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Incidence, predictors, and outcomes of post-thrombectomy seizures in the extended time window

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ABSTRACT

Mechanical thrombectomy 6–24 h after the last time where a patient was known to be without signs or symptoms of a stroke is the standard of care for patients with a stroke due to large vessel occlusion. This is referred to as thrombectomy within an extended time window. There have been very few studies looking at patients who had seizures within the first week (early post-stroke seizures) following mechanical thrombectomy in this extended time window. Our study suggests that this group of patients does not have a higher incidence of early post stroke seizures. Our findings do reveal however, that patients who do have early post-stroke seizures may have a less favorable functional outcome at 90 days than those who did not develop early seizures. Hence, rapid identification and subsequent treatment of seizures in these patients is important.

1. Introduction

Ischemic stroke accounts for 4–10% of acute symptomatic seizures in adults [1–3]. Post stroke seizures can be subdivided into early post stroke seizures (EPSS), which occur within the first week following the stroke, and late onset seizures, occurring more than one week later [2,4–6]. Recanalization with endovascular mechanical thrombectomy (MT) has become the standard of care for patients presenting with an acute ischemic stroke (AIS) with large vessel occlusion (LVO) following a series of randomized controlled clinical trials demonstrating significantly improved functional outcomes in select patient up to 24 hours from last known well (LKW) time [10]. Some recent studies have identified EPSS in 2.4 to 4.4% patients after MT [1,11]. However, at present, there is limited data regarding EPSS specifically following extended window (EW) MT. In this retrospective study, we aimed to investigate the incidence, predictors, and functional outcomes of EPSS following thrombectomy after 6h for AIS due to LVO.

2. Methods

We conducted a single-center retrospective analysis of all patients presenting with AIS LVO between May 2016 and May 2019. Patients presenting in the EW time frame, 6 to 24 hours from LKW with a LVO confirmed on imaging were included. Patients with a history of known epilepsy and those with seizures prior to presentation were excluded. MT was performed with stent retrievers (Solitaire stent-Ev3), thrombo-aspiration (Penumbra Ace61), or a combination technique according to the preference of the neurointerventionalist. The degree of recanalization achieved following thrombus removal was defined using the Thrombolysis in Cerebral Infarction (TICI) grading system. Patients who suffered EPSS, defined by clinical presentation or electrographic evidence within one week of presentation were identified. The seizure classification, electroencephalography (EEG) findings and antiseizure medication were noted based on chart review. All patients were further evaluated for disability at 90 days using the modified Rankin Scale (mRS). Additional factors were also evaluated to assess for possible confounding, including; age, sex, comorbidities, presenting National Institute of Health Stroke Scale (NIHSS) assessed by a stroke-trained physician, LKW to groin puncture time and TICI scores. Patient information was collected from the Houston Methodist Hospital Outcomes Based Prospective Endpoints in Stroke (HOPES) registry [12].

2.1. Statistical methods

We summarized continuous variables as medians and interquartile ranges (IQR), and categorical variables as proportions. Median differences between continuous variables were identified

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with the Wilcoxon rank sum test. Differences between the categorical variables were identified using the chi-squared test ($\chi 2$), and fisher-exact test, as appropriate.

Multivariate ordinal logistic regression was performed on the primary outcome. Odds ratio (OR) and 95% confidence intervals [C.I.] are reported. A p-value < 0.05 is considered significant. De-identified analyses were conducted using R version 3.6.3 (R-Foundation; Project for statistical computation and graphics).

3. Results

A total of 98 patients were evaluated, of which four were found to have EPSS following EW MT. EPSS were either focal impaired awareness (3/4) or focal to bilateral tonic- clonic (1/4). None of the patients presented with difficult to control seizures or status epilepticus. We did not capture any ictal EEG recordings. Interictal EEG did not show spikes or sharp waves in any of the patients with EPSS. Antiseizure medications used were levetiracetam in two patients, fosphenytoin in one patient and valproic acid in one patient. In two of the four patients, chest x-ray findings concerning for aspiration pneumonia were also confirmed and treatment initiated within a few days of EPSS. One of the patients had a subarachnoid hemorrhage after the stroke. All patients in the EPSS cohort achieved a TICI score between 2b-3 indicating radiographically, a successful thrombectomy.

None of the patients in the EPSS group had mRS of 0–2 compared to 27 (28.7%) patients in the non-EPSS group (Table 1) Multivariate ordinal logistic regression model showed that patients with seizures were approximately eight times more likely to have poor functional outcomes at 90 days, with a progressively severe disability of these patients when compared to patients without seizures (OR = 7.7, 95% CI. [1.1 – 54.9], p = 0.04) (Table 1).

4. Discussion

This retrospective study looks at EPSS following thrombectomy beyond 6 hours for AIS with LVO, for which current data remains scarce. Our findings indicate that 4 of 98 patients had EPSS following EW MT. This is in accordance with recent data on MT with 6–8 hours from LKW that identified EPSS in 2.4 to 4.4% of the patients [1,9]. Hence, in our single center study, thrombectomy did not increase risk for developing EPSS. In our study, none of the patients who developed EPSS had a mRS of less than two. Our analysis suggests that these patients are eight times more likely to have a poor functional outcome at 90 days.

All patients in the EPSS group had hypertension, diabetes, hyperlipidemia and coronary artery disease and two had atrial fibrillation. Based on TOAST criteria, three of the four patient had a cardioembolic source while the other was classified as stroke of undetermined etiology (Table 1). The association between cortical infarct, cardioembolic stroke and seizure occurrence has been widely recognized in previous studies as well [2,7,12].

EPSS are believed to result from neuronal injury due to blood brain barrier breakdown, excitotoxicity, damage from reactive oxidative species and disruption in ion channels [5,11]. These patients that are typically expected to present with a larger area of infarct, presumed higher risk for reperfusion injury given the late presentation. It is also important to note that we found no identifiable risk factors that would increase the incidence of seizures post-thrombectomy. In our cohort, EPSS were more commonly focal impaired awareness and required maximum of two antiepileptic drugs for treatment. The reported risk of post stroke epilepsy after EPSS in literature is variable, with a range of no increased risk to a five-fold increased risk [1,7,8]. One patient in

Table 1
Patient specific characteristics of the EPSS group.

ID	Age	Sex	Stroke risk factors	Thrombus location	ASPECTS	TOAST	Stroke areas	Time to seizure from LKW	Semiology	Seizure classification	Seizure frequency	ASD Load	ASD therapy continuation	Interictal EEG findings	mRS at 90d
1	68	M	HTN, HLD, T2DM, CAD, Smoking	RM2 and Basilar	10	Cardioembolic	R O, R posterior PO, B medial thalami	2 days	L sided shaking and staring	Focal impaired awareness	1	IV Levetiracetam 1000 mg	I.V. Levetiracetam 500 mg q12h	Diphasic and Triphasics	5
2	57	F	HTN, HLD, T2DM, CAD, hx of stroke	B ICA/R M1/LM1/ LA2	7	Stroke of undetermined etiology	B FP, L medial F, L BG, B I, B T	4–5 h	R gaze, R head turn, Tonic posturing, eyes open, GTC	Focal to bilateral tonic clonic	1	IV Fosphenytoin 20 mg/kg	I.V Fosphenytoin 100 mg q8h	Severe Diffuse depression	6
3	59	M	HTN, HLD, T2DM, Afib, CAD, PPM, hx of stroke	RM2	9	Cardioembolic	R FP , Posterior I, R O, R T	5 days	L gaze deviation, L head turning, L hemiparesis	Focal impaired awareness	2	IV Valproate 20 mg/kg	I.V. Valproate 500 mg q6h later switched to po Keppra 1000 mg BID	Focal R epileptogenic lesion, Diffuse slowing	3
4	61	M	HTN, HLD, T2DM, AFib, CAD, LVAD	L M2	9	Cardioembolic	L I, L Caudate, L FP	2 days	R sided shaking, altered mentation, R hemiparesis	Focal impaired awareness	1	None	IV Levetiracetam 750 q12h	L Slow Focus	6

Abbreviations: M = male. F-female. HTN = hypertension. HLD = Hyperlipidemia, T2DM = Type II Diabetes Mellitus, CAD = Coronary artery disease, Hx = history, PPM = Permanent Pacemaker, AFib = Atrial fibrillation, R = right, L = left, B = bilateral, O = occipital, P = parietal, F = frontal, T = temporal, BG = Basal Ganglia, I = Insula. M1 = first division of middle cerebral artery, M2 = second division of middle cerebral artery, ICA = internal cerebral artery, A2 = second division of ACA ASD = antiseizure drugs.

our cohort developed seizure at 15 days after EW MT and was found to have a new ischemic stroke at that time point.

Although our study population had 98 patients, our EPSS cohort was small and hence we were limited on the conclusions that could be drawn from a small sample size. Since we did not identify any ictal EEGs, our selection for EPSS was based on the clinician's documentation which introduces potential variability in definitive diagnosis of an event as a seizure. Our data is strengthened by the fact that post MT, all patients were monitored in the ICU and availability for continuous EEG monitoring if needed which enabled the EPSS cohort to be on long-term monitoring post seizure. On the contrary, since all patients who underwent MT did not get an EEG, there may be patients in non-convulsive seizures or even non-convulsive status epilepticus that may have been missed as is seen in 8–48 % of ICU patients [6]. Our study looks at clinical outcomes of seizure patients who underwent EW MT for which, at the time this data was collected and analyzed, the literature on EPPS was scarce. This study provides further safety data for EW MT, and given the low number of EPSS, we do not identify a need for prophylactic antiseizure medications after EW MT.

These results provide novel insight to the limited literature reporting functional outcomes in patients with EPSS after EW MT. However, larger prospective studies are needed to better understand the relationship between reperfusion therapies and early seizure development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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