A PROSPECTIVE OBSERVATIONAL STUDY ON INCIDENCE, IMPLICATIONS AND MANAGEMENT OF SEIZURES FOLLOWING STROKE

ABSTRACT: Background: Seizures following a stroke often indicate a more severe incident, typically resulting in extended hospital stays and a heightened risk of long-term disability. Management strategies generally include the use of anti-epileptic drugs to mitigate the frequency and severity of seizures**. Objectives:** this study aims to evaluate the incidence and risk factors assosciated for seizures after stroke, differentiating between acute symptomatic seizures and late seizures. Additionally, it assess dependency levels of patients after stroke and management of seizures after stroke.

METHODOLOGY: We conducted prospective observational study for 6 months which includes patients who were diagnosed with cerebrovascular accident, past history of cerebrovascular accident, experienced single or recurrent seizures of different types.

RESULTS: Out of 150 patients observed, 67 experienced seizures following stroke. Majority of these patients were male (99) predominantly aged between 50-75. Hypertension was found to be the major risk factor affecting 106(75.2%) individuals .Ischemic stroke were common. In terms of seizure occurrence, 27 patients experienced acute symptomatic seizure and 40 late onset seizure. Activity of daily living was assessed using Barthel Index Scale in which total dependency showed statistically significant relevance (P =0.01).

CONCLUSION: In summary, the leading cause of seizure in adults is stroke. While both ischemic and hemorrhagic stroke may increase the risk of seizure, our study reveals that occurrence of seizure is greater following ischemic compared to hemorrhagic. A clinical pharmacist plays a vital role in determining prophylactic AED treatment for stroke patients and monitor to improve patient's quality of life.

KEYWORDS: ischemic stroke, hemorrhagic stroke, seizures, post stroke epilepsy, antiepileptic drug.

NOTE – AED : Anti epileptic drug

1. INTRODUCTION

A seizure is the "transient occurrence of signs or symptoms due to abnormal excessive synchronous neuronal activity in the brain". Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequence of this condition.[1] The word seizure is derived from the sixth century Latin word 'seiz'[2] that means 'to take possession of'. Seizures may be provoked or unprovoked. Provoked seizures are also called as acute asymptomatic seizures, can occur as a result of electrolyte disturbances, acute toxic effects, sepsis, CNS infections, traumatic brain injury and stroke.[3] Unprovoked seizures are called as late seizures or remote symptomatic seizures.[4]

Stroke is defined as rapid onset of focal neurological deficit, resulting from diseases of the cerebral vasculature and its contents.The term 'transient ischemic attacks'(TIA) implies complete recovery of such a deficit within 24 hours. Cerebral or subarachnoid hemorrhage is consequent to rupture through some acquired or inherent weakness of the vessel wall. Stroke represents third most common cause of death in developed nations. For India, community surveys have shown a crude prevalence rate for 'hemiplegia' in the range of 200 per 100,000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical and around 20% of neurological cases.[2] The incidence rises steeply with age and in many lower and middle-income countries it is rising in association with less healthy lifestyles. About 20% of stroke patients die within a month of the event and at least half of those who survive are left with physical disability.[5]

Stroke is a significant trigger for newly diagnosed epilepsy in the elderly population. Post stroke seizure contributes to 30-50% of new seizure cases in individuals aged 60 and older.[6]

According to the Centers for Disease Control and Prevention (CDC), stroke is the fifth leading cause of death in the USA and is a major cause of serious disability in adults. Seizure is an important complication after stroke.[7] It is very difficult to predict the development of seizures after stroke,there are some known risk factors associated with a higher incidence of post-stroke seizures. In ischemic stroke: severity of the initial neurological deficit, the severity of persistent disability after the stroke, the involvement of multiple sites or a larger lesion, cortical damage and hippocampus involvement and embolic stroke are factors that predict the development of post- stroke seizures. In hemorrhage stroke: middle cerebral artery aneurysm and intra parenchymal hematoma predict the likelihood of post-stroke seizures. The presence of structural brain lesions, EEG abnormalities and partial type seizures also carry a higher recurrence rate.[8]

Seizure after stroke or post stroke seizure (PSS) can be divided into early seizure and late seizure. It has been reported that ischemic and hemorrhagic stroke accounts for about 11% of all adult epilepsy cases and 45% of epilepsy cases over 60 years of age. Early seizures are defined as seizures occurring within7- 30 days after stroke onset and seizures presenting thereafter are considered as late seizures. And this study concludes, Stroke is a very big challenge toneurology and health systems in general. Furthermore, stroke complications might be deleterious and potentially lethal. Both subtypes exert enormous damaging effect on the already suffering brain

parenchyma, with verified longer periods of hypoxia during convulsions.[7]

Note : CNS – Central Nervous System, EEG - Electroencephalogram

2. NEED FOR THE STUDY

- As stroke is the main leading cause of the seizure, so this study is conducted to summarize the recent literature regarding incidence and treatment of seizure after stroke which resulted in increased mortality rate.
- Seizures can result in loss of consciousness and voluntary control of the body increase the risk of falls, injury and trauma. So, the present study includes assessment of functional status by using Barthel Index Scale.

3. MATERIALSANDMETHODS

STUDY DESIGN: A Prospective observational study, was carried out in the Department of General Medicine, VIMS, Ballari District, Karnataka for a period of six months (From 8th of March 2023- 10th of August 2023). This study was conducted after obtaining approval from institutional ethics
committee of T.V.M college of Pharmacy Ballari (Ref.no: TVMCP/IEC/VPD/2022-23/04)

STUDY SAMPLE SIZE: The sample size was calculated by using the formula $n=Z^2pq/d^2$
$n= (1.96)^2*0.9*0.1/ (0.05)^2$
n- Required sample size,
Z-Reliability coefficient
n=138
p-estimated proportion,
d- Margin of error
The required minimum sample size was 138 patients. 150 was the achieved sample size.

SOURCE OF DATA: Data was collected from patient case sheets.

STUDY CRITERIA:
The study was carried out by considering the following inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Patient willing to sign informed consent form • Patient's age between 18 to 80 years of either sex • Patients diagnosed with and having past history of CVA • Patients experienced single or recurrent seizure of different types.	• Patients with other cerebrovascular diseases (meningitis,neuroinfection) • Pregnant women • Pediatric patient were excluded from this study.

MATERIALS USED: Materials include informed consent form, patient data collection form, BARTHEL INDEX scale.

STUDY PROCEDURE: Regarding this project pilot study was done. Various articles were collected and reviewed pertaining to the project. A study protocol, including study design and design of Performa was prepared. The ethical consent prior to study was obtained. Patients were enrolled according to the inclusion and exclusion criteria. The Patient's details were collected from the case sheet and assessed the activity of daily living using Barthel index scale. The obtained information were represented in the form of graphs and tables by using MS Excel sheets, and the report was submitted.

4. RESULTS AND DISCUSSION

4.1 Results

4.1.1 Distribution of patients according to gender

A total numberof 150 subjects were covered during the study period. Among 150 patients 99 (66%)were males and 51(34%) were female. The incidence of CVA range is more between age of 50-75(60.4%).

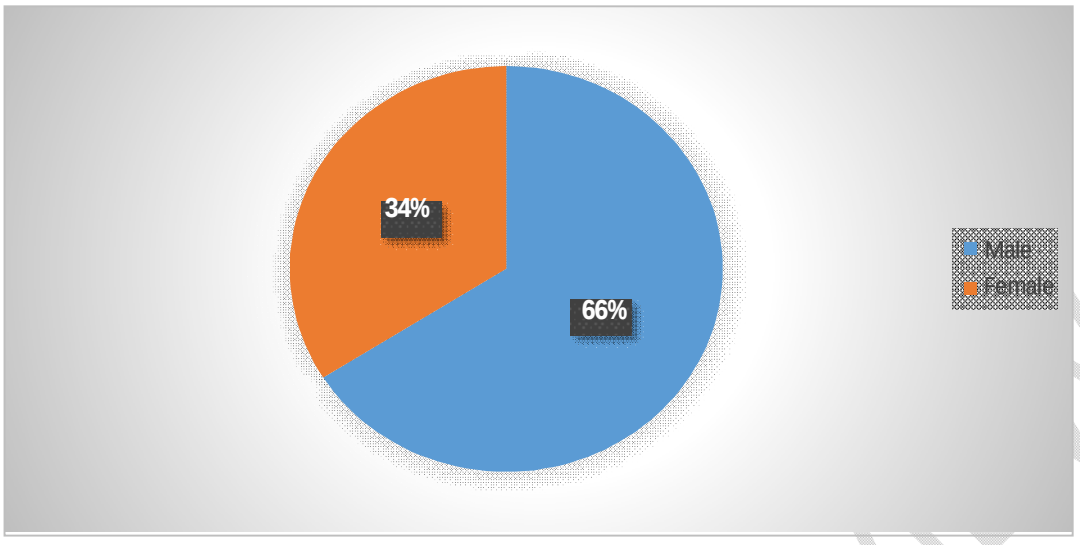

Figure01: Distribution of patients according to gender

Note : CVA – Cerebrovascular accident

4.1.2 Distribution of patients according to past history

In a study involving 150 patients, it was found that 49 individuals, accounting for 33.3% of the total participants, had a history of experiencing a stroke prior to the study. This indicates that approximately one-third of the patients had previously suffered from a stroke, suggesting a significant prevalence of prior stroke events within this group**.**

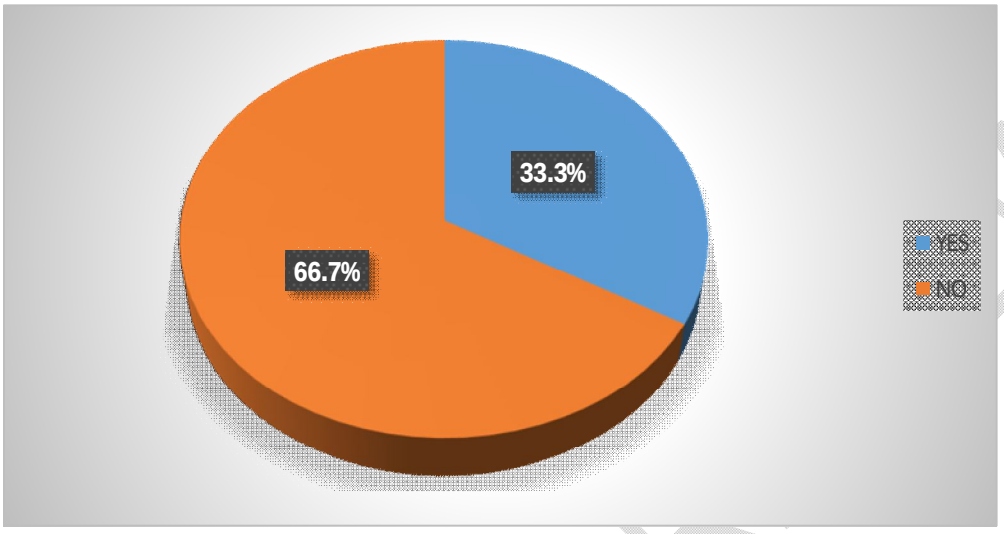

Figure02: Distribution of patients according to past history

4.1.3 Distribution of patients according to co-morbidities

Among the patients studied, a significant portion were found to have hypertension, with 106 individuals (75.2%) affected. Additionally, 27 patients (19.1%) had diabetes mellitus, while 35 patients (24.8%) were smokers. Heart disease was present in 12 patients (8.5%), and 51 individuals (36.2%) reported alcohol consumption. A smaller proportion of the group, 3 patients (2.1%), had a history of head injury or trauma. These findings highlight that hypertension was the most prevalent condition among the patients, followed by alcohol use and smoking.

RISKFACTORS	NUMBER(N=150)	PERCENTAGE(%)
HYPERTENSION	106	75.2
DM	27	19.1
SMOKING	35	24.8
HEART DISEASE	12	8.5
ALCOHOL	51	36.2
HEAD INJURY/TRAUMA	3	2.1

Table01:Distribution of patients according to co-morbidities

Note: DM:Diabetes Mellitus

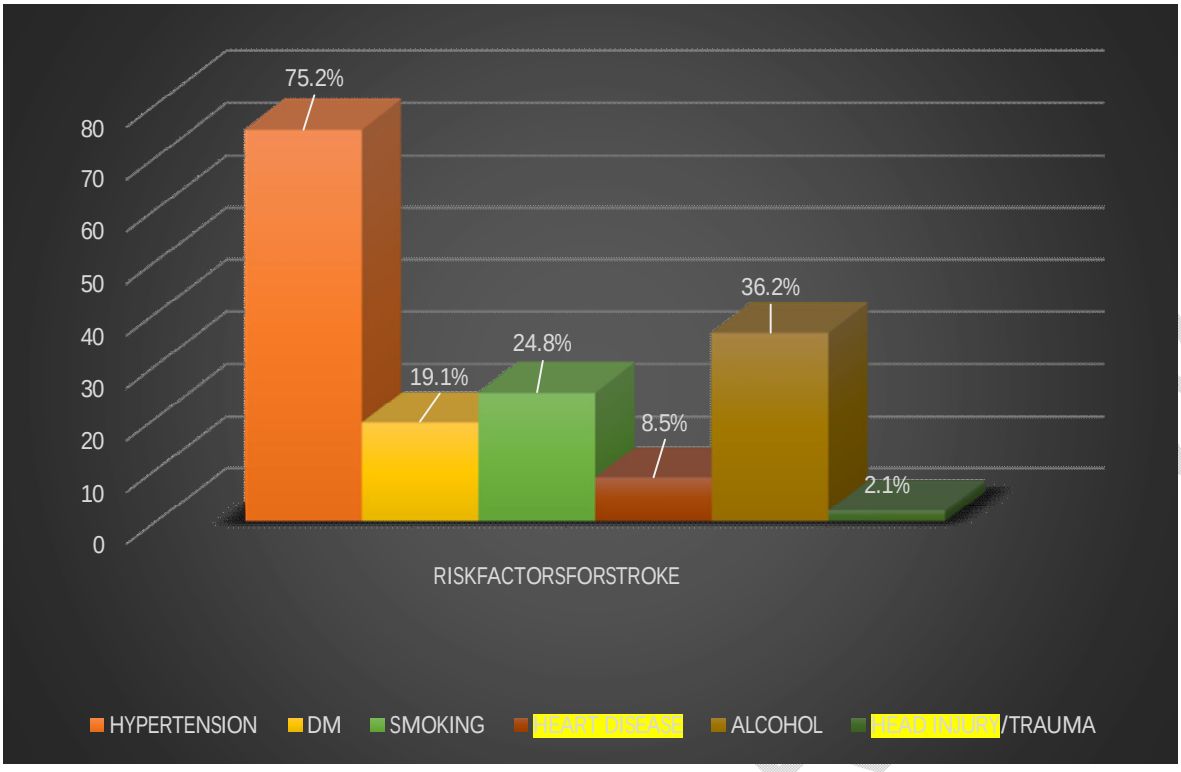

Figure03: Distribution of patients according to co-morbidities

4.1.4 Distribution of seizure in stroke patients

Upon analysis, it was found that out of the 150 subjects, 67 individuals (45.3%) experienced seizures following a stroke. This suggests that nearly half of the study population had a seizure as a complication or consequence of their stroke, indicating a substantial association between stroke and the occurrence of seizures in this group.

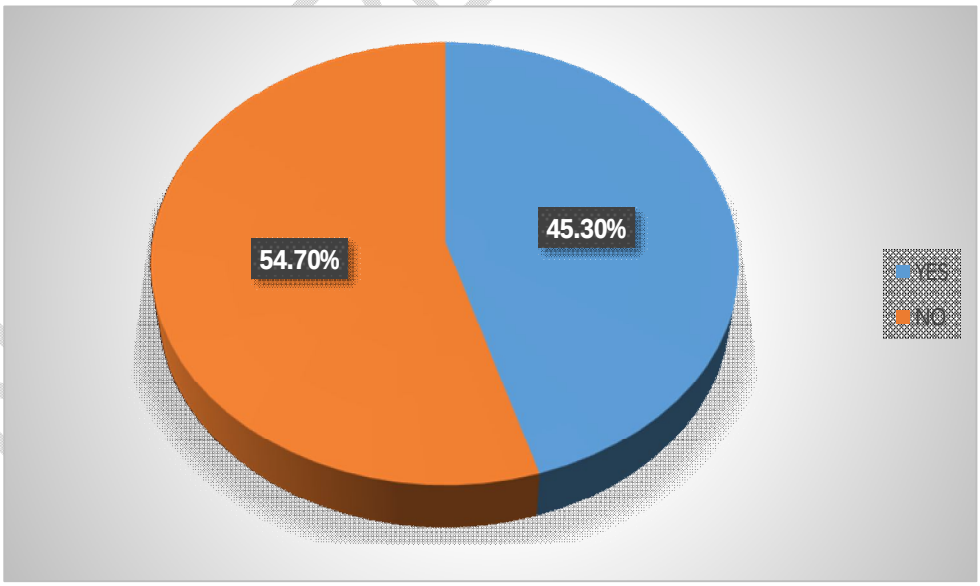

Figure04:Distribution of seizures in stroke patients

4.1.5 Risk factor of seizure following stroke

The analysis revealed that ischemic strokes were more prevalent than hemorrhagic strokes among the study population. Specifically, 71 individuals (55.5%) experienced ischemic stroke, making it the most common type. In comparison, 49 patients (38.3%) had hemorrhagic stroke. Additionally, 10 cases (7.8%) were attributed to age-related factors, while 12 patients (9.4%) had idiopathic strokes, where no specific cause could be identified. A small number of cases were linked to other factors, with 1 patient (0.8%) having a stroke due to family history and infections. These findings indicate that ischemic stroke is the dominant type in the studied group, with other causes being less common.

RISKFACTORS	NUMBER(N=150)	PERCENTAGE(%)
AGE	10	7.80%
FAMILYHISTORY	1	0.80%
IDIOPATHIC	12	9.40%
HEMORRHAGICSTROKE	49	38.30%
ISCHEMICSTROKE	71	55.50%
INFECTIONS	1	0.80%

Table02:Risk factor of seizure following stroke

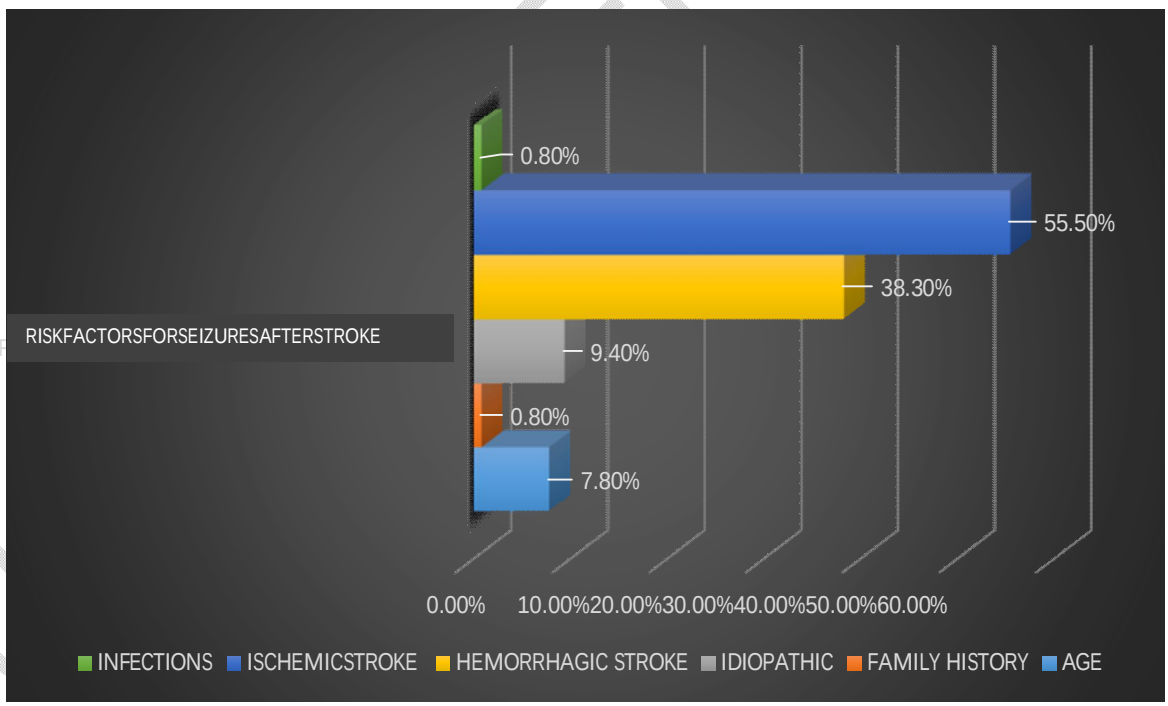

Figure05: Risk factors for seizure following stroke

4.1.6 Distribution of type of seizures

Based on the timing of seizure occurrence after a stroke, the seizures were categorized into two types. Among the 67 cases of seizures, 27 individuals (40.3%) experienced acute symptomatic seizures, which occurred shortly after the stroke event. The remaining 40 cases (59.7%) were classified as late-onset seizures, occurring later in the recovery period.

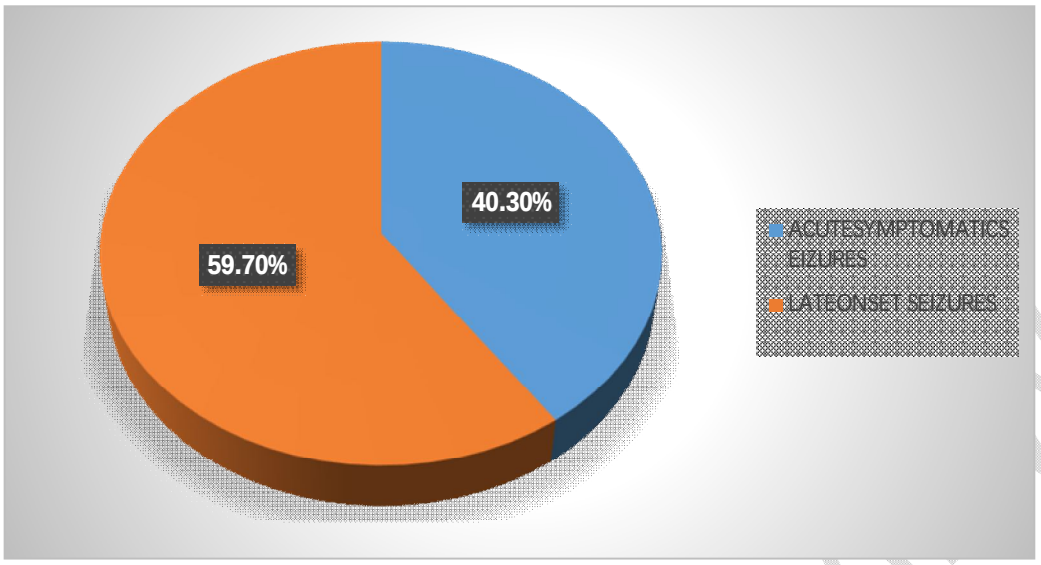

Figure06:Distribution of type of seizure

MANAGEMENT

The drugs that stroke patients receive or are prescribed may have unexpected interactions during an ischemic insult and recovery phase and even contribute to the development of PSS. The combination of ASMs must be individualized according to the patient's age, sex, co-morbidities and complications

Stroke patients require long term ant platelet drug as prevention, drug which are commonly used in our study is Aspirin, and Clopidogrel. Aspirin which has been shown to reduce risk of seizurespossibly by reduce electrolyte disturbance, tissue ischemia and hypoxia. Stroke patients require statins to reduce the cholesterol levels and in our study atorvastatin is the most prescribed drug. Statin protects cortical neurons from damage secondary to excitotoxicity and it is a neuro protective. They can also reduce the severity of stroke by increasing cerebral blood flow and decrease the risk of post stroke seizure.

The European stroke organization has issued evidence based guidelines on the management of post-stroke seizures. Due to limited evidence, guidelines offer only weak recommendations for preventing the occurrence and recurrence of post stroke acute symptomatic seizures and unprovoked seizures.

i. Primary AED prophylaxis – administration of an AED in patients without previous seizures in order to prevent seizure occurrence.

ii. Secondary AED prophylaxis – administration of AED in patients with at least 1 seizure in order to prevent seizure recurrence.

Due to very low incidence of ASS, administering primary prophylaxis is not suggested to all patients,[9] however in certain subgroups such as those with intracerebral hemorrhage involving the cortex, one in three patients may develop ASS. In these conditions, physicians may choose to temporarily administer primary AED prophylaxis on individual basis. [10]

Note: AED – Anti-epileptic drug, ASS – Acute symptomatic seizures, PSS – Post stroke seizure

DRUGS	NUMBER	PERCENTAGE(%)
LEVETIRACETAM	20	13.3
PHENYTOIN	60	40
MANNITOL	94	62
ASPIRIN	102	68
ATORVASTATIN	136	90
CLOPIDOGREL	57	38
LORAZEPAM	24	16
AMLODIPINE	75	50
METFORMIN	10	6.6
LABETALOL	20	13.3

Table03: Distribution of drugs used in management of seizures following stroke

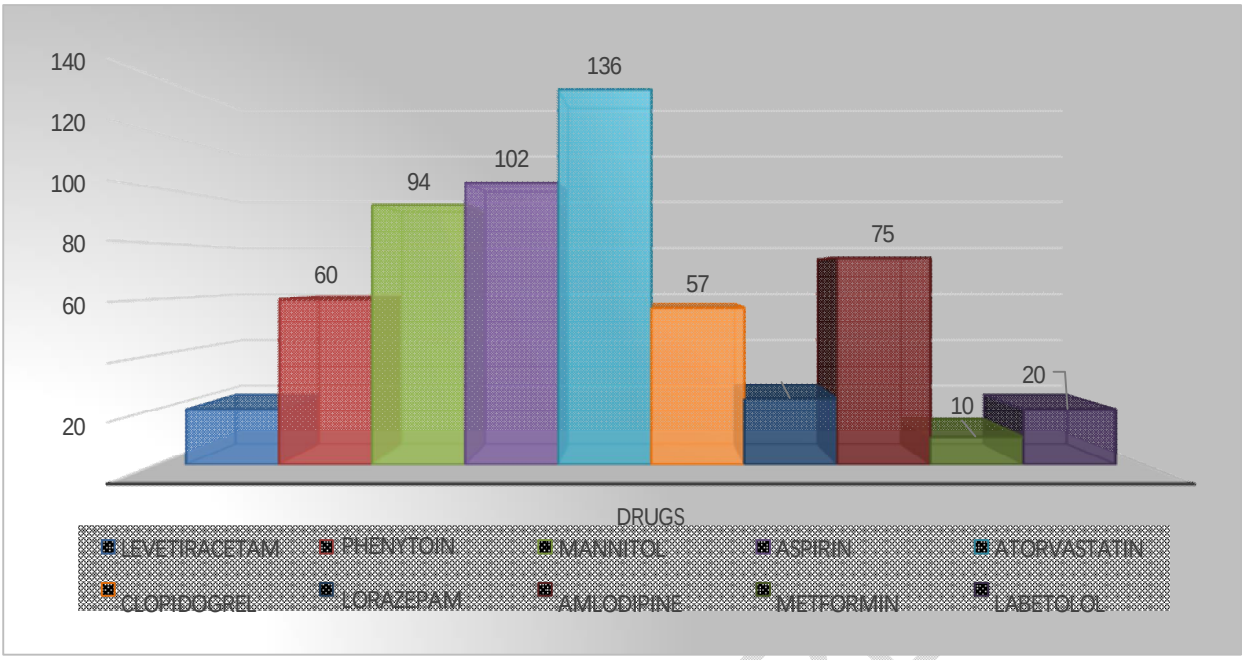

Figure07: Distribution of drugs used in management for seizures following stroke

Variables	Subjects with seizure/Total No of seizures	Percentage%	P
Sex-			
Male	49/97	50.51	0.008
Female	15/53	28.3	
Age-			
<60	36/82	43.9	0.33
>=60	22/68	32.35	
StrokeType-			
Ischemic	43/116	37.06	0.000095
Hemorrhagic	6/28	21.42	
Hemisphere-			
Left	28/74	37.31	0.49
Right	23/76	30.26	
SeizureType-			
Acute	25/67	37.31%	0.088
Late	42/67	62.68%	

Table04: Incidence of seizure based on various characteristics

DEPENDENCY	CI	Ztest	P
TOTALDEPENDENT	0.0015	-2.36	0.009
SEVERE DEPENDENT	0.0007	0.432	0.003
MODERATE DEPENDENT	0.0014	-1.08	0.14
SLIGHT DEPENDENT	0.0001	0.999	0.001

Table05: Assessment of activity of daily living using Barthel index

4.2 Discussion

A prospective observational study was conducted to investigate the incidence, implications, and management of seizures following stroke. The study considered various eligibility criteria such as age, gender, type of stroke, and past history. The patient data was collected through self-designed data collection forms, including a face, arm, limb, speech test to determine acute and late onset seizures. The dependency rate after stroke was calculated using the BARTHEL INDEX SCALE.

Stroke is the third leading cause of death and a major cause of disability in developed countries with an estimated 12 million cases annually. Stroke survivors have an increased risk of seizures,with stroke being the most common cause of acquired epilepsy in adults, accounting upto 70% of cases.People with stroke can experience both early and late seizures,seizures occurring within 7days after stroke and more than 7 days respectively. PSE associates carry higher mortality and negatively impact the quality of life.

In our study we had a sample size of 150 patients, out of which 99(68%) were male and 51(34%) were female.This is contrast with **Chienchenchouet.al;**[11] who conducted study on 132 subjects out of which 88(66.6%) were male and 44(33.3%) were female.

We included patients between the age group of 18-80,were most of these are from age group of 50-75.Of which 36 patient's of age <60 got PSE. These results were similar to the study conducted by **Chien chen chou et.al;**[11] where the majority of the patients were from theage34-94.The mean age of PSE was 74.5years.

Hypertension(75.2%), alcohol(36%) and smoking(24.8%) were the most common risk factor among stroke patients in our study, followed by Diabetes (19.1%), Heart disease (8.5%) and Head injury (2.1%) has similar results with the study conducted by **V R Bhatt et.al;**[12] among 61 patients where hypertension (74%), physical inactivity(62%) and smoking (57%) were the risk factors.

Stroke is the major cause for seizures in our study total 116(77.3%) ischemic stroke and 28(18.6%) were hemorrhagic stroke. Incontrast to **Cinziacostaet.al;**[13] most of the vascular events were ischemic stroke (n=8,428, 76%) and (2665, 24%) were hemorrhagic stroke

Patients with post stroke seizures can experience with early and late onset seizures.The ILAE classification that occur within 7 days of stroke as acute or early symptomatic seizures, seizures occurring after 7days of stroke are considered as late onset seizures. In present study among total 67 seizures patients, 42 were late onset seizures and 25 were acute or early onset seizures. This is compared with the study done by **Christopher F Bladin et.al;**[14] they concluded frequency of seizures as a late sequealae of stroke has been estimated previously at 3% to 10% with higher risk after late onset than early onset seizures.

In our study we assessed the dependency rate of stroke patients and activity of daily living using BARTHEL- INDEX scale. Which consists of 10 variables that utilizes 0-100 points rating in which 0 reflects the least favorable outcome and 100 reflects the most favourable outcome, within 0-100 points it is divided into 4 groups score, (0-20) indicates total dependency, score (21-60) indicates severe dependency, score (61- 90) indicates moderate dependency and score (91-99) indicates slightly dependency.

Among these 4 dependency rate total dependency (p=0.01) found to be statistically significant. In this way the functional status was assessed.This is in contrast with **Maria Stefanidouset.al;**[15] conducted a study in which stroke severity, disability and functional status after stroke have beenstudied as a predictor of subsequent seizures and they had found moderate and severe disability after stroke predicted a higher risk of seizures. Seizures were significantly associated with moderate (p=0.01) and severe disability (p=0.001) as well as with Barthel index scale <60 (p=0.001).

Present study determine the incidence of seizures based on characteristics such as Sex, Age, Stroke type, Hemispheric type and seizures type. The results were as follows, out of 97 male, 49 (50.51%) got PSS and out of 53 female, 15 (28.3%) got PSE and p=0.008 were found to be statistically significant.

The age group is divided into <60 and ≥60 years. 43.9% were age group of <60 years and 32.354% were of age group of ≥ 60 years (p=0.33).

Stroke is classified into 2 types Ischemic and Hemorrhagic. Out of 116 Ischemic patient 43 individuals got PSS (37.06%) out of 28 Hemorrhagic 6 got PSS (21.42%).This indicates Ischemic stroke type is a major risk factor in our study (P=0.000095) found to be statistically significant.

Out of 74 left side affected stroke early patient 28 got PSE (37.83%) and out of 76 right sided affected stroke patient 23 got PSE (30.26%).

PSE are of two types early/acute and late onset seizures. In our study total 67 individual were diagnosed as PSS, among them 25 (37.31%) were diagnosed as acute/early onset seizures and 42(62.68%) were late onset seizures. In comparison with the study done by **Christopher F Bladin et.al;**[14] they concluded frequency of seizures as a late sequalae of stroke has been estimated previously at 3% to10% with higher risk after late onset than early onset seizures.

In our prospective observation studies which is conducted for total population of 150 individuals to determine management of seizures after stroke.

In our study among 150 population, Atorvastatin has been the choice of drug for most of individual (136), which is an inhibitor of 3-hydroxy-3-methylbutaryl co-enzymeA (HMG-CoAreductase) has neuroprotective, antithrombotic, anti-inflammatory and anti-oxidation property reducing the risk of seizures and PSE and in addition to cholesterol lowering effect, statin protects cortical neuron from damage secondary to excitotoxicity, thereby preventing the development of seizures.

Aspirin has been second choice of drug which is prescribed for 120 individuals which acts as anti-platelet agent which reduces the risk seizures.Which is also shown in the study conducted by **Beata sarcha Hujar et.al;**[16] aspirin and zapamycin due to their anti-inflammatory action are considered in the prevention of PS epliliptogenesis.

Mannitol was prescribed for 94 individuals which is mainly used to treat cerebral edema in case of hemorrhagic stroke.

In our study hypertension/high blood pressure found to be the major risk factor for PSS. Amlodipine was prescribed to treat hypertension which is a calcium channel blocker (CCB) lowers the seizures threshold and possess antiepileptic properties by calcium influx. Phenytoin and leviteracetam which are antiepileptic drug acts by enhancing sodium efflux from neurons of motor cortex.This cellular events tends to stabilize the threshold against hyper excitability results fromexcessive stimulation as evidenceof prescribing phenytoin or phenobarbitone to each patient whohad early and late PSS. In our study most of individuals have DM, for management of DM, Metformin is widely accepted drug which crosses BBB and neuro protective. Chronic Metformin treatment decreases mortality, shorten the duration of GTCS.

Note : CCB – calcium channel blocker, GTCS – generalized tonic clonic seizure.

5. Conclusion

According to WHO, stroke is defined as rapidly developed clinical signs of focal disturbance of cerebral functions, lasting more than 24 hours or leading to death with no apparent cause other than vascular origin. Seizures episodes are results of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges.

In summary, cerebrovascular accident is the primary cause of new onset seizure in older adults responsible for almost 50% of all cases. The decrease in stroke mortality rates is attributed to advancements in stroke treatments such as intravenous throembolysis, improved patient care in stroke unit and better risk management. While both ischemic and hemorrhagic stroke may increase the risk of seizures. In our study ischemic stroke is greater compared to hemorrhagic stroke. The timing of seizures in relation to the onset of stroke is also an important factor. On analysis it was found that out of 150 subjects, 45.2% were having seizures following stroke.

A clinical pharmacist play a vital role in determining the prophylactic AED treatment forstroke patient and monitoring them to reduce burden of disease and improve their quality of life. Activity of daily living of the stroke patient is determined by using Barthel index scale which helps to assess patient ability to do his/her activity i.e., dependency rate. Total dependency which ranges from 0-20 determines the patient is completely dependent on others which have been found in our study population.

The clinical pharmacist in collaboration with physicians and other health care professionals contribute to the proper management of seizures occurring after stroke by monitoring treatment they receive and carrying out their own assessments of patients.

6. Recommendations/ clarifications/ suggestions.

- Stroke patients should be monitored for a longer period of time to assess the likelihood of seizures developing.
- Since seizures have a detrimental effect on patient's and their families quality of life, prompt detection and effective seizure management are crucial for enhancing patient care outcomes.
- There are currently no guidelines for the use of AEDs after strokes. Additional research is required to evaluate the advantages and risks of preventive usage following stroke.

7. Strength and Limitations.

Strength:

- Our research aids in the identification of key stroke risk factors.
- In our study incidence of seizure is associated with ischemic type of stroke.
- Activity of daily living was evaluated in post-stroke patients using the Barthel Index Scale.

Limitations:

- EEG is not used as a diagnostic tool to rule out subclinical activity of seizures.
- The activity of daily living of stroke patients was not assessed before the treatment.
- Our study did not include prophylactic treatment for seizures.
- In our study,the onset of seizures was limited to7days following stroke.
- The majority of the patients were men, demonstrating gender prejudice.

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Consent for publication

The authors have given their consent for publication

Ethical approval

The protocol was verifiedby Institutional Ethics Committee(IEC) of T.V.M College of Pharmacy, informed consent form was obtained from the guardians of the study subjects.

Abbreviations

- AED – Anti epileptic drug
- CNS – Cemtral nervous system
- TIA – Transient ischemic attack
- CDC – Centers for disease control and prevention
- EEG – Electroencephalogram
- PSS – Post stroke seizure
- CVA – Cerebrovascular accident
- DM – Diabetes mellitus
- ASM – Anti seizure medications

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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