DOI: 10.7860/JCDR/2023/63169.17821

Original Article

Internal Medicine Section

Early Post-stroke Seizures in Acute Ischaemic Stroke: A Retrospective Study

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ABSTRACT

Introduction: Seizures represent an important complication of ischaemic stroke causing a substantial burden to post-stroke patients. Seizures occurring within one week after acute stroke onset are called early onset seizures. Several studies have tried to identify the risk factors for early seizures after stroke with controversial results.

Aim: To determine the risk factors for early post-stroke seizures in a retrospective cohort of acute ischaemic stroke.

Materials and Methods: This retrospective cohort study included medical records of 552 adult patients with acute ischaemic stroke between March 2017 to September 2022 admitted to Travancore Medical College Hospital, Kollam, Kerala, India. The patients were divided into two groups: stroke patients with early onset seizures and stroke patients without early onset seizures. The following parameters were compared between the two groups: age, gender, presenting symptoms, ischaemic subtype (TOAST {Trial of Org 10172 in Acute Stroke Treatment} classification), vascular territory involved, lesion location and lateralisation, infarct size, stroke severity based on the National Institute of Health Stroke Scale (NIHSS), vascular risk factors, treatment (thrombolysis, antiplatelets, anticoagulants use) and related complications (haemorrhagic transformation, infection, gastrointestinal haemorrhage, hyponatraemia). Univariate analysis was done using Chi-square test and multivariate analysis using logistic regression test. Statistical Package for the Social Sciences (SPSS) version 27.0 statistical software was used, p-value <0.05 was considered statistically significant.

Results: Among 552 patients, 76 (13.8%) were stroke patients with early onset seizure group and 476 (86.2%) were stroke patients without early onset seizure group. A total of 84.2% of patients developed seizure within 24 hours of stroke onset. A total of 409 (74.1%) patients were males. Patients with early onset seizures were younger. The most common seizure type was unknown onset to bilateral tonic-clonic seizures (85.5%). Multivariate analysis identified severe NIHSS, supratentorial, cortical location, large artery disease, anticoagulation use, haemorrhagic transformation and hyponatraemia as independent factors for early onset seizures.

Conclusion: Severe NIHSS at presentation, large artery disease, supra tentorial, cortical location of infarct, use of anticoagulants, haemorrhagic transformation and hyponatraemia were significant risk factors for early seizures in acute ischaemic stroke. An early identification and understanding of these risk factors would help to prevent seizures in acute stroke patients.

Keywords: Cerebrovascular accident, Epilepsy, Hyponatraemia, Infarction

INTRODUCTION

Seizures in stroke patients cause significant morbidity and mortality. Seizures cause a significant hardship to post-stroke patients increasing duration of their hospital stay and disability [1]. Literature has reported that 3.1-21.8% of stroke patients develop post-stroke seizures [2]. Post-stroke seizures can be classified as early-onset and late-onset types. Seizures occurring within one week after acute stroke onset are called early onset seizures. Those occurring after one week of stroke onset are considered as late onset seizures [3]. However, the incidence of post-stroke seizures is relatively consistent with two peaks: the first day and 6-12 months post-stroke [4]. The aetiopathogenesis contemplated for early and late onset post-stroke seizures are different. The causes of early post-stroke seizures described are acute neuronal injury, glutamate induced excitotoxicity, disrupted blood brain barrier and defective function of ion channels. On the contrary, late post-stroke seizures occur due to gliotic scarring, changes in the properties of the neuronal membrane, neurodegeneration, persistent inflammation, altered synaptic plasticity and hyper-synchronisation of neuronal activities [5].

Several studies have researched on the predictive factors for early seizures after stroke with varying results. In recent meta-analysis by Ma S et al., cortical involvement, intracerebral haemorrhage, and cerebral infarction with haemorrhagic transformation were important predictors and risk factors for early seizures after stroke [6]. In study by Lee SH et al., cortical involvement, functional deficits, increasing lesion size, younger age, and haemorrhage were common predictors for early post-stroke seizures [7].

Determining and analysing such predictors in stroke patients can help identify patients at risk for seizures. This can lead to timely care and management of seizures and improve preventive and therapeutic interventions. Prophylactic short-term antiepileptic medications for ischaemic strokes are still a matter of debate. This study aims to determine the risk factors for early post-stroke seizures in a retrospective cohort of acute ischaemic stroke.

MATERIALS AND METHODS

The present retrospective cohort study was conducted at Department of Neurology, Travancore Medical College Kollam, Kerala, India. A total of 552 adult patients with acute ischaemic stroke who were admitted in the Department of Neurology between March 2017 to September 2022 were included in the study. This study was approved by Institutional Research and Ethics committee review board (TMC-IEC-131/23). The data analysis was done in November 2022.

Inclusion criteria: Data of all adult patients who were diagnosed to have acute ischaemic stroke were included in the study.

Exclusion criteria: Patients with previously confirmed stroke and transient ischaemic attacks. Also, patients with primary haemorrhagic stroke, cerebral venous thrombosis, prior history of seizures or

epilepsy, other potential epileptogenic co-morbidities like brain tumours, mass lesion, arteriovenous malformations, primary central nervous system vasculitis, or hydrocephalus, patients already on antiepileptic medications and those with less than seven days of in patient care were excluded from the study.

Acute stroke is brain cell death attributable to ischaemia based on pathological, imaging or other objective evidence of cerebral ischaemic injury in a defined vascular distribution [8]. All patient records were reviewed and retrospectively analysed. Data regarding the following variables were collected and documented from the records. Age, gender, presenting symptoms, ischaemic subtype (TOAST classification) [9], vascular territory involved, lesion location and lateralisation, infarct size, stroke severity (NIHSS), vascular risk factors (hypertension, diabetes, dyslipidaemia, coronary artery disease, smoking, atrial fibrillation, alcohol), treatment (thrombolysis, antiplatelets, anticoagulants use) and related complications (haemorrhagic transformation, infection, gastrointestinal haemorrhage, hyponatraemia). The patients were then divided into two groups-stroke patients with early onset seizures and stroke patients without early onset seizure. The various risk factors were compared between the two groups. The NIHSS was used to assess the stroke severity and classified into mild (≤3), moderate (4-10), and severe (>10) [10]. Lesion location was classified as supra or infratentorial. When infarct was confined to cortical, subcortical or lobar regions, it was considered as supra tentorial. When infarct was confined to mid brain, pons, medulla or cerebellum it was considered as infra tentorial. The lesion size was determined by measuring the largest diameter of the lesion. Lesions were characterised as small (<1 cm), medium (1-3 cm) and large (>3 cm) lesion [3].

STATISTICAL ANALYSIS

Quantitative variables were expressed as mean±Standard Deviation (SD), whereas qualitative variables were expressed as frequencies and percentages. Comparison between groups (with and without seizures) was performed using chi-square test or Fisher's exact test, as deemed appropriate. Significant risk factors that were designated as being associated with the seizure using the univariate analysis were entered in the multivariable regression analysis to identify predictors of early seizures. Measures of association were expressed as Odds Ratio (OR) and 95% Confidence Interval (CI). A p-value ≤0.05 was considered significant. Data were analysed using SPSS statistics (IBM corporation, Armonk, New York), version 27.0. A p-value <0.05 was considered to be statistically significant.

RESULTS

Among 552 patients diagnosed with acute ischaemic stroke, 76 (13.8%) were in stroke patients with early onset seizure group and 476 (86.2%) were in stroke patients without early onset seizure group. A total of 409 (74.1%) were males and 143 (25.9%) were females. Patients with early seizures were younger. The mean age was 62.3±11.2 years. Unknown onset to bilateral tonic-clonic seizures was the most common seizure type (85.5%). One patient had status epilepticus. A total of 64 patients (84.2%) had seizures within 24 hours of stroke onset and three patients (3.9%) had seizures as the presenting symptom of stroke.

The baseline characteristics of the patients are shown in [Table/Fig-1]. Risk factors for stroke were similarly distributed between the two groups. Hypertension was the most common risk factor for stroke in both the groups-83.8% in group without early seizure and 85.5% in group with early seizure.

Stroke patients with early onset seizure group had a more severe stroke at presentation (NIHSS >10), had a supratentorial, cortical location of the infarct and involved more commonly the MCA territory. Large artery disease was more common in patients with early seizures [Table/Fig-2]. Haemorrhagic transformation and hyponatraemia were the most common related complications [Table/Fig-3].

Variables	Stroke patients without early onset seizure (n=476)	Stroke patients with early onset seizure (n=76)	p-value
Mean age (years)	63±12	60±14	0.1487
Gender	**n (%)**	**n (%)**	
Male	357 (75)	52 (68.4)	0.2241
Female	119 (25)	24 (31.6)	
Risk factors			
Diabetes	325 (68.3)	53 (69.7)	0.7993
Hypertension	399 (83.8)	65 (85.5)	0.7065
Dyslipidemia	214 (44.9)	34 (44.7)	0.9713
Coronary artery disease	52 (10.9)	9 (11.8)	0.8127
Atrial Fibrillation	49 (10.3)	6 (7.9)	0.5167
Smoking	309 (64.9)	53 (69.7)	0.4140
Alcohol	292 (61.3)	41 (53.9)	0.2209
Presenting complaint			
Headache	51 (10.7)	9 (11.8)	0.7693
Limb Paresis	426 (84.5)	68 (89.5)	0.9953
Sensory loss/dysesthesia	176 (36.9)	22 (28.9)	0.1754
Cranial nerve palsy	104 (21.8)	11 (14.4)	0.1415
Speech deficits	418 (87.8)	70 (92.1)	0.2780
Ataxia	95 (19.9)	10 (13.1)	0.1607
Altered consciousness	104 (21.8)	13 (17.1)	0.3474
NIHSS			
Mild (0-3)	113 (23.7)	10 (13.1)	0.0723
Moderate (4-10)	261 (54.8)	35 (46.1)	0.1541
Severe (>10)	102 (21.5)	31 (40.8)	0.0002**

[Table/Fig-1]: Demographics, clinical presentation and risk factor profile in stroke patients without early onset seizure and with early onset seizure.
*Chi-square test or Fisher's-exact test, as deemed appropriate
(**p<0.001-statistically highly significant)

Variables	Stroke patients without early onset seizure (n=476)	Stroke patients with early onset seizure (n=76)	p-value
Stroke subtype	**n (%)**	**n (%)**	
Large artery	157 (32.9)	36 (47.3)	0.0148*
Cardioembolic	71 (14.9)	12 (15.8)	0.8432
Small vessel	130 (27.3)	13 (17.1)	0.0593
Others	24 (5.1)	1 (1.3)	0.1468
Undetermined	94 (19.8)	14 (18.5)	0.7865
Location			
Supratentorial	395 (82.9)	72 (94.7)	0.0084*
Cortical	166 (34.9)	56 (73.7)	<0.0001**
MCA Territory	352 (73.9)	61 (80.2)	0.2390
Lateralisation			
Left	251 (52.7)	41 (53.9)	0.8436
Right	195 (40.9)	34 (44.7)	0.1589
Bilateral	30 (6.4)	1 (1.4)	0.0795
Size			
Small	109 (22.9)	10 (13.1)	0.0552
Medium	272 (57.2)	38 (50)	0.2439
Large	95 (19.9)	28 (36.9)	0.0010*

[Table/Fig-2]: Comparison between stroke subtype, site and size between stroke patients without early onset seizure and with early onset seizure.
*Chi-square test or Fisher's-exact test, as deemed appropriate
(*p<0.05-statistically significant,**p<0.001-statistically highly significant)

Variables	Stroke patients without early onset seizure	Stroke patients with early onset seizure	p-value
Treatment	**n (%)**	**n (%)**	
Thrombolysis	31 (6.5)	4 (5.2)	0.6781
Antiplatelet use	428 (89.9)	69 (90.8)	0.8134
Anticoagulant use	57 (11.9)	18 (23.7)	0.0057*
Related complications			
Haemorrhagic transformation	33 (6.9)	28 (36.8)	<0.0001**
Infection	68 (14.3)	9 (11.8)	0.5680
Gastrointestinal haemorrhage	18 (3.8)	0	0.1536
Hyponatraemia	42 (8.8)	14 (18.4)	<0.0001**

[Table/Fig-3]: Comparison between treatment and related complications between stroke patients without early onset seizure and with early onset seizure.
*Chi-square test or Fisher's-exact test, as deemed appropriate
(*p<0.05-statistically significant, **p<0.001-statistically highly significant)

In univariate analysis, NIHSS>10, supratentorial, cortical location, large artery disease, large infarct size, anticoagulation use, haemorrhagic transformation and hyponatraemia were associated with development of early post-stroke seizures. Logistic regression analysis was done to assess the independent predictors. In multivariate analysis, severe NIHSS, supratentorial, cortical location, large artery disease, anticoagulation use, haemorrhagic transformation and hyponatraemia were significant risk factors for early onset seizures [Table/Fig-4]. The strongest predictor for early seizure was haemorrhagic transformation (OR=45.61); followed by cortical location (OR=25.40) and hyponatraemia (OR=21.51).

Variables	OR	95% CI		p-value
		Lower	Upper	
Severe NIHSS	13.61	5.52	33.51	<0.0001**
Large artery subtype	4.67	2.14	10.18	0.0001**
Supratentorial	4.43	1.36	14.40	0.0131*
Cortical	25.40	12.3	66.7	<0.0001**
Large size infarct	1.26	0.62	2.54	0.5120
Anticoagulant use	2.50	1.17	5.32	0.0171*
Haemorrhagic transformation	45.61	18.65	111.55	<0.0001**
Hyponatraemia	21.51	8.19	56.46	<0.0001

[Table/Fig-4]: Independent risk factors associated with early post-stroke seizures identified by multivariable regression analysis.
(*p<0.05-statistically significant, **p<0.001-statistically highly significant)

DISCUSSION

Stroke is a health problem of concern causing disability and death in adult population. Post-stroke seizures often result in a poor functional outcome and a higher morbidity [11]. The studies conducted in various countries yielded different patterns of risk factors for post-stroke seizures. Early seizures occurred in 13.8% of patients with acute ischaemic stroke in this study. In the study by Agarwal A et al., early seizures were observed in 12.7% of patients [10]. Another study that was conducted in India, reported a higher incidence rate of 17.9% [12]. In the study by Shehta N et al., the incidence of early post-stroke seizures in Egypt was 9.3% [3]. The majority of early seizures occurred within 24 hours of stroke onset. There were no differences in gender between the two groups. In this study, 85.5% of the seizure type was unknown onset to bilateral tonic-clonic seizures. Similar semiology was reported in Agarwal A et al., study in 94.6% [10]. In the study by Stefanidou M et al., 72% of the seizure type was focal in onset compared to the generalised type; regardless of stroke type or time of seizure occurrence [4]. These findings support the fact that the focal lesion following an infarction acts as the seizure focus.

The occurrence of early seizure significantly depends upon the location of the infarct. Cortical location and supratentorial location of the infarct was seen in 73.7% and 94.7% of early onset seizures in this study respectively, with cortical location predisposing to all. Galovic M et al., revealed that patients who have larger strokes involving the cortex, have acute symptomatic seizures and are at highest risk of developing post-stroke epilepsy [13]. This was concurrent with the study by Shehta N et al., [3]. Cortical irritation can increase the excitability and lead to seizure onset. Early onset seizures were associated with large artery disease stroke subtype (47.3%). This was 43.2% in Agarwal A et al., study [10]. Large artery disease will indeed lead to larger size infarct volumes, thus involving larger cortical brain tissue. This could increase the probability of post-stroke seizures.

Patients with early seizures had a significantly higher NIHSS score (NIH stroke scale) at admission than those without. A 40.8% had a severe NIHSS at onset. Similar corroboration was seen in the study by Agarwal A et al., where stroke severity was based on the NIHSS and modified Rankin scale [10]. The stroke risk factors were nearly equally distributed between the early seizure group and group without early seizure. However, hypertension was present in significantly less frequency in those with early seizure in Agarwal A et al., study and Hundozi Z et al., study [10,14]. The use of anticoagulants was found to be associated with an increased risk of early seizures. It was seen in 23.7% of patients. Studies have showed that thrombin was a key factor for seizure by predisposing to maladaptive plasticity [15]. Haemorrhagic transformation and hyponatraemia were significant risk factors for early onset seizures in this study. In study by Castro-Apolo R et al., presence of haemorrhage in infarct was the primary risk factor for seizure occurrence [16]. Haemorrhage often acts as an irritative focus, thus predisposing to seizures. However, in the study by Agarwal A et al., hyponatraemia was not a predictive factor for early onset seizures [10].

In this study, multivariable regression analysis showed that severe NIHSS at presentation, large artery disease, supra tentorial and cortical location of infarct, use of anticoagulants, haemorrhagic transformation and hyponatraemia showed a positive association with development of early post-stroke seizures. These factors would help to determine those who are at high-risk of developing early seizure. Managing acute ischaemic stroke patients and these risk factors with prophylactic antiepileptic medications needs to be considered in the stroke management protocol. This would indeed reduce the morbidity, mortality and in hospital stay for such stroke patients.

Limitation(s)

The greatest limitation of the present study was the retrospective design and conclusions were based on observation from a single study centre. Also, the sample size was relatively low. Thus, a prospective multicentre study is required to further evaluate the risk factors.

CONCLUSION(S)

Severe NIHSS at presentation, large artery disease, supra tentorial, cortical location of infarct, use of anticoagulants, haemorrhagic transformation and hyponatraemia were significant risk factors for early seizures in acute ischaemic stroke patients. Early identification of these factors and improved knowledge about them will help in better care and prevention of seizures in acute stroke patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 06, 2023
- Manual Googling: Feb 20, 2023
- iThenticate Software: Mar 22, 2023 (20%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 30, 2023**
Date of Peer Review: **Mar 18, 2023**
Date of Acceptance: **Apr 05, 2023**
Date of Publishing: **May 01, 2023**