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Epilepsia®

LETTER

Low statistical power in a study predicting seizure outcome

To the Editors

We read with great interest the recent article by Kang et al titled "Magnetic resonance-guided laser interstitial thermal therapy: Correlations with seizure outcome." They report the important finding that the presence of bilateral interictal epileptiform discharges (IEDs) was associated with a lower odds of seizure freedom (odds ratio 0.05, 95% confidence interval 0.01–0.46) following magnetic resonance-guided laser interstitial thermal therapy (MRgLiTT) in patients with unilateral mesial temporal sclerosis (MTS). An odds ratio of 0.05 for bilateral IEDs (or 20 for unilateral IEDs) is a large effect size. However, a trial of 56 patients is underpowered to examine the differences in surgical outcome, based on previously reported effect sizes.

We are concerned that the true effect size may be overestimated,[1] which could impact counseling of patients. We reviewed the prior studies cited by Kang and colleagues to determine, conservatively, how many subjects would be needed to have a reasonable power to detect their reported effect size. The authors cite four study reports that examined the association of unilateral IEDs and seizure freedom after anterior temporal lobectomy (ATL).[2–5] The odds ratio for seizure freedom with unilateral IEDs varied from 2.1 to 3.6. Pooling data across the four studies gives an estimate of 80% (292/367) seizure-free after ATL with unilateral IEDs, vs 61% (93/152) seizure-free after ATL with bilateral IEDs (Supplementary Material). This corresponds to an odds ratio of 2.5 for unilateral IEDs, or 0.4 for bilateral IEDs. Based on those published results after ATL, achieving 80% power to detect a difference in seizure freedom of 80% vs 61% would require at least 174 patients, using a normal approximation and assuming equal group sizes.[6] We estimate that the present study of Kang and colleagues has around 20% power to detect a difference in seizure freedom of 80% vs 61%, based on simulation (100,000 repetitions, Fisher's exact test). Underpowered studies necessarily overestimate the effect size of significant results, since the true effect size will not be significant.[1] The issue of low statistical power is not unique to this article but rather is a common problem in epilepsy where studies often have a small number of subjects.

We agree with the authors that bilateral IEDs, based on available evidence, predicts a lower chance of seizure freedom. The seizure-free rate for patients with unilateral IEDs was 72% (33/46). The pre-hoc odds ratio of 0.4 for bilateral IEDs, albeit derived from ATL studies, decreases the chance of seizure freedom from 72% to 50%. However, the reported odds ratio of 0.05 decreases the chance of seizure freedom from 72% to 11%. Those numbers have a very different significance for counseling patients considering surgery. Depending on other data, the presence of bilateral typical medial temporal IEDs in the setting of unilateral MTS may indicate the need for intracranial studies, but bilateral IEDs may not be a contradiction to MRgLiTT. We propose cautious use of these results in counseling patients. We agree with the authors' conclusion that further studies with larger cohorts will be needed to clarify the true effect size for predicting seizure freedom.

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CONFLICT OF INTEREST

N.P.P. has served as a paid consultant for DIXI Medical USA, who manufactures products used in the workup for epilepsy surgery. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. A.S.D has no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Epilepsia®

LETTER

Response: "Low statistical power in a study predicting seizure outcome"

Dear Editors-in-Chief of *Epilepsia*,

We thank Drs. Dickey and Pederson for their interest in our article and raising important points for clarification. Magnetic resonance-guided laser interstitial thermal therapy (MRgLiTT) is a novel procedure, and there is a current gap in knowledge of presurgical prognostic factors that are associated with surgical outcome. It is important to note that MRgLiTT is a more selective procedure than anterior temporal lobectomy (ATL), and our results demonstrate that prognostic factors for MRgLiTT may not be the same as for ATL. Therefore, we are cautious about extrapolating seizure-freedom rates from ATL data and applying them to MRgLiTT. We agree that findings from small studies should be interpreted cautiously, including the possibility of overestimation of effect size. Meta-analysis provides the best estimate of the true effect size, albeit with limitation that the individual studies that contribute to them are subject to low power. Despite this reduced chance of detecting a true effect, our study demonstrates that the presence of bilateral interictal epileptiform discharges (IEDs) is associated with poor outcome, with *adjusted* odds ratio of 0.05 with 95% confidence interval of 0.01–0.46. This adjusted confidence interval includes the pre hoc unadjusted odds ratio of 0.4 that the authors derived from ATL studies. The presence of bilateral IEDs is not a contraindication for MRgLiTT, and we agree that their presence may prompt the clinician to be more cautious in interpreting the presurgical evaluation results. Further studies are needed and necessary to improve surgical outcomes and our findings remain to be replicated in larger cohorts.

CONFLICT OF INTEREST

M.R.S. has research contracts through Thomas Jefferson University with UCB Pharma, Eisai, Medtronics, Takeda, SK Life Science, Neurelis, Engage Therapeutics, Xenon, and Cavion. He has consulted for Medtronic and NeurologyLive. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

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LETTER

SUDEP-3: probable improvement in risk stratification for sudden death in epilepsy

To the Editors,

We thank Dr. Tarighati Rasekhi et al. for raising an important issue in sudden unexpected death in epilepsy (SUDEP) research: the risk stratification for sudden death in epileptic patients. We have carefully reviewed their recent article in *Epilepsia* titled, *Improving prediction of sudden unexpected death in epilepsy: From SUDEP-7 to SUDEP-3*,[1] and we wish to share our experience regarding SUDEP-3 and SUDEP-7 scales for sudden death risk stratification in patients with epilepsy.

In our center at Hospital del Mar Barcelona, part of the European reference network EpiCARE, we have an active SUDEP line of research. From our cohort of 1250 patients, 7 patients died of SUDEP from 2010 to 2018, which makes an adult incidence in our population of 1.3 per 1000 epileptic patient-years.[2]

Of the seven patients who died of SUDEP, six had SUDEP-7 scores of <6 at their last clinical follow-up, which would mean that they were at low risk of SUDEP according to this scale. However, when applying the SUDEP-3 scale, six of the seven deceased patients had scores ≥3, which was considered high risk.[1]

The SUDEP-3 scale mainly weights the number of seizures but does not add cardiac or pulmonary risk factors that could make it a useful tool in clinical practice. However, in our cohort, it demonstrates a higher capacity to identify patients at risk of SUDEP than the SUDEP-7 scale, which could be of more help when considering comparative studies of high- and low-risk patients for identification of new biomarkers and risk factors.

Keywords
epilepsy, experience, risk stratification, SUDEP

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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