K, Furtado C, Silver L, Rothwell PM. Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry *Stroke* 2005; 36:1001–1005

21. Maree AO, Curtin RJ, Dooley M, Conroy RM, Crean P, Cox D, Fitzgerald DJ. Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. *J Am Coll Cardiol* 2005;46:1258–1263
22. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. *J Am Coll Cardiol* 2005;46:1705–1709
23. Wenaweser P, Dorffler-Melly J, Imboden K, Windecker S, Togni M, Meier B, Haerberli A, Hess OM. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol* 2005;45:1748–1752
24. Kranzhofer R, Ruef J. Aspirin resistance in coronary artery disease is correlated to elevated markers for oxidative stress but not to the expression of cyclooxygenase (COX) 1/2, a novel COX-1 polymorphism or the PLA(1/2) polymorphism. *Platelets* 2006;17:163–169.
25. Lev EI, Patel RT, Maresh KJ, Guthikonda S, Granada J, DeLao T, Bray PF, Kleiman NS. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. *J Am Coll Cardiol* 2006; 47:27–33.
26. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ (2003) A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 41:961–965.
27. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S (2002) Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 105:1650–1655
28. Mueller MR, Salat A, Stangl P, Murabito M, Pulaki S, Boehm D, Koppensteiner R, Ergun E, Mittlboeck M, Schreiner W, Losert U, Wolner E (1997) Variable platelet response to low-dose ASA and the risk of limb deterioration in patients submitted to peripheral arterial angioplasty. *Thromb Haemost* 78:1003–1007
29. Wang JC, Aucoin-Barry D, Manuelian D, Monbouquette R, Reisman M, Gray W, Block PC, Block EH, Ladenheim M, Simon DI (2003) Incidence of aspirin nonresponsiveness using the Ultegra Rapid Platelet Function Assay-ASA. *Am J Cardiol* 92:1492–1494
30. Grotemeyer KH, Scharafinski HW, Husstedt IW (1993) Two-year follow-up of aspirin responder and aspirin non responder. A pilot study including 180 post-stroke patients. *Thromb Res* 71:397–403.