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Comparison of outcomes after stereoelectroencephalography and subdural grid monitoring in pediatric tuberous sclerosis complex

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OBJECTIVE Patients with tuberous sclerosis complex (TSC) epilepsy present with unique clinical challenges such as early seizure onset and high rates of intractability and multifocality. Although there are numerous studies about the safety and efficacy of stereoelectroencephalography (SEEG), this topic has not been studied in TSC patients who have distinct epilepsy profiles. The authors investigated subdural grid (SDG) and SEEG monitoring to determine whether these procedures lead to similar seizure and safety outcomes and to identify features unique to this pediatric population.

METHODS TSC patients who underwent SDG or SEEG placement and a second epilepsy surgery during the period from 2007 to 2021 were included in this single-center retrospective cohort analysis. Various patient, hospitalization, and epilepsy characteristics were collected.

RESULTS A total of 50 TSC patients were included in this study: 30 were included in the SDG cohort and 20 in the SEEG cohort. Baseline weekly seizure count did not significantly differ between the 2 groups ($p = 0.412$). The SEEG group had a greater mean baseline number of antiepileptic drugs (AEDs) (3.0 vs 2.0, $p = 0.003$), higher rate of previous surgical interventions (25% vs 0%, $p = 0.007$), and larger proportion of patients who underwent bilateral monitoring (50% vs 13.3%, $p = 0.005$). Despite this, there was no significant difference in seizure freedom between the SDG and SEEG cohorts. The mean reduction in seizure count was 84.9% and 47.8% of patients were seizure free at last follow-up (mean 79.4 months). SEEG trended toward being a safer procedure than SDG monitoring, with a shorter mean ICU stay (0.7 days vs 3.9 days, $p < 0.001$), lower blood transfusion rate (0% vs 13.3%, $p = 0.140$), and lower surgical complication rate (0% vs 10%, $p = 0.265$).

CONCLUSIONS In the comparison of the SDG and SEEG cohorts, the SEEG group included patients who appeared to receive more aggressive management and have a higher rate of multifocality, more prior surgical interventions, more AEDs at baseline, and a higher rate of bilateral invasive monitoring. Despite this, the SEEG cohort had similar seizure outcomes and a trend toward increased safety. Based on these findings, SEEG appears to allow for monitoring of a wider breadth of TSC patients given its minimally invasive nature and its relative simplicity for monitoring numerous regions of the brain.

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KEYWORDS tuberous sclerosis complex; pediatric epilepsy; subdural grids; SEEG; seizure outcomes

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder affecting multiple organ systems.[1] It occurs in 1 of 6000 to 10,000 live births. Intracranial disease is characterized by subependymal nodules, subependymal giant cell tumors, and cortical tubers, which are often epileptogenic. Approximately 80% of TSC patients go on to develop epilepsy.[2–4]

Management of epilepsy in TSC patients has several

ABBREVIATIONS AED = antiepileptic drug; CCHMC = Cincinnati Children's Hospital Medical Center; ILAE = International League Against Epilepsy; LITT = laser interstitial thermal therapy; mTOR = mammalian target of rapamycin; pRBC = packed red blood cell; SDG = subdural grid; SEEG = stereoelectroencephalography; TSC = tuberous sclerosis complex.

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unique clinical challenges. Although patients with a single tuber may have easily localized seizures, multifocality typically predominates because the majority of TSC patients have multiple tubers bilaterally and seizure types that often require intracranial monitoring for localization.[5–8] As a result, seizure control in TSC patients tends to be more difficult than in the general pediatric epilepsy population. Approximately 60% of TSC epilepsy patients develop refractory epilepsy, whereas only 20%–30% of epilepsy cases in the general population become refractory.[9,10] Despite these challenges, management of TSC patients has improved in recent years with increased utilization of mammalian target of rapamycin (mTOR) inhibitors such as everolimus, which was approved by the US Food and Drug Administration in 2010.[1] Such therapies have not only provided novel management strategies for lesions, such as subependymal giant cell tumors, but also led to a reduction in seizure burden.[11]

Similarly, the field of epilepsy surgery has experienced significant changes within the past decade. Stereoelectroencephalography (SEEG) was first performed in the 1950s and has been routinely performed in Europe since that time. However, SEEG only recently became popular in North America, with most pediatric epilepsy centers in the United States having used this technique for less than 5 years.[12–15] The SEEG technique has gradually become the dominant invasive surgery for localization of both adult and pediatric seizure foci, although both subdural grid (SDG) and SEEG monitoring are still practiced. This shift occurred due to the higher rate of morbidity in SDG monitoring cases despite similar or improved seizure localization with SEEG.[16–18]

Although numerous studies have evaluated the safety and efficacy of SEEG for pediatric epilepsy patients, these have yet to be studied in TSC patients, who have distinct epilepsy profiles with high rates of multifocality due to cortically based tubers.[2,16,17,19,20] The aim of this study was to compare SDG and SEEG monitoring in pediatric TSC and to report the results of the safety, efficacy, seizure localization, and outcome measures, as well as the demographic and clinical features, unique to this patient population.

Methods

Study Population

This retrospective cohort study included all TSC patients treated at Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, who underwent implantation of SDG or SEEG and a follow-up second epilepsy surgery for the treatment of identified seizure foci performed by the authors (F.T.M. or J.S.) between 2007 and 2021. IRB approval from CCHMC was obtained prior to data collection and analysis.

All data were obtained through chart review. Patients who underwent resection with or without electrocorticography were excluded from this study if a previous intracranial monitoring procedure had not been performed. Patients were excluded if they did not have appropriate seizure outcome data for at least 6 months after resection/ablation. All SDG monitoring cases were performed earlier in the study period, whereas all SEEG cases were performed in the later part of the study. Vagus nerve stimulation was adopted after US Food and Drug Administration approval in 1999, whereas laser interstitial thermal therapy (LITT) and responsive neurostimulation were adopted during the second half of the study period in 2016 and 2019, respectively.

Surgical Technique

In both the SDG and SEEG groups, patients with tubers adjacent to an eloquent cortex underwent language and/or motor mapping, as indicated. Patients who underwent SDG implantation also subsequently underwent resection at the time of SDG explantation. One SDG patient also had 1 depth electrode; otherwise, this group was not evaluated with any adjunct monitoring modalities aside from the SDG/strips. All SEEG leads were implanted using robotic assistance with ROSA (Zimmer Biomet), and patients underwent resection, ablation, or neuromodulation at a later admission (in general, 4–6 weeks after explantation). All resection patients underwent intraoperative electrocorticography.

Seizure Outcomes

Seizure count was based on the family reports found in the neurology clinic notes. This was extrapolated to a weekly rate and percent reduction for comparison with initial presentation. Seizure outcomes were classified according to the Engel and International League Against Epilepsy (ILAE) classification schemes.[21]

Statistical Analysis

Categorical variables were reported as number (percent). Continuous variables were summarized as mean ± SD. Categorical variables were assessed using the chi-square test and Fisher exact test. Continuous variables were assessed using the 2-tailed Student t-test. A generalized linear equation was used to assess whether there was a trend in seizure freedom across the 3 follow-up periods of 6 months, 1 year, and through last follow-up, as well as whether the monitoring modality affected this outcome. McNemar's test was used to determine whether there was a significant change in seizure freedom between the different periods in a pairwise fashion. A multivariate logistic regression model was created with all the variables investigated in the univariate analysis of the ILAE groups. This was used to estimate the odds ratios of these variables for determination of good seizure outcomes. Statistical analysis was performed with SPSS Statistics version 28.01 (IBM Corp.).

Results

A total of 64 TSC patients underwent epilepsy surgery at CCHMC during this period, and a subset of 50 patients underwent invasive monitoring with SDG or SEEG. Among these 50 patients, 30 SDG patients were compared with 20 SEEG patients to evaluate safety and efficacy. Regarding the phase 3 interventions performed, 43 patients underwent resection (1 at another hospital), 4 underwent

TABLE 1. Patient characteristics

Variable	Total (n = 50)	SDG (n = 30)	SEEG (n = 20)	p Value
Sex				
Male	27 (54.0)	15 (50)	12 (60.0)	
Female	23 (46.0)	15 (50)	8 (40.0)	0.487
Handedness				
Rt	24 (48.0)	16 (53.3)	8 (40.0)	
Lt	12 (24.0)	4 (13.3)	8 (40.0)	
Ambidextrous	2 (4.0)	0 (0)	2 (10.0)	
Undetermined	12 (24.0)	10 (33.3)	2 (10.0)	0.016
Previous interventions	5 (10.0)	0 (0)	5 (25.0)	0.007
Age*				
At onset, mos	9.0 ± 13.2	8.5 ± 11.7	9.8 ± 15.8	0.747
At resection/ablation, yrs	8.0 ± 7.9	6.7 ± 6.2	10.2 ± 10.0	0.206
Duration btwn seizure onset & resection/ablation, yrs*	7.4 ± 7.6	6.2 ± 6.0	9.6 ± 9.5	0.133
Baseline*				
Seizures/wk	44.5 ± 64.4	38.6 ± 56.2	54.9 ± 77.1	0.412
No. of AEDs	2.4 ± 1.1	2.0 ± 1.0	3.0 ± 1.0	0.003

Values are expressed as mean ± SD or number (%) unless indicated otherwise.
* Only resective/ablative cases were considered (SDG [n = 29] vs SEEG [n = 17]).

TABLE 2. Seizure outcomes at 6 months

Variable	Total (n = 36)	SDG (n = 20)	SEEG (n = 16)	p Value
Seizure freedom	13 (36.1)	7 (35.0)	6 (37.5)	0.877
Global seizures				
Seizures/wk	7.1 ± 11.9	7.3 ± 11.3	6.8 ± 13.0	0.895
% reduction	76.7 ± 36.0	75.0 ± 38.8	78.9 ± 33.4	0.753
Target seizures				
Seizures/wk	6.1 ± 12.0	6.1 ± 11.3	6.1 ± 13.1	0.995
% reduction	81.7 ± 30.4	82.7 ± 28.3	80.4 ± 33.8	0.826
No. of AEDs	2.3 ± 1.1	1.8 ± 0.8	2.8 ± 1.2	0.012
Change in AED no. from baseline	−0.2 ± 0.9	−0.2 ± 0.9	−0.3 ± 0.9	0.897
ILAE class				
1–3	15 (41.7)	9 (45.0)	6 (37.5)	
4–6	21 (58.3)	11 (55.0)	10 (62.5)	0.650
Engel class				
I–II	16 (44.4)	9 (45.0)	7 (43.8)	
III–IV	20 (55.6)	11 (55.0)	9 (56.3)	0.940

Values are expressed as mean ± SD or number (%) unless indicated otherwise.

LITT, and 3 underwent neuromodulation including 2 cases of responsive neurostimulation and 1 case of vagus nerve stimulation. All patients who underwent LITT or neuromodulation were in the SEEG cohort. All 46 patients who underwent resective or ablative procedures at the study hospital were included in the analysis of seizure outcomes, whereas those who underwent palliative neuromodulation were excluded.

Patient Characteristics

The baseline characteristics of the patients included in both groups were collected (Table 1). There were no significant differences between the groups, with a nearly even ratio between male and female patients in both groups ($p = 0.487$). The SDG group had significantly greater proportions of right-handed patients (53.3% vs 40%) and those with undetermined handedness (33.3% vs 10%), but a lower proportion of left-handed patients (13.3% vs 40%, $p = 0.016$). The SEEG cohort had a significantly greater proportion of patients who had undergone previous interventions (25% vs 0%, $p = 0.007$). Importantly, there were no significant between-group differences in terms of mean age at onset ($p = 0.747$), age at resection/ablation ($p = 0.206$), or duration between these 2 points ($p = 0.133$), although there was a trend toward longer duration between onset and intervention in the SEEG cohort (9.6 ± 9.5 years vs 6.2 ± 6.0 years). The numbers of young patients ≤ 2 years of age at monitoring were similar between groups (10 [33.3%] in the SDG group vs 6 [30%] in the SEEG group, $p = 0.804$). The baseline weekly seizure count was 38.6 ± 56.2 for the SDG group versus 54.9 ± 77.1 for the SEEG group, and this difference was nonsignificant ($p = 0.412$). The SEEG group was receiving a greater mean number of antiepileptic drugs (AEDs) at baseline (3.0 ± 1.0 vs 2.0 ± 1.0, $p = 0.003$).

Seizure Outcomes

Seizure outcomes after resection or ablation were reported 6 months after intervention, 1 year after intervention, and at last follow-up (Tables 2–4). Among all patients, there was a large percent reduction in global seizure burden (84.9% ± 33.1%) and an even larger percent reduction in target seizure burden (90.6% ± 22.3%) at last follow-up. Global seizure count and percent reduction and target seizure count and percent reduction were not significantly different between the 2 groups during any period. Among all patients, 91.3% of patients had an ILAE class 1–4 outcome, 56.5% of patients had an ILAE class 1–3 outcome, and 60.9% had Engel class I–II outcome at last follow-up. Among the seizure outcome variables, only 2 variables were significantly different between groups: 1) the number of AEDs, which was likely due to the difference in the numbers of AEDs at baseline because the change in number of AEDs was nonsignificant, and 2) time to last follow-up, which was significantly longer in the SDG group (118.0 ± 49.1 months vs 15.6 ± 13.5 months, $p < 0.001$).

In total, 47.8% of all patients were seizure free at last follow-up. There were no significant differences between the SDG and SEEG groups at any time point. From the 1-year follow-up to last follow-up, there was a trend for an increasing proportion of patients who were seizure free (from 34.2% to 47.8%). A generalized linear equation indicated that although there was no statistically significant in-

TABLE 3. Seizure outcomes at 1 year

Variable	Total (n = 38)	SDG (n = 27)	SEEG (n = 11)	p Value
Seizure freedom	13 (34.2)	10 (37.0)	3 (27.3)	0.714
Global seizures				
Seizures/wk	6.6 ± 12.1	7.4 ± 13.9	4.4 ± 5.2	0.491
% reduction	79.3 ± 34.3	76.8 ± 37.7	85.4 ± 24.4	0.493
Target seizures				
Seizures/wk	5.0 ± 11.2	5.4 ± 12.9	4.1 ± 5.4	0.748
% reduction	86.2 ± 28.3	86.2 ± 30.1	86.2 ± 24.8	0.999
No. of AEDs	2.0 ± 0.9	1.8 ± 0.8	2.5 ± 0.9	0.012
Change in AED no. from baseline	−0.3 ± 0.8	−0.3 ± 0.9	−0.3 ± 0.5	0.963
ILAE class				
1–3	19 (50.0)	15 (55.6)	4 (36.4)	
4–6	19 (50.0)	12 (44.4)	7 (63.6)	0.283
Engel class				
I–II	19 (50.0)	15 (55.6)	4 (36.4)	
III–IV	19 (50.0)	12 (44.4)	7 (63.6)	0.283

Values are expressed as mean ± SD or number (%) unless indicated otherwise.

TABLE 4. Seizure outcomes at last follow-up

Variable	Total (n = 46)	SDG (n = 29)	SEEG (n = 17)	p Value
Seizure freedom	22 (47.8)	15 (51.7)	7 (41.2)	0.489
Global seizures				
Seizures/wk	6.0 ± 17.4	8.1 ± 21.6	2.3 ± 3.7	0.169
% reduction	84.9 ± 33.1	83.1 ± 37.4	88.0 ± 24.9	0.628
Target seizures				
Seizures/wk	2.7 ± 6.7	3.0 ± 8.0	2.1 ± 3.7	0.650
% reduction	90.6 ± 22.3	91.8 ± 21.0	88.5 ± 25.0	0.640
No. of AEDs	1.9 ± 1.1	1.5 ± 0.9	2.5 ± 1.2	0.004
Change in AED no. from baseline	−0.5 ± 1.2	−0.5 ± 1.3	−0.5 ± 0.9	0.858
ILAE class				
1–3	26 (56.5)	19 (65.5)	7 (41.2)	
4–6	20 (43.5)	10 (34.5)	10 (58.8)	0.108
Engel class				
I–II	28 (60.9)	20 (69.0)	8 (47.1)	
III–IV	18 (39.1)	9 (31.0)	9 (52.9)	0.142
Time to last follow-up, mos	79.4 ± 63.8	118.0 ± 49.1	15.6 ± 13.5	<0.001
Post-resection/ablation intervention*	5 (10.6)	4 (13.3)	1 (5.9)	0.640

Values are expressed as mean ± SD or number (%) unless indicated otherwise.
* Number of patients, not number of procedures, is shown.

teraction between monitoring modality and time across the 3 time points (p = 0.815), there was a directional effect of time on seizure freedom (p = 0.073). Post hoc comparisons showed that there was a statistically significant difference between seizure freedom at 1 year and seizure freedom at last follow-up (p = 0.014). All those patients who were seizure free at 1 year remained seizure free at last follow-up (13 of 13); of those who were not seizure free at 1 year, 24% (6 of 25) were seizure free at last follow-up.

Predictors of Seizure Outcome

Variables were analyzed with patients dichotomized as ILAE class 1–3 versus ILAE class 4–6 (Table 5). There were no significant differences between the 2 class groupings in terms of sex, handedness, age at onset, baseline seizure count, baseline number of AEDs, number of electrode contacts, age at resection/ablation, or duration between seizure onset and resection/ablation. There was a trend toward longer duration between onset and resection/ablation in the ILAE class 4–6 group versus the ILAE class 1–3 group (9.9 ± 9.4 years vs 6.1 ± 6.2 years, p = 0.138). There was a significant difference between the 2 groups in terms of time to last follow-up, with the ILAE class 1–3 group receiving 95.5 ± 62.8 months of follow-up versus 57.7 ± 59.7 months for the ILAE class 4–6 group (p = 0.044). On multivariate regression analysis, there were no significant predictors of ILAE class 1–3 outcomes, including intracranial monitoring procedure type, time to last follow-up, or duration between seizure onset and age at resection/ablation (Table 6).

Monitoring Procedure Characteristics

Several key characteristics differed between procedure groups (Table 7). In total, 50% of SEEG procedures were bilateral, whereas only 13.3% of SDG procedures were bilateral (p = 0.005). The number of electrode contacts was smaller in the SDG group than the SEEG group (88.7 ± 21.3 vs 126.8 ± 47.8, p < 0.001). The mean ± SD number of leads inserted for SEEG cases was 13.0 ± 3.5, which required 7.0 ± 2.3 minutes per lead. Procedure duration was significantly longer in the SDG group than the SEEG group (182.7 ± 58.2 minutes vs 88.5 ± 32.9 minutes, p < 0.001). The mean length of stay in the ICU was longer in the SDG cohort than the SEEG cohort (3.9 ± 2.8 days vs 0.7 ± 1.6 days, p < 0.001). There were no significant differences in the numbers of packed red blood cell (pRBC) transfusions, any complications, or reoperations for hematoma/edema, although there were nonsignificant trends toward higher rates in the SDG group (13.3%, 10%, and 10%, respectively) than in the SEEG group (0% for all events).

Resection Characteristics

Variables specific to the resection cases alone are reported in Table 8. There were no significant differences between the SDG and SEEG groups in terms of age at resection, resection laterality, pRBC transfusions, length of stay, or complication occurrence. Among all TSC patients included in this study, 14.3% required pRBC transfusion intraoperatively or during postoperative hospitalization for resection. Length of stay after epileptogenic tissue resection was on average 5.7 ± 4.1 days. Complications occurred in 4.8% of all resection cases.

TABLE 5. Univariate comparison of the ILAE class 1–3 and 4–6 groups at last follow-up

Variable	Total (n = 46)	ILAE Class 1–3 (n = 26)	ILAE Class 4–6 (n = 20)	p Value
Sex				
Male	24 (52.2)	12 (46.2)	12 (60.0)	
Female	22 (47.8)	14 (53.8)	8 (40.0)	0.351
Handedness				
Rt	23 (50.0)	12 (46.2)	11 (55.0)	
Lt	9 (19.6)	7 (26.9)	2 (10.0)	
Ambidextrous	2 (4.3)	0 (0)	2 (10.0)	
Undetermined	12 (26.1)	7 (26.9)	5 (25.0)	0.239
Age at onset, mos	9.0 ± 13.2	9.0 ± 12.3	9.3 ± 14.7	0.949
Baseline				
Seizures/wk	44.5 ± 64.4	48.4 ± 81.6	39.7 ± 31.7	0.655
No. of AEDs	2.4 ± 1.1	2.3 ± 1.1	2.5 ± 1.2	0.756
Intracranial monitoring procedure				
SDG	29 (63.0)	19 (65.5)	10 (34.5)	
SEEG	17 (37.0)	7 (41.2)	10 (58.8)	0.133
Bilat monitoring	11 (23.9)	6 (23.1)	5 (25.0)	>0.999
No. of electrode contacts	101.4 ± 36.8	97.8 ± 31.0	107.5 ± 44.6	0.407
Age at resection/ablation, yrs	8.0 ± 7.9	6.5 ± 6.3	9.9 ± 9.4	0.160
Duration btwn seizure onset & resection/ablation, yrs	7.4 ± 7.6	6.1 ± 6.2	9.4 ± 8.9	0.138
Time to last follow-up, mos	79.4 ± 63.8	95.5 ± 62.8	57.3 ± 59.7	0.044

Values are expressed as mean ± SD or number (%) unless indicated otherwise.

TABLE 6. Multivariate regression analysis for OR estimation of ILAE class 1–3 at last follow-up

Variable	OR (95% CI)	p Value
Sex		
Male	Reference	
Female	0.80 (0.12–5.23)	0.812
Handedness		
Rt	1.87 (0.23–15.13)	0.947
Lt	6.56 (0.42–103.10)	0.925
Ambidextrous	<0.001 (<0.00 to >999.99)	0.944
Undetermined	Reference	
Age at onset, mos	0.87 (0.65–1.14)	0.310
Baseline seizure count	1.00 (0.99–1.02)	0.644
No. of AEDs at baseline	3.04 (0.96–9.60)	0.059
Intracranial monitoring procedure		
SDG	6.70 (0.20–225.94)	0.290
SEEG	Reference (0.12–5.23)	0.812
Bilat monitoring	21.87 (0.66–730.10)	0.085
No. of electrode contacts	0.98 (0.934–1.01)	0.201
Age at resection/ablation, yrs	13.10 (0.52–327.65)	0.117
Duration btwn seizure onset & resection/ablation, yrs	0.07 (0.00–1.88)	0.114
Time to last follow-up, mos	1.01 (0.99–1.03)	0.354

Discussion

Epilepsy in TSC

Epilepsy patients with TSC have several features that make them distinct. Seizure onset is typically at a younger age, with approximately 90% of patients experiencing their first seizure at age younger than 1 year compared with 20%–30% of general pediatric epilepsy patients who have onset before 1 year of age.[2,22–24] TSC-associated epilepsy is also typically more difficult to treat, with almost two-thirds of TSC epilepsy patients having seizures refractory to medical treatment.[9,24] Medically refractory epilepsy in TSC patients is often characterized by its multifocal nature.[25–27] This was corroborated in this study because nearly 30% of patients required bilateral monitoring. Despite this initial surgical approach, nearly all cases (94%) had the epileptogenic foci localized and patients were able to undergo resection or ablation of epileptogenic tissue. In our series, all cases who underwent resection/ablation had unilateral presentation. In the vast majority of cases, a single intervention led to a significant reduction in seizure burden, with an 84.9% mean reduction in global seizures; eventual seizure freedom was noted for 47.8% of resective/ablative cases at last follow-up. However, it is important to interpret these results in context. Because the primary objective of this study was to determine whether outcomes were equivalent between the SDG and SEEG cohorts, patients who underwent epileptogenic focus resection without the utilization of one of these modalities were excluded. The excluded patients had a localizable epileptogenic focus on noninvasive monitoring alone and were most likely able to achieve seizure freedom with single-step resection/ablation; therefore, these outcomes were likely underreported as compared with historical studies that included only patients with TSC-associated epilepsy.[8,22,28]

In this study, we noted a trend for increasing seizure freedom with longer follow-up. The study was unique because a large single center captured all patients who were observed for a significantly longer period than those included in most reported studies of TSC.[8,29] Although the trend for seizure freedom was nonsignificant across the 3 time points, the seizure freedom rates were significantly different between the 1-year and the last follow-up evaluations. Patients with ILAE class 1–3 versus those with ILAE class 4–6 outcomes also had significantly longer follow-up, although follow-up duration did not have a significant effect on ILAE class 1–3 outcome on multivariate regression analysis. Although this study alone provides no conclusions that explain this observation, this phenomenon is likely multifactorial.[30,31] This observation may have been due, in part, to the increase in the neurologist's armamentarium of AEDs that allow for further

TABLE 7. Monitoring procedure characteristics

Variable	Total (n = 50)	SDG (n = 30)	SEEG (n = 20)	p Value
Age at monitoring procedure, yrs	8.1 ± 8.2	6.5 ± 6.2	10.5 ± 10.2	0.132
Bilat monitoring	14 (28.0)	4 (13.3)	10 (50.0)	0.005
Procedure duration, mins	138.9 ± 67.2	182.7 ± 58.2	88.5 ± 32.9	<0.001
No. of electrode contacts	101.4 ± 36.8	88.7 ± 21.3	126.8 ± 47.8	0.009
Electrode contacts inserted/min	1.0 ± 0.7	0.5 ± 0.2	1.6 ± 0.6	<0.001
No. of leads	NA	NA	13.0 ± 3.5	NA
Time per lead insertion, min	NA	NA	7.0 ± 2.3	NA
Motor mapping performed*	29 (61.7)	17 (58.6)	12 (66.7)	0.581
Language mapping performed†	11 (25.0)	6 (23.1)	5 (27.8)	>0.999
Length of monitoring, days	5.2 ± 2.4	5.2 ± 2.1	5.2 ± 2.8	0.976
Length of ICU stay, days	2.6 ± 2.8	3.9 ± 2.8	0.7 ± 1.6	<0.001
pRBC transfusion	4 (8.0)	4 (13.3)	0 (0)	0.140
Any complication occurrence‡	3 (6.0)	3 (10.0)	0 (0)	0.265
Reop for hematoma/edema	3 (6.0)	3 (10.0)	0 (0)	0.265

NA = not applicable.
Values are expressed as mean ± SD or number (%) unless indicated otherwise.
* n = 47 because data were unavailable for several cases.
† n = 44 because data were unavailable for several cases.
‡ Complications included any infection treated surgically, hydrocephalus, cerebrospinal fluid leak, treated pseudomeningocele, and reoperation for hematoma/edema.

TABLE 8. Resection characteristics

Variable	Total (n = 42)	SDG (n = 29)	SEEG (n = 13)	p Value
Age at resection, yrs	7.9 ± 8.0	6.7 ± 6.2	10.7 ± 10.8	0.230
Laterality				
Rt	16 (37.2)	11 (36.7)	5 (38.5)	
Lt	27 (62.8)	19 (63.3)	8 (61.5)	>0.999
pRBC transfused	6 (14.3)	5 (17.2)	1 (7.7)	0.647
Length of stay for resection, days	5.7 ± 4.1	5.4 ± 5.2	6.3 ± 5.0	0.617
Any complication occurrence*	2 (4.8)	2 (6.9)	0 (0)	0.562

Values are expressed as mean ± SD or number (%) unless indicated otherwise.
* Complications included any infection treated surgically, hydrocephalus, cerebrospinal fluid leak, treated pseudomeningocele, and reoperation for hematoma/edema.

fine-tuning with longer follow-up, in addition to seizure-reducing mTOR inhibitor medications such as everolimus that have not been historically prescribed early in the disease course.[11,32]

SDG Versus SEEG Monitoring in TSC Patients

Although seizure localization in patients with TSC follows the same general principles as other epilepsy etiologies, there are some nuances that make this process unique. Noninvasive seizure monitoring is the first step of any evaluation for surgical management of epilepsy. Scalp EEG is the neurologist's primary diagnostic test in the management of epilepsy, and this also plays an important role in preoperative evaluation.[33] However, multiple seizure types are often present in patients with TSC-associated epilepsy, limiting the utility of this modality alone.[25–27] Therefore, other modalities such as MRI, single-photon emission computerized tomography, functional MRI, positron emission tomography, and magnetoencephalography are all commonly used at high-volume epilepsy centers to further delineate epileptogenic foci. If there is clear concordance among the various noninvasive modalities regarding the location of the epileptogenic focus with correlation to a single seizure semiology, resection/ablation of the tuber may proceed without intracranial monitoring.[8,28,34,35] In cases without a dominant tuber or epileptogenic focus but with clear lateralization, unilateral intracranial monitoring is indicated. If no dominant tuber is identified and/or multiple seizure semiologies/discordant data prevail but a regional network is suggested on noninvasive workup, then bilateral intracranial monitoring may be indicated. If there is no evidence of a regional network on noninvasive workup, no intracranial monitoring is indicated and palliative measures should be considered. Intracranial monitoring should also be considered in cases with an epileptogenic focus that is in close proximity to regions that may be an eloquent cortex.

Although SDG and SEEG monitoring are both effective invasive techniques for seizure localization in most instances, each modality has slightly different characteristics.[18,35,36] SDG monitoring has the advantage of a high density of cortical contacts in a specific area, which produces reliable results when electrical stimulation is required for motor or language mapping. SDG monitoring is less optimal if functional mapping is performed over areas that are more dispersed, whereas SEEG may be better suited. In cases with several possible epileptogenic foci or those that require bilateral monitoring, SEEG is the preferable option because of its ability to monitor numerous locations, as well as owing to the technical difficulty and operative time required to perform the large or bilateral craniotomies necessary for SDG placement. SEEG also provides a 3-dimensional understanding of epileptogenic foci because its contacts are not limited to the cortex. Early reports advised against performing SEEG monitoring in children 2 years of age and younger due to poor bone quality, but numerous studies have demonstrated the safety of this approach.[37–39] In this report, 30% of the SEEG cohort was ≤ 2 years of age. It is strongly recommended to monitor the TSC population at this early age, in particular, because many of these patients have early-onset seizures

and intervention as soon as possible may allow for the best neurodevelopment.[9,40,41]

Although the SDG and SEEG groups were quite similar, investigation (including analysis of baseline seizure count) showed several key findings that suggested the use of different seizure management strategies. Practice patterns changed to consider a wider array of patients for intracranial monitoring with SEEG rather than SDG because SEEG can be used to sample multiple bilateral areas of the brain without the risks associated with bilateral craniotomy. There was a higher rate of prior surgical interventions, baseline number of AEDs, and rate of bilateral monitoring in the SEEG group than the SDG group. These 3 variables taken together suggest that the patients in the SEEG group had seizures that were more difficult to medically manage and localize. Despite these findings, both groups had similar seizure outcomes. Although SDG monitoring may require a greater number of electrodes with direct cortical contact, SEEG has the advantage of covering diverse and distant regions in the brain; this may be critical for the evaluation of TSC-associated epilepsy given the multifocal nature and inherent 3-dimensional structure of tubers. SEEG allows for bilateral coverage with a minimally invasive approach; therefore, poorly localized epilepsy cases that may not have been deemed appropriate for surgery previously may now be considered for invasive EEG monitoring. All this information taken together suggests that for pediatric TSC patients, in particular, SEEG may be the preferred intracranial monitoring modality. In short, SEEG capability may transform previously poor candidates for SDG intracranial monitoring into acceptable candidates for SEEG monitoring, leading to procedures that result in significant seizure reduction or seizure freedom in a larger cohort.

As evidenced by numerous studies in the general epilepsy population, SEEG appears to be as safe as SDG.[16–18] Despite requiring a significantly larger average number of electrode contacts than the SDG group, the SEEG group had an average procedure duration that was more than 90 minutes shorter. Reducing time under anesthesia not only reduces the risks of anesthesia-related complications but may also be beneficial to neurodevelopment, as some studies have suggested that anesthesia in pediatric patients may negatively impact cognitive and behavioral outcomes.[42,43] We also identified a significant decrease in ICU utilization in the SEEG group (mean 0.7 days) as compared with the SDG group (mean 3.9 days). Although not statistically significant in this study, the SEEG group had rates of 0% for pRBC transfusion and complications compared with rates of 13% and 10% for the SDG group, respectively.

Limitations

There are several limitations to consider in the interpretation of this study. There was likely some degree of selection bias for the patients who were initially evaluated and offered invasive monitoring. The higher rate of bilateral monitoring among SEEG patients may have been, in part, due to the evolution of the greater array of interventions besides resection that are available in the event of poor localization after monitoring. The experience levels of the surgeons likely varied throughout the study, although this was unlikely to have significantly affected seizure outcomes. This study was carried out at a single center in a retrospective manner; therefore, global generalizability may be limited. Future prospective studies on this subject matter may help to reduce bias and broaden applicability.

Conclusions

The management of pediatric patients with TSC has evolved with significant improvements in the past several decades. The introduction of TSC-specific medications such as mTOR inhibitors and the addition of minimally invasive monitoring techniques such as SEEG, as well as new neuromodulation procedures, have allowed new possibilities for better clinical results. Epilepsy in TSC poses several unique challenges, such as early onset, high rate of intractability, and its multifocal nature. Compared with SDG monitoring, it appears that the use of SEEG addresses many of these considerations and potentially further broadens the scope of patients who may be deemed appropriate for invasive monitoring. Comparison of SDG with SEEG surgical techniques demonstrated equivalent seizure outcomes in the TSC population.

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Disclosures

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Author Contributions

Conception and design: Mangano, Larrew, Skoch, Greiner. Acquisition of data: Larrew. Analysis and interpretation of data: all authors. Drafting the article: Mangano, Larrew, Greiner. Critically revising the article: Mangano, Larrew, Skoch, Krueger, Greiner. Reviewed submitted version of manuscript: Mangano, Larrew, Skoch, Arya, Krueger, Greiner. Approved the final version of the manuscript on behalf of all authors: Mangano. Statistical analysis: Larrew, Horn. Study supervision: Mangano, Greiner.

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