COMPARISON OF FUNCTIONAL OUTCOMES AND AED DRUGS USED IN ISCHEMIC STROKE PATIENTS WITH AND WITHOUT SEIZURES.

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ABSTRACT

Introduction: stroke is common neurological disorder all over the world. **Objective:** To compare the functional outcome of acute ischemic stroke patients presenting with and without seizures and to evaluate the preferred antiepileptic drug used in those patients. **Methods:** This was a cohort study conducted at the department of emergency and neurology of Liaquat University of medical and health sciences hospital, Hyderabad and Jamshoro from September 2017 to December 2019. Two hundred patients of age 16-80 years of either gender presenting with acute ischemic stroke were included using non-random consecutive sampling method. Patients were investigated for information consisting of demographic details, comorbids, imaging reports and stroke etiology. EEG was done to classify the seizure types and the severity of stroke was measured by NIHSS (National institutes of health stroke scale) score. Patients were then treated with antiepileptic drug according to co-morbid conditions. Stroke functional outcome was measured by modified Rankin scale on discharge while seizure control was monitored by recurrence of clinical and subclinical seizures. Statistical software SPSS version 23 was used to analyze data. **Results:** The mean age of the patients was estimated as 56.98±8.78 years.Statistically significant association was found between functional outcomes and NIHSS score, stroke etiology and seizures ($p \leq 0.05$).Out of 28 patients with treated with levitiracetam, 85.7% experienced recurrence of clinical and subclinical seizures while in 20 patients treated with lacosamide, no recurrence was observed. The statistically significant association was found between AED drug used and recurrence of seizures ($p<0.05$). **Conclusion:** In stroke patients stoke severity in terms of higher NIHSS score, stroke etiology and seizures are the independent determinants of poor outcome. Lacosamide was observed best AED drug in terms of prevention of recurrence and better outcome of stroke.

Key Words: Acute ischemic stroke, seizures, antiepileptic drugs, poststroke seizures, early seizures, mRS score, NIHSS score

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INTRODUCTION

Globally, cerebrovascular accidents (stroke) is the 2nd leading cause of mortality and 3rd leading cause of disability.[1] Overall 70 percent of strokes and 87 percent of both disability-adjusted life years and deaths happen in low and middle income nations. Whereas in high income nations the burden of stroke is appears to be decreasing.[2] Stroke is classified asischemic or hemorrhagic stroke based on thesite,etiology or age of the patient. Of all the strokes, the ischemic stroke account for 85%.[3]In Pakistan, the prevalence of ischemic stroke is reported as 72%.[4]

Seizures is an established potential complication of ischemic stroke and can occur either during acute stage (within 24 hours to 14 days) or during follow-up period (up to the initial 4 weeks) of the stroke.[5] The overall frequency of post ischemic stroke is estimated as 2 to 33%[6,7], out of which 1.8 to 15% occur at stroke onset and 50-78% occur within 24 hours after stroke.[7,8] Evidence on potential predictorsfor the incidence of post-stroke are vague. Hence, a meta- analysis showed that severity and type of stroke, cortical involvement and use of alcohol are potential predictors for the development of seizures.[9] The data regarding the impact of post-seizures on functional outcome are inconsistent[10-12], few researches showed high fatality and worse outcomes, while other researchers reported no such effect.[13, 14]

There is no specific protocols for the managingpost stroke seizures patients. Therefore, the treatment through antiepileptic drug (AED) is the only option for physicians and patients. Recent research by Larsson et al., showed patients with post stroke epilepsy, survival rates are highest withlamotrigine and levetiracetam, and lowest for phenytoin and carbamazepine.[15] Another review revealed that

the treatment with lamotrigine and levetiracetam were better tolerated than carbamazepine.[16]

Best functional outcome after this disabling is mainstay of management that needs early recognition and treatment of variables contribute in poor functional outcome. In developing countries like Pakistan there is limited resources allocated for such patient's welfare and rehabilitation leading to burden for patients and their families. Therefore in such scenario it is primary duty of stoke physicians to identify and treat the factors of poor outcome during acute care /hospital stay, which can forecast the optimal functional outcome of the patient. Further, there is scarcity of local data from which we can assess the effect of post stroke seizures in patients of acute ischemic stroke. So, the aim of this research was to compare the functional outcome of acute ischemic stroke patients presenting with and without seizures and to assess the best AED used in stroke related seizures.

METHODOLOGY

This was a cohort study conducted at the department of emergency and neurology of Liaquat University of medical and health sciences hospital, Hyderabad and Jamshorofrom September 2017 to December 2019. Sample size of 199≈200 was estimated using frequency of seizure among ischemic stroke patients as 7.2%[6], bond on error as 3.6% and 95% confidence level. All the patients of age 16-80 years of either gender presenting with acute ischemic stroke were included using non-random consecutive sampling method. Patients with pre-existing neurologic disorders (like stroke, head stroke, head trauma, and hypoxic encephalopathy, seizure disorders or epilepsy or patients taking AEDs for trigeminal neuralgia or neuropathic pain) were excluded.

The research protocol was approved by Ethical Review Committee. Informed consent was obtained from attendants of each patient. Patients were admitted and investigated for consisting of demographic details, comorbids, imaging reports and stroke etiology. EEG was done to classify the seizure types. For patients with post-stroke seizure, the severity of stroke was measured by NIHSS (National institutes of health stroke scale) score. Patients were then treated with antiepileptic drugs according to co-morbid conditions. Mainly used drugs were levitiracetam, sodium valproate and lacosamide. Stroke functional outcome was measured by modified Rankin scale on discharge while seizure control was monitored by recurrence of clinical and subclinical seizures. All themedications and outcomes were recorded in the proforma by researcher himself.

Statistical software SPSS version 23 was used to analyze data. Mean and SD was reported for numeric variables. Frequency and percentage was reported for categorical variables. Fisher exact/Chi square test was applied to see the association of NIHSS at admission, stroke etiology, seizures, type of seizures and AED drugs with functional outcomes.P-value≤0.05 was taken as statistically significant.

RESULTS

Total 200 patients were enrolled in the study with acute ischemic stroke. The mean age of the patients was estimated as 56.98±8.78 years. Most of the patients were of age 51-60 years (n=104, 52%), followed by more than 60 years (n=68, 34%) and less than 51 years (n=28, 14%). Out of 200 patients, 141 were males (70.5%) and 59 were females (29.5%). One thirty two patients had hypertension (62.4%), 126 had diabetes mellitus (65.3%), 47 had dyslipidemia (23.3%), 38 were smokers (18.8%), 27 had ischemic heart disease (13.4%) and 13 had atrial fibrillation (3.5%).

The NIHSS score at the time of admission was estimated as 18.20±3.85 ranging from 10 to 28.The most common etiology of stroke was thromboembolic (42.5%), followed by intracranial arterial stenosis (31%) and cardioembolic (19.5%) respectively. (Fig 1)

Among 200 patients, 49 patients had seizures (24.5%). Of these 49 patients, 38 patients had focal seizures (19%) and 11 had *generalized* seizures (5.5%).(Fig 2)

Regarding medication, 49 patients with seizures were treated with AED. Of these 49 patients, 28 were treated with levitiracetam (14%), 20 were treated with lacosamide (10%) and only one with valproate (0.5%). Out of 28 patients treated with levitiracetam, 85.7% experienced recurrence of clinical and subclinical seizures while 20 patients treated with lacosamide, experienced no recurrence. The statistically significant association was found between AED drug used and recurrence of seizures ($p<0.05$).

Out of 200 patients at the time of discharge, 80 patients had mRS score 4 (moderately severe disability) (40%), 41 had mRS score 5 (severe disability) (20.5%), 39 had mRS score 3 (moderate disability) (19.5%), 17 had mRS score 2 (slight disability) (8.5%) and 23 had mRS score 6 (expired) (11.5%). (Fig 3)

The patients with NIHSS 16-20, 17.4% expired, 63.4% had severe disability and 67.5% had moderately severe disability. There was statistically significant association between NIHSS score and functional outcome ($p\leq0.05$). Patients with thromboembolic etiology, 56.5% died, 43.9% had severe disability and 36.3% had moderately severe disability. The relationship between stroke etiology and functional outcomes was statistically significant ($p\leq0.05$).Forty nine patients who had seizures, 42.9% had severe disability, 26.5% had moderately severe disability, 22.4% died, 6.1% had moderate disability and only 1 had slight disability. The relationship between presence of seizures and functional outcome was statistically significant ($p\leq0.05$). Patients with focal seizures, 54.5% expired and 76.2% had severe disability. The association between type of seizures and functional outcomes was statistically insignificant ($p>0.05$). The patients who were treated with lacosamide 50% had severe disability and 10% died, whereas patients who were being treated with levitiracetam 39.3% had severe disability and 28.6% died. Only one

person was being treated with valproate and that patient died. Statistically there was no association between AED and functional outcome (p>0.05). (Table 1)

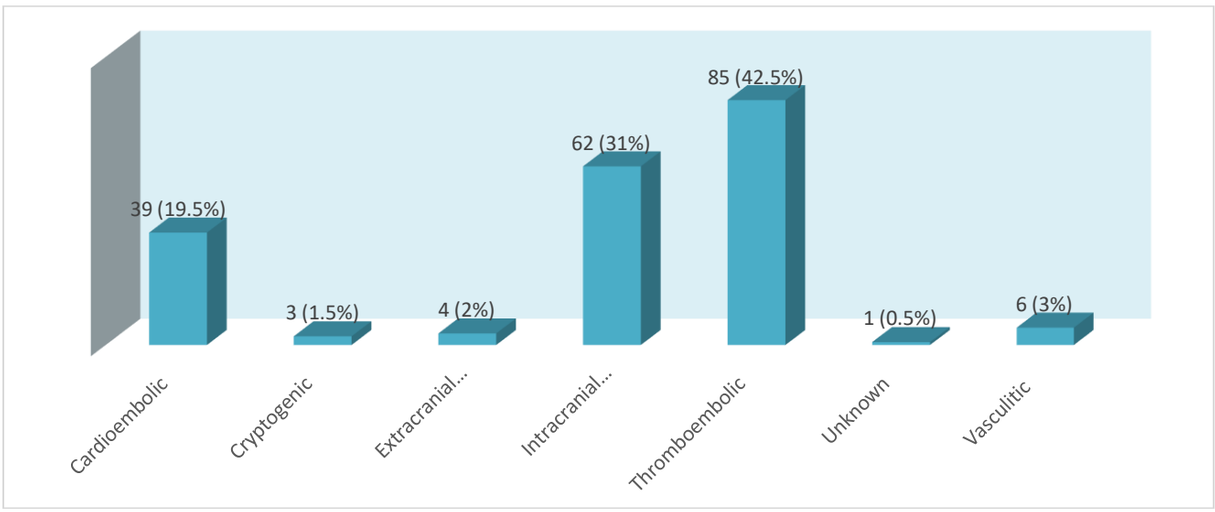

FIG 1: FREQUENCY DISTRIBUTION OF ETIOLOGY OF STROKE

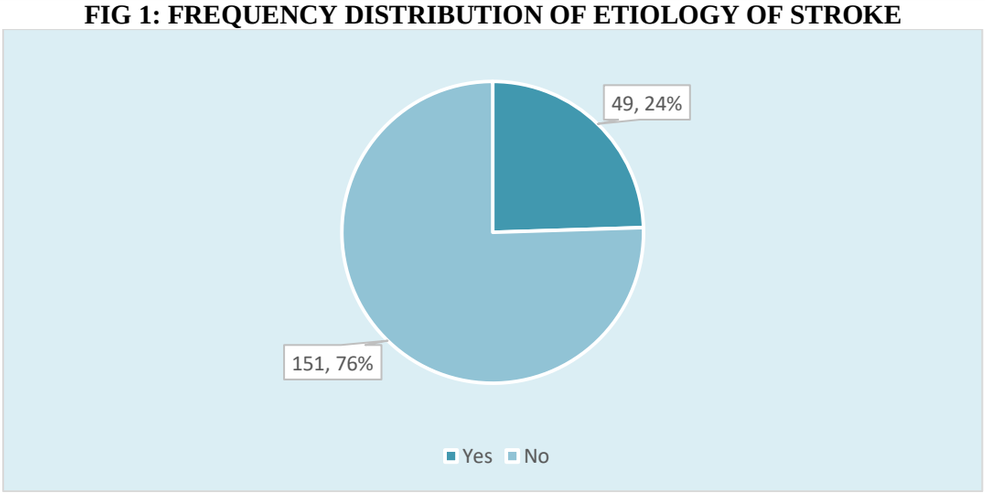

FIG 2: FREQUENCY DISTRIBUTION OF SEIZURES.

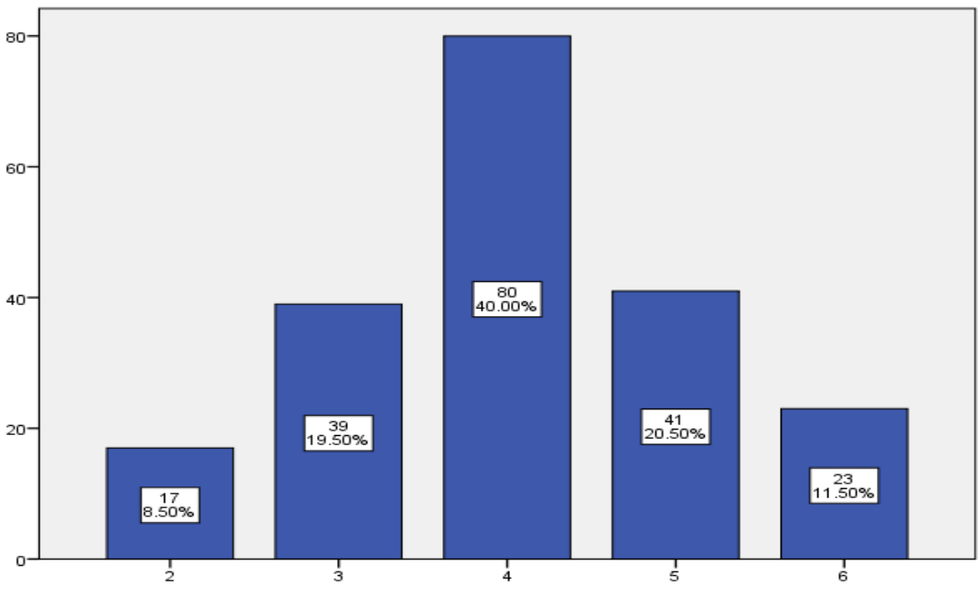

FIG 3: FREQUENCY DISTRIBUTION OF FUNCTIONAL OUTCOME.

TABLE 1: COMPARISON OF POST STROKE SEIZURES, AED DRUGS AND FUNCTIONAL OUTCOMES.

	mRS on discharge (Functional outcomes)					p-value
	2 (n=17)	3 (n=39)	4 (n=80)	5 (n=41)	6 (n=23)	
NIHSS at admission						
5-15	16(94.1%)	23(59%)	14(17.5%)	2(4.9%)	0	
16-20	1(5.9%)	16(41%)	54(67.5%)	26(63.4%)	4(17.4%)	
21-42	0	0	12(15%)	13(31.7%)	19(82.6%)	0.001
Stroke etiology						
Cardioembolic	2(11.8%)	7(17.9%)	19(23.8%)	6(14.6%)	5(21.5%)	
Cryptogenic	0	0	2(2.5%)	1(2.4%)	0	
Extracranial stenosis	0	0	1(1.3%)	1(2.4%)	2(8.7%)	
Intracranial arterial stenosis	5(29.4%)	11(28.2%)	28(35%)	15(36.6%)	3(13%)	0.046
Thromboembolic	5(29.4%)	20(51.3%)	29(36.3%)	18(43.9%)	13(56.5%)	
Vasculitic	4(23.5%)	1(2.6%)	1(1.3%)	0	0	
Unknown	1(5.9%)	0	0	0	0	
Seizure						
Yes	1(2%)	3(6.1%)	13(26.5%)	21(42.9%)	11(22.4%)	0.001
No	16(10.6%)	36(23.8%)	67(44.4%)	20(13.2%)	12(7.9%)	
Type of seizures						
Focal seizures	1(100%)	3(100%)	12(92.3%)	16(76.2%)	6(54.5%)	
Generalized seizures	0	0	1(7.7%)	5(23.8%)	5(45.5%)	0.211
AED drugs						
Lacosamide	1(5%)	2(10%)	5(25%)	10(50%)	2(10%)	
Levitiracetam	0	1(3.6%)	8(28.6%)	11(39.3%)	8(28.6%)	0.303
Valproate	0	0	0	0	1 (100%)	

DISCUSSION

Seizures are the well-recognized complication of an acute ischemic stroke and various researches have been carried out to measure the epidemiology.[10-12,17-19] Yet the statistics on post-stroke seizure, its predictors and its impact on survivor's fatality and functional outcome differs greatly across studies.[9,20,21] Hence, the present research was conducted to compare the functional outcome of acute ischemic stroke patients presenting with and without seizures and to evaluate the best AED used in stroke related seizures.

Average age of patients in the current research was 57 years, and most patients were over 50 years of age, which is close to the previous studies showinghigh incidence rate of post-stroke seizures in middle age to elder patients.[22] A younger agewithaverage age of 45 years was observed in the research by Dhanuka et al. at first seizure after stroke but that could be because they have recruited a broad spectrum of patients (age span from 5 months to 76 years).[23] In our study, 70.5% were males and 29.5% were females, showing males were more likely to be affected than females. Similarfindings were obtained in previous regional and international researches.[5,22,24,25] Hence, Bhojoet al. have found the same incidence rate of post-stroke seizures among males and females.[[26]]

The incidence rate of epilepsy has been estimated as 44/100,000 person-years, with cerebrovascular disorder being the commonest antecedent to seizure initiation.[6]

]The incidence of post-seizures after acute ischemic stroke in the present study is 24% which is slightly higher than previously published researches. [11,27]

] Bryndziar T et al. identified 489 first ischemic stroke patients with mean follow up time of 6.5 years and 35 patients experienced new onset of seizures (7.2%).[6] In present study, 19% patients had focal seizures and 5.5% had *generalized* seizures. Similar results were found by Bhojokhealani et al who found in their study that during the three year period 1548 patients with stroke were admitted to the hospital, 28% had intracerebral hemorrhage and 72% had ischemic stroke. The frequency of generalized seizures after ischemic strokes was found to be 9%.[26]In the study by Jung S et al. found 26 patients had early onset of seizures and 18 had late seizures and 761 patients were seizure free. They further found patients with early onset of seizures, 38.5% had focal seizures and 61.5% had generalized seizures, whereas patients with late seizures, 44.4% had focal, 16.7% had complex focal and 38.9% had generalized type of stroke. [28] The occurrence of *generalized* tonic–clonic *seizures (*GTCS) in patients with ischemic stroke is unclear. Possible explanations include that the GTCS may simply have been a secondarily generalized seizure in which the partial portion was either not observed or skipped momentarily enough; or the GTCS was triggered by certain precipitating causes such as biochemical disorders such as electrolyte deficiency or hypoglycemia, and was not a direct consequence of the coexisting stroke.

The first line treatment (AEDs) for both generalized and focal seizures are levitiracetam,

lamotrigine, carbamazepine, topiramate and sodium valproate, while phenobarbital, phenytoin and clonazepam are the alternative AEDs.[29,30] We preferred levitiracetam, followed bylacosamide and sodium valproate as the medication for patients with seizures after acute ischemic stroke. These drugs were prescribed because of its cost effectiveness and parenteral administration. According to our results, no recurrence of seizures was observed in patients treated with lacosamide. It shows 100% efficacy of lacosamide in preventing recurrence of clinical and subclinical seizures.

In the present research,NIHSS score at the time of admission was estimated as 18.20±3.85 and according to mRS score at the time of discharge 40% patients had moderately severe disability, 20.5% had severe disability, 19.5%had moderate disability, 8.5% had slight disabilityand 11.5% expired.In the study by Alberti A et al. found the mean NIHSS score at the time of admission as 10.1±7.5 which is lower than current study. Further they found 10.3% of the patients died and 44.2% had disability at the time of discharge. There was statistically significant association between NIHSS score at admission and functional outcome.[31] Similarly in the present study, the patients with NIHSS 16-20, 17.4% expired and more than 62% of the patients had moderately severe to severe disability and hence NIHSS score at admission is the significant predictor of poor outcome.

We found significant association between stroke etiology and functional outcome ($p<0.05$) and patients with thromboembolic etiology, 56.5% died, 43.9% had severe disability and 36.3% had moderately severe disability. Whereas Alberti A et al. found no relationship between etiology of stroke and functional outcome.[31]

In our study 49 patients who had seizures, 42.9% had severe disability and 22.4% died at the time of discharge and the correlation between seizures and functional outcome was statistically significant ($p\leq0.05$). Similarly Jung et al. found patients with seizures had significantly high mortality rate as compared to patients without seizures ($p<0.05$) and very less patients had good outcome. [28]

The sample size of the current study was small therefore it limits the ability to generalize the results for the target population of acute ischemic stroke. Also there was scarcity of EGG data which disabled us to differentiate between status epilepticus or non-convulsive seizures. Hence, further prospective study with larger sample size is required to enhance the information about post-stroke seizures and their effect on the individual and community, translating into an evidence-based and better health care provision.

CONCLUSION

In stroke patients stoke severity in terms of higher NIHSS score, stroke etiology and seizures are the independent determinants of poor outcome.Lacosamide was observed as the best AED in terms of prevention of recurrence and better outcome of stroke.

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