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Approximation Is Not Randomization; Lessons From Comparative Observational Studies of Invasive EEG Methods

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Comparative Effectiveness of Stereo-EEG versus Subdural Grids in Epilepsy Surgery.

Lara Jehi, Marcia Morita-Sherman, Thomas E. Love, et al. *Ann Neurol.* 2021;90(6):927-939. doi: 10.1002/ana.26238.

Objective: The aim was to compare the outcomes of subdural electrode (SDE) implantations vs stereotactic electroencephalography (SEEG), the 2 predominant methods of intracranial electroencephalography (iEEG) performed in difficult-to-localize drug-resistant focal epilepsy.

Methods: The Surgical Therapies Commission of the International League Against Epilepsy created an international registry of iEEG patients implanted between 2005 and 2019 with =1 year of follow-up. We used propensity score matching to control exposure selection bias and generate comparable cohorts. Study endpoints were the following: (1) likelihood of resection after iEEG; (2) seizure freedom at last follow-up; and (3) complications (composite of postoperative infection, symptomatic intracranial hemorrhage, or permanent neurological deficit)

Results: Ten study sites from 7 countries and 3 continents contributed 2012 patients, including 1468 (73%) eligible for analysis (526 SDE and 942 SEEG), of whom 988 (67%) underwent subsequent resection. Propensity score matching improved covariate balance between exposure groups for all analyses. Propensity-matched patients who underwent SDE had higher odds of subsequent resective surgery (odds ratio [OR]1.4, 95% confidence interval [CI] 1.05, 1.84) = and higher odds of complications (OR 2.24, 95% CI 1.34, 3.74; unadjusted: 9.6% after SDE vs 3.3% after SEEG).=Odds of seizure freedom in propensity-matched resected patients were 1.66 times higher (95% CI 1.21, 2.26) for SEEG compared with SDE (unadjusted: 55% seizure free after SEEG-guided resections vs 41% after SDE).

Interpretation: In comparison to SEEG, SDE evaluations are more likely to lead to brain surgery in patients with drug resistant epilepsy but have more surgical complications and lower probability of seizure freedom. This comparative effectiveness study provides the highest feasible evidence level to guide decisions on iEEG.

Commentary

When planning for resective surgery for treatment of drug-resistant focal epilepsy, accurate and safe localization of the epileptogenic zone (EZ) is imperative for identifying appropriate candidates. When non-invasive methods are inconclusive, an intracranial EEG study can help localize the EZ. An inherent limitation to all methods of intracranial EEG sampling is the issue of finite or limited cortical coverage. Given that approximately two-thirds of cortical gray matter resides within fissures or deep sulci, surface electrodes cannot readily sample deep epileptogenic foci. When the EZ is localized in deep areas, such as sulcal dysplasia or insula, stereo-encephalography (SEEG) seems to be the preferred technique. When the EZ is localized near eloquent cortex, subdural electrode implantations (SDE) offer the advantage of functional mapping. Age favors

the use of SDE as SEEG is nearly impossible to perform in children 2 years or younger given the thickness of bone at this age.[1] Therefore, these modalities intrinsically evaluate somewhat different populations. In terms of safety, SEEG is reported to have a lower rate of complications and less perioperative pain than SDE.[2,3] In terms of efficacy, is there a difference in the accuracy for identification of the EZ? The answer is not known as data from head-to-head comparison studies is lacking. In the absence of such data, do comparative observational studies provide guidance on which method is superior for identification of the EZ?

Jehi et al[4] recently published the results of a multicenter (10 sites), observational study comparing the yield of both techniques in the likelihood of subsequent resection, seizure-freedom following resection and morbidity and mortality in a

cohort of 837 patients (531 SEEG and 306 SDE). These patients had medically refractory focal-onset seizures, age 16 years or older and at least 1 year of follow-up post-implantation and resection. Because of its retrospective design, propensity score matching (PSM) was utilized as a statistical instrument to generate comparable cohorts. This score reflects the probability of undergoing a given procedure. (More on PSM later). A logistic regression model, based on 18 baseline patient characteristics potentially related to treatment choice or outcome, then yielded a propensity score for each patient. Patients in each group were then matched to each other creating comparable cohorts; thus, mimicking a randomized clinical trial. Matching was done with replacement, meaning that the same SEEG subjects could be used to match to different SDE subjects in creating matched pairs. This procedure evaluated whether matching with replacement provided meaningful improvement in covariate balance over not performing the matching adjustment. Despite clear baseline differences between the SDE and SEEG groups, such as in the incidence of generalized tonic-clonic seizures, temporal lobe and dominant hemisphere disease, and age at implantation, there were no substantial differences between the propensity score-matched cohorts.

The authors report that after SDE implantation, 78.6% of patients underwent resective surgery vs 66.5% after SEEG; seizure-freedom after surgery was 54.6% for SEEG vs 41.1% after SDE-guided resections. Complication rates were 9.6% after SDE vs 4.4% after SEEG implantation; two patients died, 1 in each group. The authors conclude that by using PSM, pairs of similar patients could be created that only differ regarding treatment type; thus, permitting statistically robust inferential analyses that were attributable to treatment type alone. Important data that were not reported and could impact surgical outcome and complication rates are the number of seizures captured and duration of implantation, respectively.

PSM is a statistical matching technique that attempts to reduce the intervention assignment bias and mimics randomization by creating a sample of units that received the intervention that is comparable on all observed covariates to a sample of units that had different interventions. Its disadvantage is that it only accounts for observed covariates and not latent characteristics.[5] Robust inference is therefore not the same as Class 1 evidence and no statistical method can generate a meaningful comparison between cases that are truly dissimilar. Not surprisingly, heterogeneity in epilepsy features continues to guide the preferential selection of the invasive EEG method.

Strengths of this study include a large patient cohort collected from multiple centers, selected to ensure uniformity in neurosurgical standards and level of SEEG expertise, and seizure outcome data after at least 12 months of follow-up. Retrospective descriptive case series support the conclusions of higher resection rates after SDE and lower rates of overall complications with SEEG, 1.3% vs 3.5% for SDE.[6] For hemorrhagic complications, a single-center study of 500 cases (145 SEEG and 355 SDE) reported an incidence of 1.4% for SEEG compared to 2.6% for SDE.[7] In another comparative analysis of a single-center study of 239 patients, a significantly higher proportion of SDE cases underwent resection or ablative surgery while a significantly greater proportion of SEEG cases had a good outcome at 1 year of follow-up (76% % vs 54.6%). An interesting difference in the baseline patient characteristics of this cohort was the higher number of lesional cases that underwent SGE (71.2% vs 43.8%), although seizure control was better in lesional SEEG cases.[3]

In contrast, a recent single-center retrospective study of 66 patients (47 SEEG and 19 SDE) who underwent resection and with follow-up of at least 12 months found similar rates of localization and postintervention seizure control.[8] Similar to Jehi's cohort,[4] there was an unbalanced proportion between mesial temporal and neocortical seizure onsets. Benefits of SEEG over SDE were improved pain control, decreased narcotic usage, and minimal need for ICU care. Given the small sample size, a type II error could have led to the erroneous conclusion of the lack of difference in outcome between the 2 groups.

In conclusion, Jehi's et al[4] study to discern a difference between SDE and SEEG is the best attempt so far at answering the question. But should we take the apparent superiority of SEEG at face value? In my opinion, selection biases are too difficult to overcome with statistics. Moving forward, can a randomized control trial (RCT) in a cohort of patients with overlapping seizure semiology and similar preoperative EZ hypothesis be sanctioned? Most likely not as these methods do not have equivalent indications and should be used selectively for different focal epilepsies. Additionally, these methods are not mutually exclusive and combining them can be helpful for select patients.[9]

In the absence of an RCT, patient selection based on epilepsy features and a strong localization hypothesis should serve as the guiding principles in deciding which method to pursue. An important question that remains unanswered is whether there is a difference in the information obtained from stimulation-induced seizures, which seem to occur more frequently with SEEG.[8,10]

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