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EVALUATION OF ANTI-PLATELET DRUGS IN ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACK PATIENTS

Ayesha Ambereen[1], Fakiha Firdous[1], Sara Ahmed Yadallah[1], Ruqsar Samreen[1], Suhail Syed[1], Dr. J. Raghuram[2*]

[1]PharmD, Sultan-ul-Uloom college of Pharmacy, JNTUH, Telangana, India – 500034

[2]HOD, Dept. of PharmD, Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India– 500034

Abstract:

Stroke is a neurological disorder that is characterized by blockage of blood vessels. Clots are formed in the brain and interrupt blood flow, thereby clogging arteries and causing blood vessels to break, leading to bleeding. The study evaluates the effective use of anti-platelet drugs in ischemic and transient ischemic attack patients by various parameters that contribute to the platelet therapy which include the safety, efficacy, and cost-effectiveness. Anti-platelet drugs like Aspirin and Clopidogrel are the most frequently prescribed drugs in the treatment of stroke presently. But studies have shown the risk symptoms worsen leading to adverse drug reactions in patients. 100 patients data were collected and analysed with different statistical methods.

OBJECTIVE: To determine the aptness, safe and effectiveness use, frequency of adverse drug reactions, cost-effectiveness of anti-platelet drugs in ischemic and transient ischemic attack patients.

MATERIAL AND METHODS: This is a prospective observational study done for six months in the neurology department. A minimum of 100 cases of stroke were collected. These data were noted in the data collection sheet. Data include age, gender, diagnosis, lab reports, and drug therapy (drug prescribed, brand/generic name, dose, and duration). All the parameters were followed and this study analysis involve SPSS software version - 22.

RESULTS: In our study of 100 patients data were collected and analysed with different statistical methods which includes the mean method, standard deviation method, chi-square method, and ANOVA test. Our study showed the most common age group of patients was 61-70 years. The incidence for the males was 65% (N=65) and for females was 35% (N=35). The most common drug prescribed was Aspirin (78%) in the maximum number of patients. Results illustrate that the majority of patients were diagnosed with Acute ischemic stroke. The adverse reaction was seen in maximum percent of patients taking dual anti-platelet drug therapy. TAB ECOSPRIN is the most cost-effective drug among all the anti-platelet drugs prescribed.

CONCLUSION: It concludes the evaluation of anti-platelet drugs for safety, efficacy, and cost-effectiveness in ischemic stroke and transient ischemic attack patients. Among all the anti-platelet drugs prescribed for stroke patients - Aspirin (TAB ECOSPRIN) has shown fewer adverse effects, more efficacy in treatment, and the highest percentage of cost-saving in stroke patients compared to all other mono and dual anti-platelet drug therapy.

Key Words: *Anti-platelet drugs, Ischemic stroke, Transient ischemic attack, Aspirin, Adverse drug reactions, cost effectiveness.*

Corresponding author:

Dr. J. Raghuram,

HOD, Dept. of Pharm D,

Sultan-ul-Uloom College of Pharmacy, JNTUH, Telangana, India– 500034.

Email ID: raghuram143ind@gmail.com.

QR code

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I. INTRODUCTION:

Stroke is a neurological disorder that is characterized by blockage of blood vessels. Clots are formed in the brain and interrupt blood flow, thereby clogging arteries and causing blood vessels to break, leading to bleeding. Rupture of the arteries in the brain during stroke results in the sudden death of brain cells due to lack of oxygen [1]. World Health Organization defined stroke as a clinical syndrome that consists of rapidly developing clinical signs of focal disturbance of cerebral function which lasts more than 24 hours or leads to death with no clear cause [2]. Stroke is broadly classified into three categories: ischemic stroke, hemorrhagic stroke, and transient ischemic attack (TIA). Ischemic stroke occurs due to blockage of blood vessels, which reduces the blood supply to the brain. Hemorrhagic stroke, the second type, occurs due to the rupture of blood vessels in the brain, leading to blood spillage in the intracranial cavity. Hemorrhagic stroke can be further classified as intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematomas, depending on the site of blood spillage [3]. Transient ischemic attack (TIA) is self-resolving focal cerebral ischemia rather than acute infarction with symptoms lasting less than 24 hours [4].

An ischemic stroke occurs due to the blood clot blockage, which blocks blood from flowing to the brain. The reason for a blood clot is often atherosclerosis, which is the build-up of fatty deposits on the inner lining of blood vessels. A portion of these deposits breaks off and blocks blood flow in your brain. An ischemic stroke can be embolic or thrombotic. Embolic, meaning the blood clot from another part of your body travels to the brain. Thrombotic, meaning the blood clot formed in the blood vessels of the brain. About 15% of embolic strokes are due to a condition called atrial fibrillation, or irregular heartbeats [5]. According to (TOAST) multicenter Trial of Acute Stroke Treatment, there are three kinds of ischemic stroke:

Ø Large vessel stroke
Ø Small vessel stroke or Lacunar stroke
Ø Cardioembolic stroke

Large artery strokes occur due to thrombotic or embolic occlusion in the brain's major arteries like the internal carotid artery, middle cerebral artery, and anterior cerebral artery. Lacunar strokes occur more often because of the involvement of smaller or perforating blood vessels that supply the brain's deeper structure [6]. Large vessel atherothrombosis refers to the formation of lipid-loaded atherosclerotic plaques on the inner lining of a large vessel and this can affect both intra and extracranial arteries. Cardioembolism occurs when the blood clots are formed within the heart and break into the circulation and then get lodged in a cerebral artery. The small-vessel disease occurs due to occlusive disease involving the microcirculation of the brain [7].

American Heart Association (AHA) and American Stroke Association (ASA) endorse a definition of TIA as an episode of focal ischemia rather than acute infarction instead of a time-based definition [8]. TIAs are often neglected because of the symptoms which tend to improve faster. Symptoms of TIA vary widely from patient to patient depending on different areas of the brain. Since the blockage period in TIA is very short-lived, there is no permanent damage [9].

II. PATHOPHYSIOLOGY

Ischemic stroke contributes to around 85% of stroke patients, with the remaining due to intracerebral bleeding. Ischemic occlusion includes thrombotic and embolic conditions in the brain. In thrombotic occlusion, the blood flow is affected by the narrowing of vessels due to atherosclerosis. Plaque Buildup in the blood vessel walls will eventually constrict the vascular chamber and form clots, causing a thrombotic stroke. In an embolic occlusion, decreased blood flow to the brain causes an embolism; the blood flow to the brain decreases, causing severe stress and untimely cell death(necrosis). Necrosis further leads to the disruption of the plasma membrane, organelle swelling and leaking of cellular contents into extracellular space, and loss of neuronal function. Other key events contributing to stroke pathology include inflammation, energy failure, loss of homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, complement activation, and impairment of the blood-brain barrier, activation of glial cells, oxidative stress and infiltration of leukocytes. [Figure-1][10]

A transient ischemic attack (TIA) is defined as an episode of temporal and focal cerebral dysfunction of vascular origin, which is sometimes called a mini-stroke, with symptoms that last less than 24 hours [11]. While TIA generally do not cause permanent brain damage but they are a serious warning sign of stroke [12]. The causes of cellular injury following ischemia are multifactorial.

Increasing evidence suggests that reactive oxygen species- superoxide anion, hydrogen peroxide, and highly reactive hydroxyl radical can play a crucial role in the pathogenesis of stroke. Reactive oxygen species generate oxidative stress which is involved in neuronal damage with ischemia-reperfusion, and the antioxidant activity of plasma may play an an important factor in protecting from neurological damage caused by stroke-associated oxidative stress [13]. An increase in the free radical formation and reduced antioxidant defense cause oxidative stress. This may play a key role in the formation of reactive intermediates like hydroxyl radical, superoxide, hydrogen peroxide, and lipid peroxides which contribute to the pathogenesis of stroke-associated neuronal injury [14,15].

III. ETIOLOGY:

According to American Heart Association (AHA), 2012 reports ischemic stroke contributes 87%, with the remaining 13% contributing hemorrhagic. Ischemic strokes can be either by thrombus formation or embolic. 20% of ischemic stroke are due to embolic and the majority contributes to thrombus formation, although 30% are cryptogenic.

IV. RISK FACTORS:

Risk factors are classified into non-modifiable, modifiable, and potentially modifiable. It is also sub-divided as well documented or less well documented. The most important risk factors are hypertension, cigarette smoking, diabetes, and atrial fibrillation. The presence of atrial fibrillation is one of the most potent risk factors for ischemic stroke, with rates from 5% to 20% per year [16].

TABLE-1: RISK FACTORS OF STROKE [16].

Non-modifiable risk factors	Modifiable well documented	Potentially modifiable, less well documented
Age Sex Low birth weight Family history of stroke/TIA	Cigarette smoking Hypertension Diabetes High total cholesterol Low HDL cholesterol Atrial fibrillation Sickle cell disease Postmenopausal hormone therapy Oral contraceptives High Na/low K diet Obesity Physical inactivity Other cardiac diseases	Migraine with aura Metabolic syndrome Drug and alcohol abuse Hemostatic and inflammatory factors Homocysteinemia Sleep-disordered breathing Periodontal disease Infectious diseases

FIGURE-1: MOLECULAR MECHANISM OF ISCHEMIC STROKE [10].

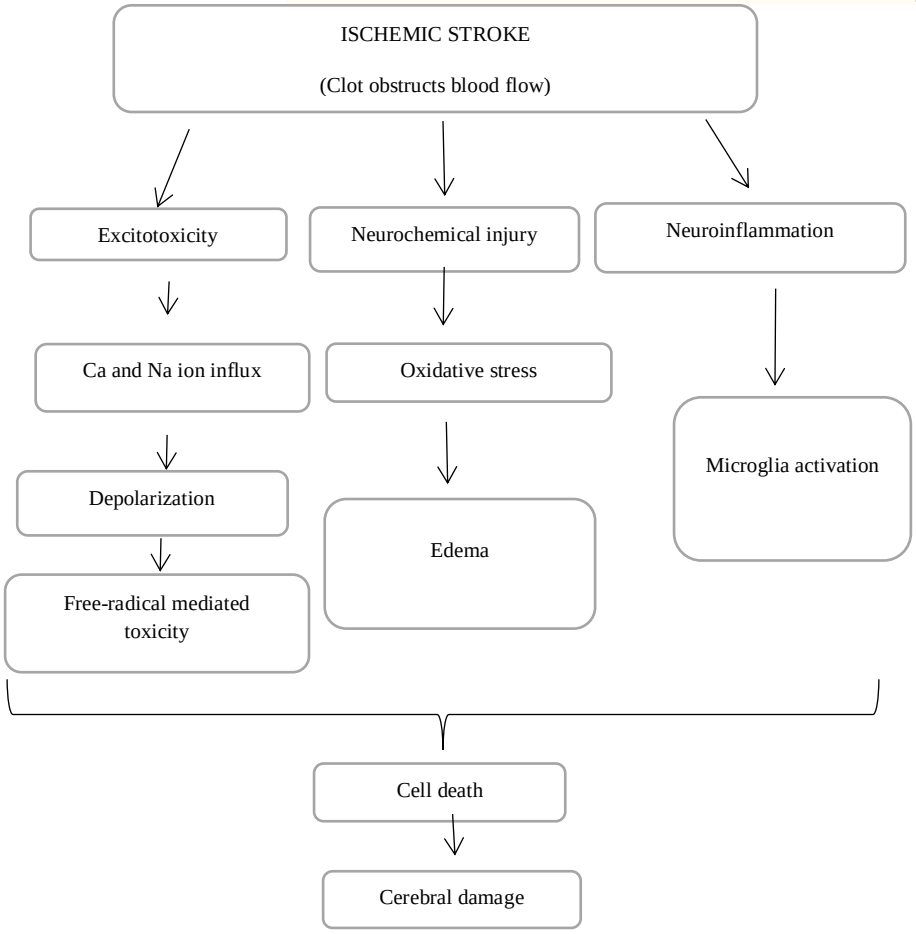
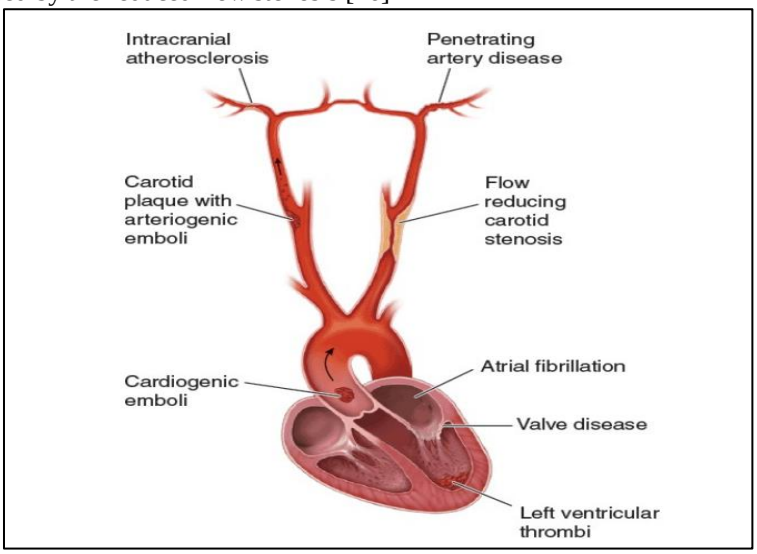


FIGURE-2: Diagram illustrating pathophysiology of ischemic stroke, where it shows the three major mechanisms underlying ischemic stroke, blockage of an intracranial vessel by an embolus (e.g., cardiogenic embolus), thrombosis of an intracranial vessel, affecting the small penetrating arteries, and hypoperfusion in the major extracranial artery caused by the reduced flow stenosis [16]



V. MATERIAL AND METHODS:

A total of 100 patients data was collected for prospective study from the neurology department specified to only stroke patients taking anti-platelet drugs for a study duration of 6 months. The data was collected in the data collection form or sheets which includes age, gender, diagnosis, co-morbidities, lab reports, and therapy (drug prescribed, brand/generic name, dose, ROA, Frequency, and duration). The study analysis involved SPSS software version 22.

❖ ***Data collection:***

Patient details like age, gender, diagnosis, medical history, and social history.

Drugs(anti-platelets) prescribed for the treatment in the hospital(Brand name, generic, dose, ROA, frequency, and duration).

❖ ***Sources of data:***

Patient case collection forms.

Laboratory reports.

Treatment chart during patient counselling.

SELECTION CRITERIA:

a)Inclusion criteria:

- Patient diagnosed with ischemic stroke and transient ischemic stroke.
- Both male and female patients.
- Age group: ≥ 35 years.

b)Exclusion criteria:

- Pregnant and lactating women.
- Pediatric population and age group below 30 years.
- Patients diagnosed with hemorrhagic stroke.

VI. RESULTS:

TABLE-2: GENDER WISE AGE DISTRIBUTION

Age Group	Gender		Total
	Male	Female	
31 - 40 Years	3	1	4
41 - 50 Years	15	4	19
51 - 60 Years	19	6	25
61 - 70 Years	18	12	30
71 - 80 Years	7	9	16
81 - 90 Years	3	3	6
Grand Total	65	35	100

X^2 test =7.224,P value =0.204

FIGURE-3: COMMON CO-MORBIDITIES THAT ARE RISK FACTORS FOR STROKE

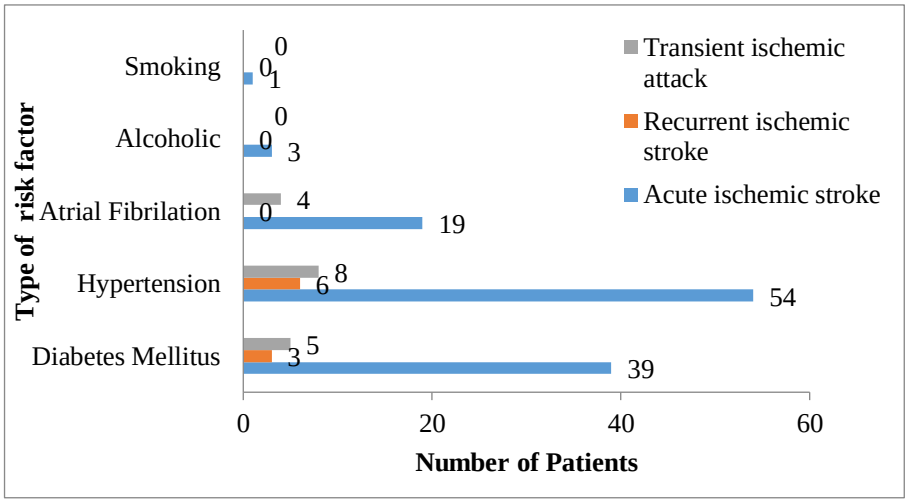


FIGURE-4: CLASSIFICATION OF DRUGS USED AS A MEDICATION FOR STROKE

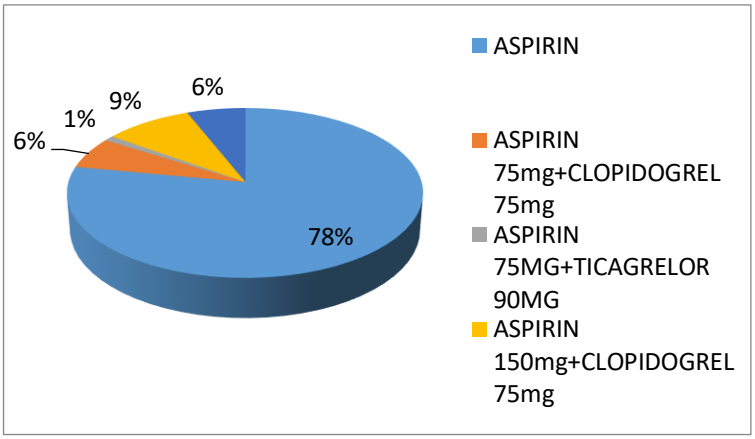


TABLE-3: COMPARISON OF VITALS AFTER USING DRUG

Vitals	Name of Generic drug					F Value from ANOVA	P value
	ASPIRIN (n=78)	ASPIRIN 75mg+ CLOPIDOGREL 75mg (n=6)	ASPIRIN 75MG+ TICAGRELOR 90MG (n=1)	ASPIRIN 150mg+ CLOPIDOGREL 75mg (n=9)	CLOPIDOGREL (n=6)		
SBP	134.5±18.8	130±16.7	120±0	143.3±18.7	116.7±33.9	1.8423	0.1271
DBP	81.3±8.6	80±11	90±0	83.3±10	76.7±18.6	0.1069	0.9798
Pulse rate	84.7±11.4	78.8±7.8	90±0	75.9±15.3	93.7±6	2.6688	0.0369

TABLE-4: COMPARISON OF BLOOD TEST AFTER USING DRUG

Parameter	Name of Generic drug					F Value from ANOVA	P value
	ASPIRIN (n=78)	ASPIRIN 75mg+ CLOPIDOGREL 75mg (n=6)	ASPIRIN 75MG+ TICAGRELOR 90MG (n=1)	ASPIRIN 150mg+ CLOPIDOGREL 75mg (n=9)	CLOPIDOGREL (n=6)		
Hb	13.28±2.12	13.35±1.7	13.3	13.44±1.73	11.4±0.68	1.2639	0.2897
Platelets	2.66±0.94	2.77±0.48	1.56	2.65±1.25	3.5±0.78	1.4894	0.2115
PCV	37.96±6.88	38.97±4.97	40	37.33±5.35	33.57±2.57	0.7294	0.5741
RBC	4.44±0.82	4.75±0.66	5.03	4.1±0.65	3.73±0.52	1.9234	0.1128
WBC	16279.49 ± 21555.72	10966.67± 1788.48	10700	34111.11 ±38120.06	7966.67 ± 722.96	1.7145	0.1532

TABLE-5: COMPARISON OF COAGULATION TEST AFTER USING DRUG

TESTS	Name of Generic drug					F Value from ANOVA	P value
	ASPIRIN (n=78)	ASPIRIN 75mg+ CLOPIDOGREL 75mg (n=6)	ASPIRIN 75MG+ TICAGRELOR 90MG (n=1)	ASPIRIN 150mg+ CLOPIDOGREL 75mg (n=9)	CLOPIDOGREL (n=6)		
Bleeding Time	2.24±0.25	2.25±0.27	2.5	2.22±0.26	2.33±0.26	0.4541	0.7692
Prothrombin Time	14.64±1.31	14.23±1.47	15.4	14.37±0.81	15.07±2.3	0.4525	0.7703

TABLE-6: ADVERSE EFFECT OF MEDICATION ON PATIENTS WITH RESPECT TO TYPE OF DRUG

Name of Generic drugs	Urine Analysis		Total
	Nil	Positive	
ASPIRIN	74	4	78
ASPIRIN 75mg+CLOPIDOGREL 75mg	5	1	6
ASPIRIN 75MG+TICAGRELOR 90MG	1	0	1
ASPIRIN 150mg+CLOPIDOGREL 75mg	6	3	9
CLOPIDOGREL	6	0	6
Grand Total	92	8	100

X^2 test =9.943,P value =0.041

FIGURE-5: OUTCOME OF URINE ANALYSIS WITH RESPECT TO TYPE OF DRUG WITH BRAND NAME

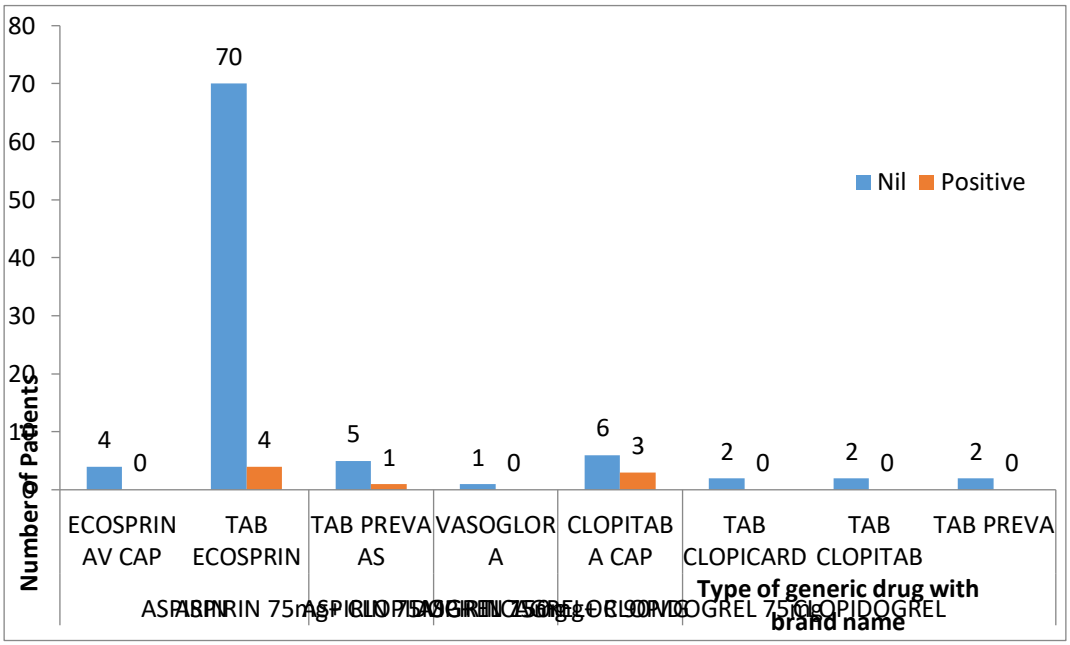
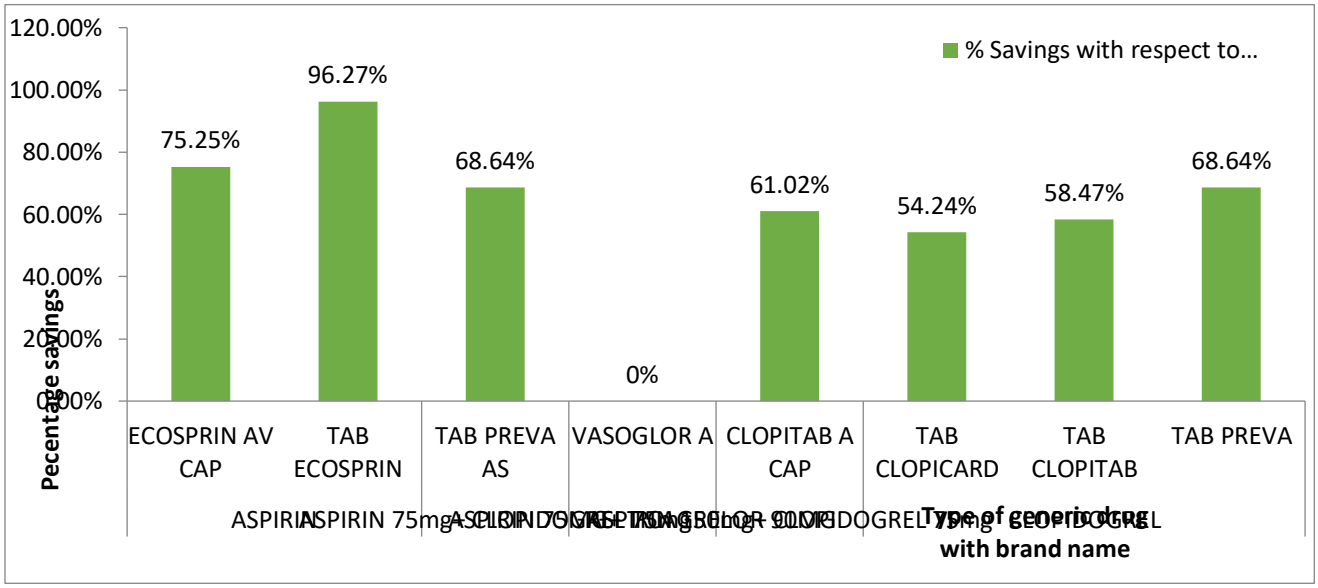


TABLE-7: COST CALCULATION FOR 30 DAYS PER PATIENTS WITH RESPECT TO TYPE OF DRUG

Generic Drug	Brand name	No of Patients	Avg. Cost of Medicine in Rs. for 30 days per patients	% Savings with respect to VASOGLOR A
ASPIRIN	ECOSPRIN AV CAP	4	116.8	75.25%
	TAB ECOSPRIN	74	17.6	96.27%
ASPIRIN 75mg+ CLOPIDOGREL 75mg	TAB PREVA AS	6	148	68.64%
ASPIRIN 75MG+ TICAGRELOR 90MG	VASOGLOR A	1	472	0%
ASPIRIN 150mg+ CLOPIDOGREL 75mg	CLOPITAB A CAP	9	184	61.02%
CLOPIDOGREL	TAB CLOPICARD	2	216	54.24%
	TAB CLOPITAB	2	196	58.47%
	TAB PREVA	2	148	68.64%
	Grand Total	100		

FIGURE-6: SAVING PERCENTAGE WITH RESPECT TO VASOGLOR A DRUG



VII. DISCUSSION:

1. A total of 100 patient data were collected and analyzed with different statistical methods using SPSS software version - 22.
2. According to our study 4% of patients were in the age range 31 -40 years, 19% of patients were in the age range 41 - 50 years, 25% of patients were in the age range 51 - 60 years, 30% of patients were in the age range 61 - 70 years, and 16% of patients were in the age range 71 - 80 years. There were only 6% of patients had an age in the range of 81 - 90 years. Hence it can be concluded that more than 77% of patients had an age greater than 50 years.

3. In our study 65 (65%) were male and 35 (35%) were female. Hence it shows that males are more prevalent than females.
4. The gender distribution concerning different age groups showed X^2 test =7.224, P-value =0.204. Statistically, no significant difference was found in the age group for the male/female ratio. (P-value <0.05 is considered significant since the confidence interval is 95%)
5. Types of stroke showed 80 (80%) were Acute ischemic strokes, 14 (14%) were Transient ischemic attacks, and 6 (6%) were Recurrent ischemic strokes. The majority of patients were diagnosed with Acute ischemic stroke.
6. The gender distribution was assessed concerning the type of stroke, the maximum number of male and female patients were diagnosed with Acute ischemic stroke with a total of 49 and 31 respectively. The minimum range was seen in Recurrent ischemic attack with the male and female count of 4 and 2 respectively showing X^2 test =9.3142, P-value =0.2078 which shows statistically no significant difference.
7. Stroke-based age distribution assessment showed X^2 test =9.157,P-value =0.5172 with no statistically significant difference.
8. Assessment of risk factors concerning the type of stroke shows maximum count in Hypertension with 54, 6, 8 (68 in total) in Acute ischemic stroke, Recurrent ischemic stroke, and Transient ischemic attack patients respectively. The test statistics were found to be X^2 test =3.709, P value =0.0882 with no statistically significant difference.
9. Classification of drugs used for different types of stroke showed a maximum of Aspirin (78%) use and minimum of Aspirin + Ticagrelor (1%) use. The test statistics were found to be X^2 test =6.667, P-value =0.572 with no statistically significant difference.
10. Comparison of age concerning the different types of drug prescribed showed ANOVA test statistics of f value of 2.1989 and corresponding p-value is 0.075 which is greater than 0.05, so there is no statistically significant difference.
11. Comparison of vitals (systolic blood pressure, diastolic blood pressure, and pulse rate) was assessed and the f value was found to be 1.8423, 0.1069, 2.6688 respectively and the corresponding p-value was found to be 0.1271, 0.9798 for SBP and DBP which is greater than 0.05, 0.0369 for pulse rate which is less than 0.05. Hence it can be concluded that there is a statistical significant difference in pulse rate.
12. Comparison of lab parameters (Haemoglobin, RBC, PCV, WBC, Platelet count) were assessed with ANOVA test statistics and their corresponding p-values showed no statistically significant difference.
13. Comparison of coagulation tests after drug use was assessed with ANOVA test statistics with f value for bleeding time and prothrombin time was found to be 0.4541 and 0.4525 and the corresponding p-value was found to be 0.7692 and 0.7703 respectively with no statistically significant difference.
14. The adverse effect of medication on patients concerning the type of drugs showed a total of 8 patients positive with maximum positive seen in patients taking Aspirin (4 out of 74), Aspirin-150mg+Clopidogrel-75mg (3 out of 6), Aspirin-75mg+Clopidogrel-75mg (1 out of 5). The test statistics were found to be X^2 test =9.943, P-value =0.041 with a statistical significant difference. The adverse reaction was seen in the maximum percentage of patients taking dual anti-platelet drug therapy.
15. Pharmacoeconomics study was done using the Cost Minimization Analysis (CMA) method.
16. The highest cost was seen in VASOGLOR A is Rs.472. The assessment showed a maximum % saving with respect to VASOGLOR A in TAB ECOSPRIN (96.27%) and a minimum % saving in TAB CLOPICARD (54.24%). So, TAB ECOSPRIN is the cost-effective drug among all the anti-platelet drugs prescribed.

VIII. CONCLUSION:

The prospective observational study with a sample size of 100 cases concludes that the evaluation of anti-platelet drugs for safety, efficacy, and cost-effectiveness in ischemic stroke and transient ischemic attack patients. In our study, the most common age group of patients was 61-70 years. The incidence for the males was 65% (N=65) and for females was 35% (N=35). Our study determined the prescribed drugs and conclude the safety, efficacy, and cost-effectiveness of anti-platelet drugs in stroke patients. For the appropriate use of prescribed drugs, several guidelines published should be followed in the daily clinical practice. Anti-platelet drugs prescribed for stroke patients in our Hospital were appropriate and followed ACC/AHA guidelines 2021. Anti-platelet drugs are safe and well-tolerated but may show negative effects in some patients leading to adverse drug reactions. Bleeding was seen as an adverse drug reaction in some patients which is dose-related or dual-therapy related. With the latest evidence of anti-platelet therapy, we reassured the clinician about the safety of anti platelet drugs.

Treatment with TAB ECOSPRIN costs 96.27% of saving compared with all other drugs shows a maximum percentage of saving and is cost-effective. Hence aspirin (TAB ECOSPRIN) has shown fewer adverse effects, more efficacy in treatment, and the highest percentage of cost-saving in stroke patients compared to all other mono and dual anti-platelet drug therapy.

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