Go Ahead! Use that Reperfusion Treatment, don't Worry About Subsequent Seizures!

Keywords

Acute symptomatic seizure, post-stroke epilepsy, IV tPA, propensity-score matching

---

Seizures after Ischemic Stroke: A Matched Multicenter Study

Ferreira-Atuesta C, Döhler N, Erdélyi-Canavese B, et al. *Ann Neurol.* 2021;90(5):808-820.

Objective: The purpose of this study was to identify risk factors for acute symptomatic seizures and post-stroke epilepsy after acute ischemic stroke and evaluate the effects of reperfusion treatment. Methods: We assessed the risk factors for post-stroke seizures using logistic or Cox regression in a multicenter study, including adults from 8 European referral centers with neuroimaging-confirmed ischemic stroke. We compared the risk of post-stroke seizures between participants with or without reperfusion treatment following propensity score matching to reduce confounding due to treatment selection. Results: In the overall cohort of 4229 participants (mean age 71 years, 57% men), a higher risk of acute symptomatic seizures was observed in those with more severe strokes, infarcts located in the posterior cerebral artery territory, and strokes caused by large-artery atherosclerosis. Strokes caused by small-vessel occlusion carried a small risk of acute symptomatic seizures. 6% developed post-stroke epilepsy. Risk factors for post-stroke epilepsy were acute symptomatic seizures, more severe strokes, infarcts involving the cerebral cortex, and strokes caused by large-artery atherosclerosis. Electroencephalography findings within 7 days of stroke onset were not independently associated with the risk of post-stroke epilepsy. There was no association between reperfusion treatments in general or only intravenous thrombolysis or mechanical thrombectomy with the time to post-stroke epilepsy or the risk of acute symptomatic seizures. Interpretation: Post-stroke seizures are related to stroke severity, etiology, and location, whereas an early electroencephalogram was not predictive of epilepsy. We did not find an association of reperfusion treatment with risks of acute symptomatic seizures or post-stroke epilepsy.

Commentary

The temporal relation of seizures to an underlying stroke has important clinical implications, primarily because it signals differences in their pathogenic mechanisms. A landmark study investigated seizures after acute brain injury, including stroke, in Rochester county residents during 30 years ending in 1984. It found that 33% of stroke patients with a convulsive seizure within 7 days of a stroke have a subsequent unprovoked seizure. In contrast, the risk of subsequent unprovoked seizure jumped to 71.5% if the first seizure was more than 7-days following the stroke.[1] This remarkable finding has influenced our understanding and definition of acute symptomatic seizures (ASyS; ≤7 days) and new-onset epilepsy (late seizures; >7 days) after stroke (post-stroke epilepsy [PSE]).[2,3] Overall, around 6% – 8% of adults with acute ischemic stroke develop seizures, a large majority within the first 1 – 2 years.[4] While the incidence of seizure after stroke may not seem substantially high, PSE accounts for almost one in every eight (11.9%) adults with epilepsy in high-income countries.[5] Additionally, more than half of new-onset epilepsy in older adults worldwide is secondary to strokes.[5] With ischemic strokes accounting for 90% of all strokes, there is an urgent need to understand factors that predispose and help predict post-stroke (hereafter ischemic stroke) seizures.

The introduction of reperfusion therapies, including intravenous and intra-arterial tPA and mechanical thrombectomy, has led to a paradigm shift in treating acute strokes. However, there remains uncertainty about the impact of such treatment on post-stroke seizures.[6] The study by Ferreira-Atuesta et al. reviewed here attempts to provide a definitive answer to this question using multicenter data and skillful statistical analysis.[7] They included 4229 adults with ischemic stroke, without prior epilepsy history, from 8 centers in 6 European countries. Of note, a sub-cohort of this study population was used for devising SeLECT score, a prognostic model to predict PSE. Variables included in SeLECT score are severity of stroke (based on NIHSS), large artery atherosclerosis, early seizure (ASyS), cortical involvement, and territory of middle cerebral artery (MCA).[8] Among current study population, 29% received reperfusion treatment. ASyS and PSE were noted in 5% and 6% of the overall study population, respectively; 6% and 8% of reperfusion treatment group, respectively; and 4% and 5% of no reperfusion treatment group, respectively. The study's primary outcome was time to PSE, which was a median of 1.1 (IQR 1.0 – 2.2) years in the reperfusion treatment group and 1.87 (IQR 1.0 – 3.2) years in the no reperfusion (control) group. Independent predictors of increased ASyS risk included stroke severity (NIHSS ≥11; adjusted OR [aOR] = 1.7),

posterior circulation stroke (aOR = 1.5), and strokes due to large artery atherosclerosis (aOR = 1.4). Small-vessel occlusion strokes had lower ASyS risk (aOR = .2). Independent predictors of shorter time to PSE development were similar to SeLECT score, except for MCA territory strokes.[8] In regards to the primary research question, reperfusion treatment was not independently associated with the risk of ASyS or PSE after adjustment of other covariates.

Individuals with severe, large artery strokes are more likely to receive reperfusion treatment. Given that these factors are independent predictors of ASyS and PSE, the authors went beyond the routine regression analysis. They used propensity score matching (PSM) to overcome this treatment selection bias and confounding. The propensity score's primary property is that it is a balancing score such that in a subgroup of participants with the same value of this score, the distribution of measured baseline covariates is the same among the treated (reperfusion treatment) and the untreated (control) group. Hence, it removes the confounding effect of measured covariates, which is akin to randomization in RCTs. However, while randomization can balance even unmeasured covariates, PSM only balances the known and measured covariates. Nonetheless, it permits better use of real-world clinical practice data when an RCT for measuring exposure or treatment effects is impractical or unethical.[9] A well-powered analysis of the reperfusion treatment and the control cohorts (n = 936 in each group), which was well-balanced and matched for their propensity to receive reperfusion treatment, did not reveal an association between the treatment and ASyS and time to PSE. Several other, likely underpowered but well-matched secondary analyses did not find an association between the 2 outcomes of interest (ASyS and time to PSE) and IV thrombolysis (using tPA), mechanical thrombectomy, time to IV thrombolysis, successful recanalization, and hemorrhagic conversion.

The study overcomes several limitations of previous investigations by including a sufficiently large, multicenter, sample size and using a methodology and analysis that comes quite close to replicating an RCT. Therefore, it provides us the most definitive evidence, so far, that reperfusion therapies, overall, do not increase the risk of post-stroke seizures. A similar statement can be made with reasonable confidence for IV tPA reperfusion treatment as well. However, some limitations need to be considered when interpreting the study results. The outcome determination methods were different at the participating centers. The analysis did not account for prior ischemic stroke and factors like statin therapy after stroke, which may have potential anti-epileptogenesis properties. The data only pertains to convulsive or clinical seizures. The study was performed in 6 European countries and may lack a racially diverse study population. Cerebrovascular factors differentially impact epilepsy development risk in African-Americans compared to the Caucasian population.[10] Additionally, the incidence of late-onset epilepsy, commonly secondary to underlying cerebrovascular disease, is significantly higher among African-Americans.[11] The validity of PSM analysis relies on the assumption that each participant has a nonzero probability of receiving treatment. Seizures at onset (SaO) have been considered a relative contraindication for IV tPA. While the authors only included ASyS after reperfusion therapy, it is unclear how many patients were not given IV tPA due to a SaO.

Neuroimaging findings have a clear predictive value in PSE.[8] However, given that seizures are essentially electrophysiological perturbation, a clinically critical and ambitious sub-analysis in the current study investigated the predictive role of acute (≤7 days) EEG. Compared to the diligent data gathering and analysis for the primary research question, authors here rely on data from routine EEGs, available only for 28% (n = 673) of patients from 3 out of 8 study centers. After multivariable analysis, no EEG abnormalities (epileptiform or non-epileptiform) were predictive of PSE. This is in contrast to several smaller studies that either included all consecutive stroke patients[12] or patients with acute brain injury undergoing continuous EEG monitoring and found that acute EEG abnormalities have a significant association with epileptogenesis.[13,14] Although the current study does little to add to the burgeoning literature on prognostic value of acute EEG in PSE, its lasting impact will hopefully be that it settles the debate and resolve doubts about the ictogenic and epileptogenic potential of reperfusion therapies after strokes.

By Vineet Punia, MD, MS 🟢

ORCID iD

Vineet Punia 🟢 https://orcid.org/0000-0002-0552-6736

References

1. Hesdorffer DC, Benn EKT, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia*. 2009;50(5):1102-1108.
2. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*. 2010;51(4):671-675.
3. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
4. Galovic M, Ferreira-Atuesta C, Abraira L, et al. Seizures and epilepsy after stroke: epidemiology, biomarkers and management. *Drugs Aging*. 38(4):285-299.
5. Thurman DJ, Begley CE, Carpio A, et al. The primary prevention of epilepsy: a report of the prevention task force of the International League against epilepsy. *Epilepsia*. 2018;59:905-914.
6. Bentes C, Brigo F, Zelano J, Ferro JM. Reperfusion therapies and poststroke seizures. *Epilepsy Behav*. 2020;104:106524.
7. Ferreira-Atuesta C, Döhler N, Erdélyi-Canavese B, et al. Seizures after ischemic stroke: a matched multicenter study. *Ann Neurol*. 2021;90:808-820.
8. Galovic M, Döhler N, Erdélyi-Canavese B, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *Lancet Neurol*. 2018;17:143-152.

9. Austin PC, Xin Yu AY, Vyas MV, Kapral MK. Applying propensity score methods in clinical research in neurology. *Neurology.* 2021;97:856-863.

10. Johnson EL, Krauss GL, Lee AK, et al. Association between midlife risk factors and late-onset epilepsy: results from the atherosclerosis risk in communities study. *JAMA Neurol.* 2018;75:1375-1382.

11. Choi H, Pack A, Elkind MSV, Longstreth WT, Ton TGN, Onchiri F. Predictors of incident epilepsy in older adults: the cardiovascular health study. *Neurology.* 2017;88:870-877.

12. Bentes C, Martins H, Peralta AR, et al. Early EEG predicts poststroke epilepsy. *Epilepsia Open.* 2018;3:203-212.

13. Punia V, Fitzgerald Z, Zhang X, et al. Electroencephalographic biomarkers of epilepsy development in patients with acute brain injury: a matched, parallel cohort study. *Ann Clin Transl Neurol.* 2019;6:2230-2239.

14. Kim JA, Boyle EJ, Wu AC, et al. Epileptiform activity in traumatic brain injury predicts post-traumatic epilepsy. *Ann Neurol.* 2018;83: 858-862.