

APROSPECTIVEOBSERVATIONALSTUDYONINCIDENCE,IMPLICATIONSAND MANAGEMENT OF SEIZURES FOLLOWING STROKE

ABSTRACT:Background: Seizure following stroke are generally associated with more severe stroke which can lead to longer hospital stays, higher risk of disability, management typically involves anti-epileptic drugs or anti-convulsant to reduce seizure frequency and severity. **Objectives:** To determine incidence and risk factors for seizures after stroke. To determine acute symptomatic seizures and late seizures. To assess dependency of patients after stroke. To assess seizure management after stroke.

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

RESULTS: Among 150 patients, 67 were having seizures following stroke. Majority of the patients were males (99) and of age range between 50-75. Hypertension was found to be the major risk factor 106(75.2%). Ischemic stroke were common. On the basis of time of occurrence, 27 were found to be acute symptomatic seizure and 40 were late onset seizure. Activity of daily living was assessed using Barthel Index Scale in which total dependency was statistically significant ($P = 0.01$).

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, poststroke epilepsy, antiepileptic drug.*

1. INTRODUCTION

SEIZURE

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. The word seizure is derived from the sixth century Latin word ‘seiz’ 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. Unprovoked seizures are called as late seizures or remote symptomatic seizures.

STROKE

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.[I] 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.[II]

SEIZURES AFTER STROKE

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.[13] 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 intraparenchymal 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.[23]

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 within 7- 30 days after stroke onset and seizures presenting thereafter are considered as late seizures. And this study concludes, Stroke is a very big challenge to neurology 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.

2. MATERIALS AND METHODS

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 March 2023-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 $n = Z^2 pq / d^2$
 $n = (1.96)^2 * 0.9 * 0.1 / (0.05)^2$ 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: Patient willing to sign informed consent form, patient's age more than 18 years, patients diagnosed with and having past history of CVA, patients experienced single or recurrent seizure of different types.

EXCLUSION CRITERIA: 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.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Distribution of patients according to gender

A total number of 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%)

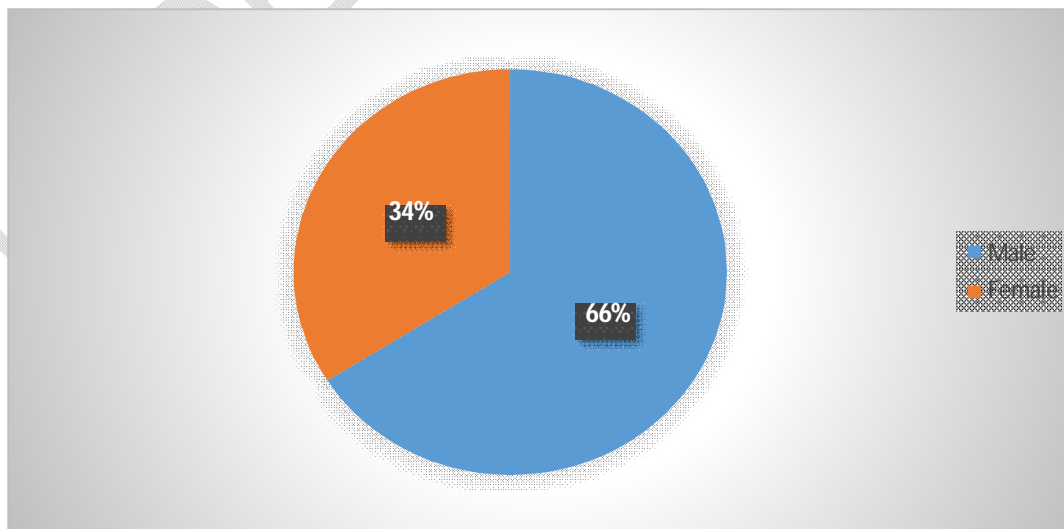


Figure01:Patientsaccordingtogender

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3.1.2 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.

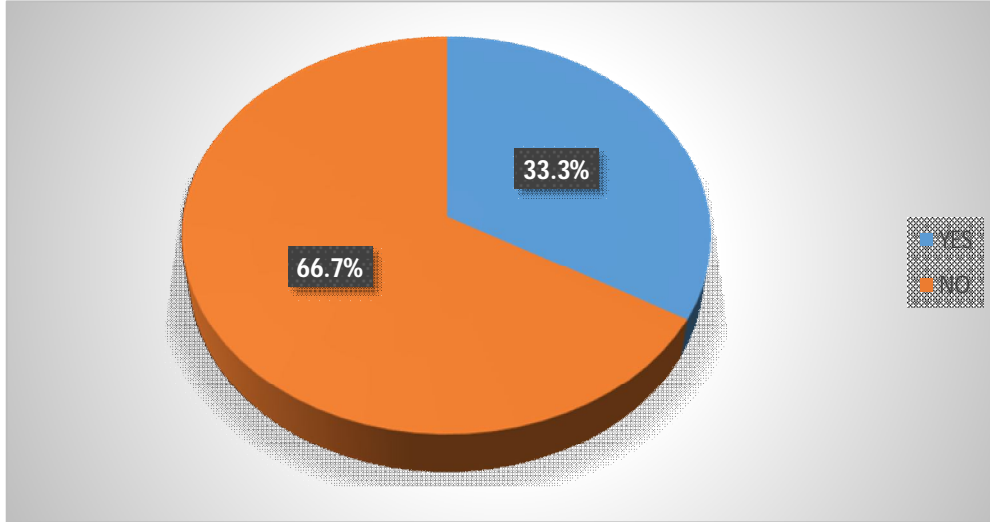


Figure02: Patient according to past history

3.1.3 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.

RISK FACTORS	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

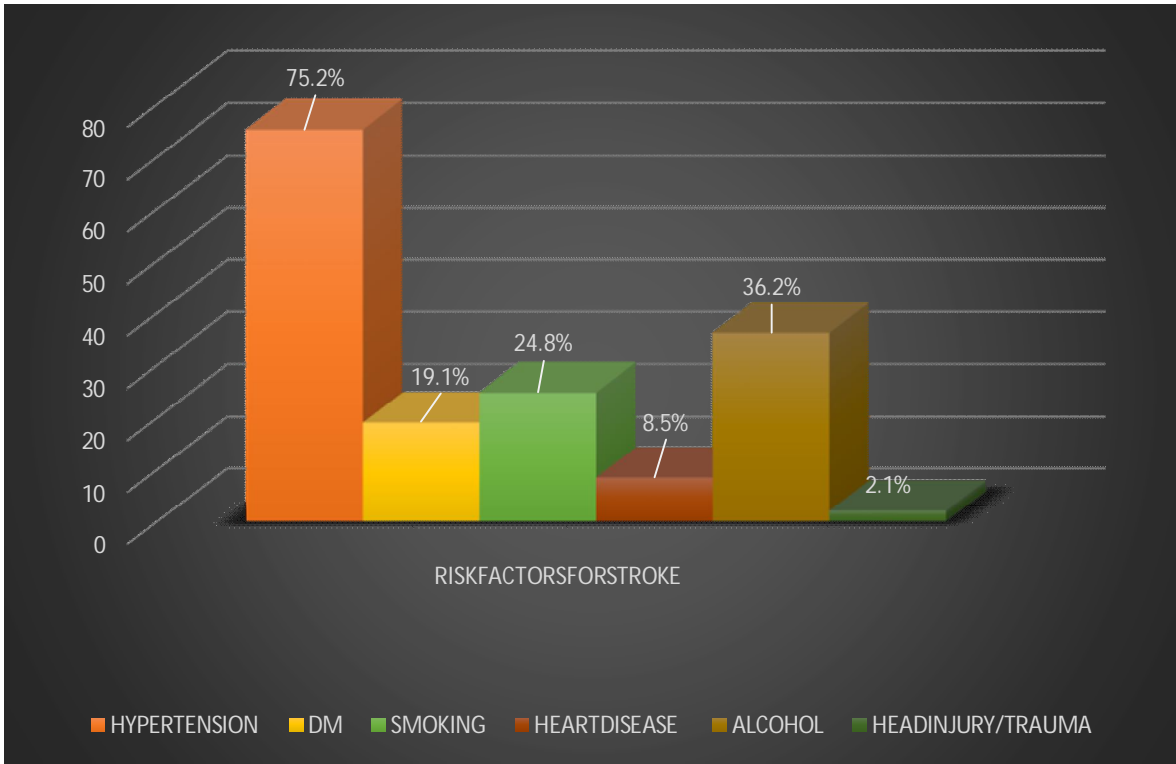


Figure03:Patientaccordingtoco-morbidities

3.1.4 Distributionofseizureinstrokepatients

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.

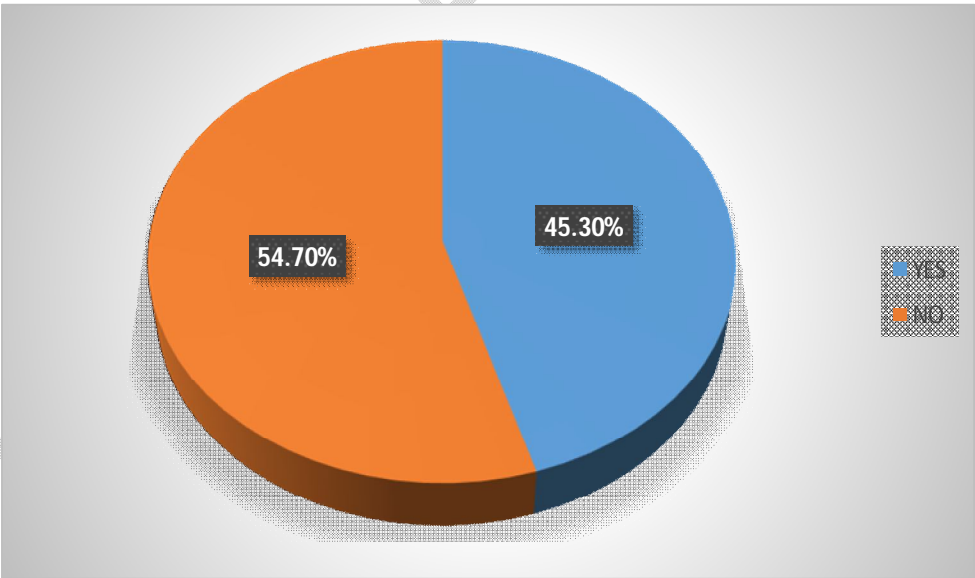


Figure04:Patientaccordingtoseizuresinstrokepatients

3.1.5 Riskfactorofseizurefollowingstroke

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.

RISKFACORS	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:Riskfactorofseizurefollowingstroke

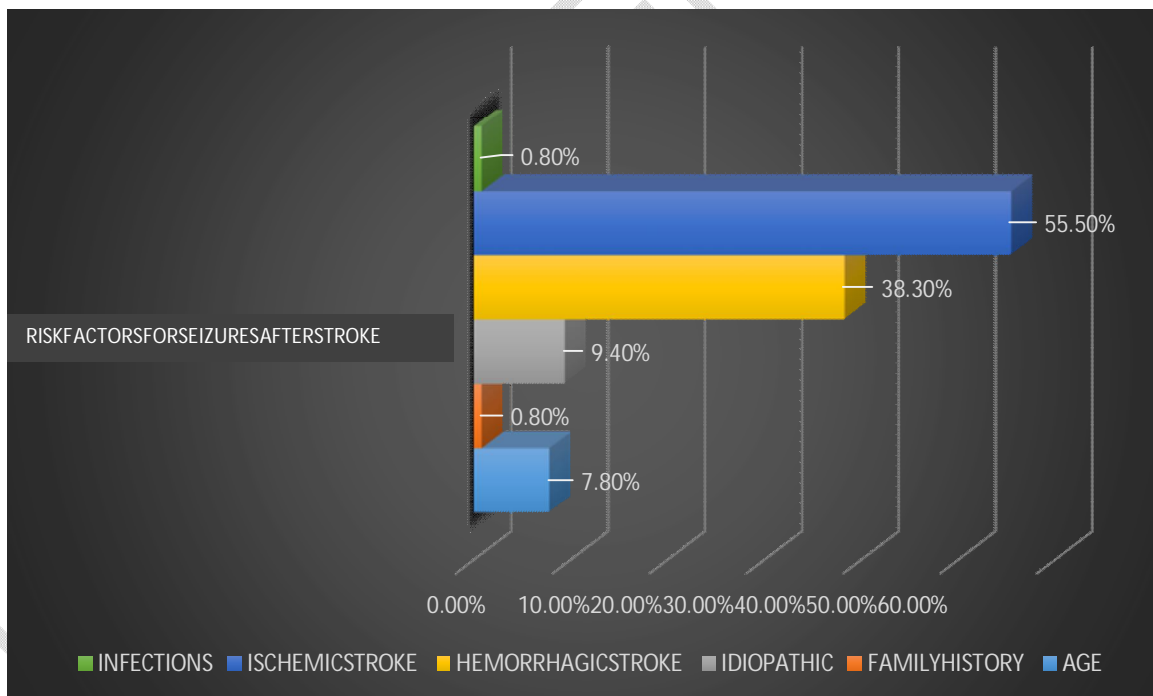


Figure05:Riskfactorsforseizurefollowingstroke

3.1.6 Distributionoftypeofseizures

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.

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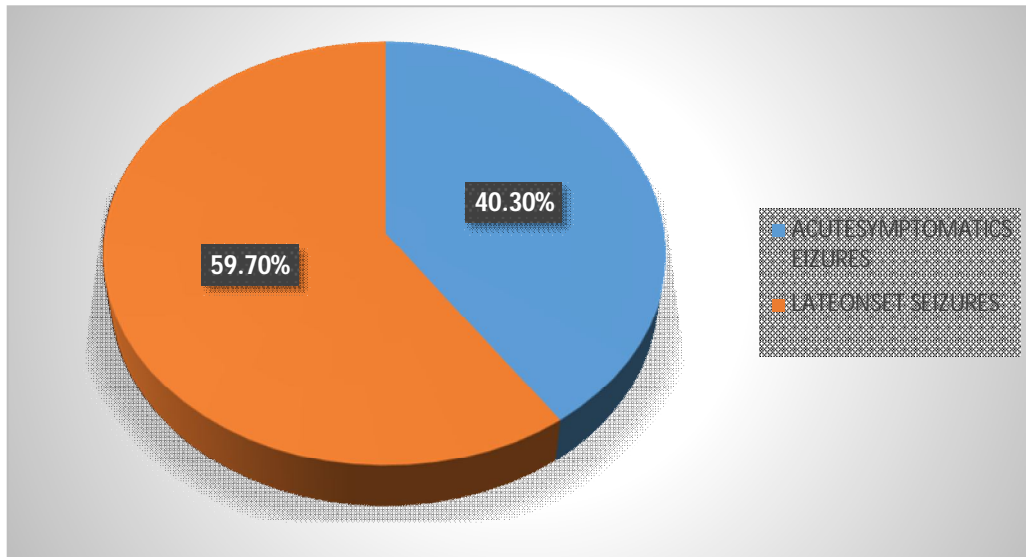


Figure06:Typeofseizure

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 PSE. 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 seizure possibly by reduce electrolyte disturbance, tissue ischemia and hypoxia. Stroke patients require statins to reduce the cholesterol levels and in our study atorvastatin was mostly prescribed drug. Statin protects cortical neurons from damage secondary to excitotoxicity and it is a neuroprotective. They can also reduce the severity of stroke by increasing cerebral blood flow and decrease the risk of 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:Distributionofdrugsusedinmanagementofseizuresfollowingstroke

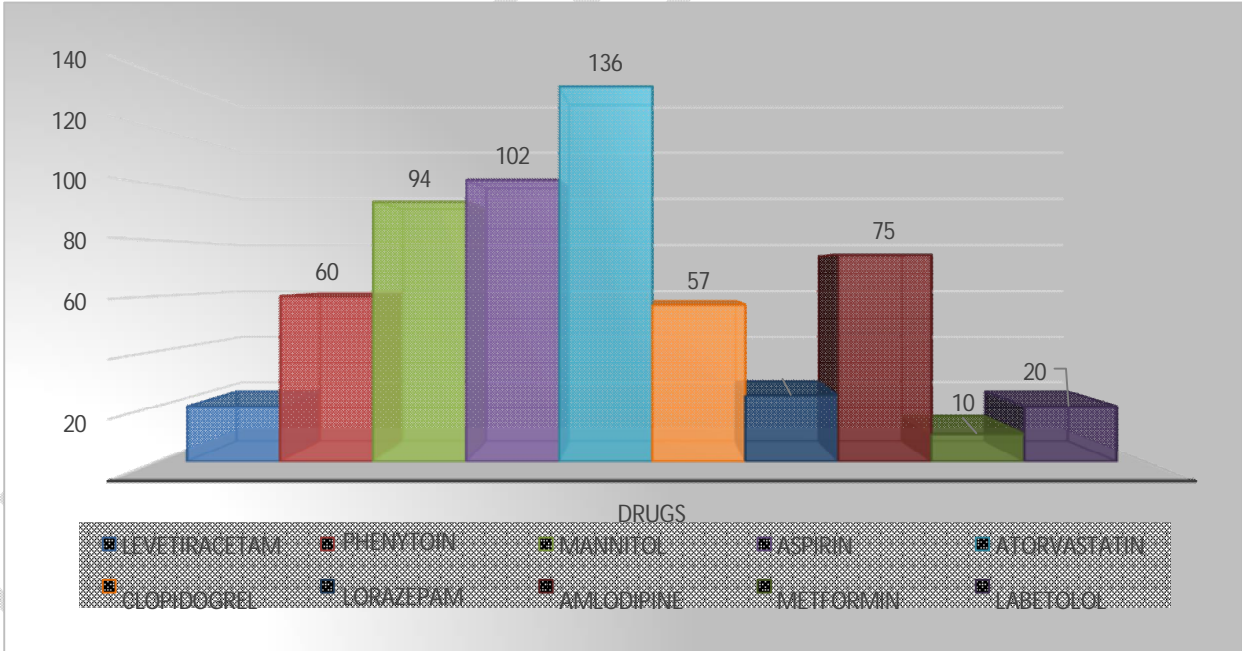


Figure07 :Distributionofdrugsusedinmanagementforseizuresfollowingstroke

Variables	Subjectswithseizure/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:Incidenceofseizurebasedonvariouscharacteristics

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:AssessmentofactivityofdailylivingusingBarthelindex

3.2 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 up to 70% of cases. People with stroke can experience both early and late seizures, seizures occurring within 7 days 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 **Chien chen chou et.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 patients 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 the age 34-94. The mean age of PSE was 74.5 years.

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. In contrast to **Cinziacosta et al.**;[13] most of the vascular events were ischemic stroke (n=8,428, 76%) and (2665, 24%) were hemorrhagic stroke

Patient with poststroke seizures can experience with early and late onset seizures. The LAE classification that occur within 7 days of stroke as acute or early symptomatic seizures, seizures occurring after 7 days 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 sequelae 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 Stefanidou et al.**;[15] conducted a study in which stroke severity, disability and functional status after stroke have been studied as a predictor of subsequent seizures and they had found moderate and severe disability after stroke predicted a high 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 seizure type the results were as follows, out of 97 male, 49 (50.51%) got PSE 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 PSE (37.06%) out of 28 Hemorrhagic 6 got PSE (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 PSE, 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 sequelae of stroke has been estimated previously at 3% to 10% 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-enzyme A (HMG-CoA reductase) 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 agents which reduce the risk of seizures. Which is also shown in the study conducted by **Beetasarcha Hujar et.al**; [16] aspirin and zapamycin due to their anti-inflammatory action are considered in the prevention of PS epileptogenesis.

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

In our study hypertension/high BP found to be the major risk factor for PSE. 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 drugs act by enhancing sodium efflux from neurons of motor cortex. This cellular event tends to stabilize the threshold against hyper excitability results from excessive stimulation as evidence of prescribing phenytoin or phenobarbitone to each patient who had 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, shortens the duration of GTCS.

4. 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.

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges.

In summary, the leading cause of seizures in adults is stroke which ranges between age of 50-75. Hypertension was found to be the major risk factor for seizures. 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 for stroke 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 helpsto 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.

5. Strength and Limitations

STRENGTHS:

- 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 to 7 days following stroke
- The majority of the patients were men, demonstrating gender prejudice.

6. Scope for future study

- 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 patients' and their families' quality of life, prompt detection and effective seizure management are crucial for enhancing patient care outcomes.
- There are recurrently no guidelines for the use of AEDs after strokes. Additional research is required to evaluate the advantages and risks of preventive usage following stroke.

Consent for publication

The authors have given their consent for publication

Ethical approval

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

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