Long-term outcomes after surgery for catastrophic epilepsy in infants: institutional experience and review of the literature

Vincent C. Ye, MD,¹ Ashish H. Shah, MD,² Samir Sur, MD,² Justin K. Achua, MS,² Shelly Wang, MD, MPH,³ George M. Ibrahim, MD, PhD,¹ Sanjiv Bhatia, MD,³ and John Ragheb, MD^{2,3}

¹Division of Neurosurgery, Department of Surgery, Hospital for Sick Children, University of Toronto, Ontario, Canada;

²Department of Neurosurgery, University of Miami; and ³Division of Neurosurgery, Nicklaus Children's Hospital, Miami, Florida

OBJECTIVE Uncontrolled epilepsy is associated with serious deleterious effects on the neurological development of infants and has been described as “catastrophic epilepsy.” Recently, there has been increased emphasis on early surgical interventions to preserve or rescue neurodevelopmental outcomes in infants with early intractable epilepsy. The enthusiasm for early treatments is often tempered by concerns regarding the morbidity of neurosurgical procedures in very young patients. Here, the authors report outcomes following the surgical management of infants (younger than 1 year).

METHODS The authors performed a retrospective review of patients younger than 1 year of age who underwent surgery for epilepsy at Miami (Nicklaus) Children's Hospital and Jackson Memorial Hospital between 1994 and 2018. Patient demographics, including the type of interventions, were recorded. Seizure outcomes (at last follow-up and at 1 year postoperatively) as well as complications are reported.

RESULTS Thirty-eight infants (median age 5.9 months) underwent a spectrum of surgical interventions, including hemispherectomy (n = 17), focal resection (n = 13), and multilobe resections (n = 8), with a mean follow-up duration of 9.1 years. Hemimegalencephaly and cortical dysplasia were the most commonly encountered pathologies. Surgery for catastrophic epilepsy resulted in complete resolution of seizures in 68% (n = 26) of patients, and 76% (n = 29) had a greater than 90% reduction in seizure frequency. Overall mortality and morbidity were 0% and 10%, respectively. The latter included infections (n = 2), infarct (n = 1), and immediate reoperation for seizures (n = 1).

CONCLUSIONS Surgical intervention for catastrophic epilepsy in infants remains safe, efficacious, and durable. The authors' work provides the longest follow-up of such a series on infants to date and compares favorably with previously published series.

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KEYWORDS infant; epilepsy; surgery; outcomes; hemispherectomy

SEIZURE disorders in childhood can either follow a benign and relatively inconsequential course or have significant deleterious effects on neurocognitive development. These latter epilepsies are so-called catastrophic.^{1–4} Despite maximal medical management, a significant number of infants (roughly 25%) continue to progress with seizures.^{5–8} The considerable adverse effects of unrelenting seizure activity on the developing brain result in cognitive, psychological, and functional impairment and have been

associated with up to a 20% risk of mortality in some series.^{7,9}

Epilepsy surgery has played an important role in the treatment of patients affected by medically intractable seizures, resulting in excellent seizure control and improvement in quality of life in a greater number of patients with hemispheric epileptogenic conditions.^{7,10–15} In cases of catastrophic epilepsy, it has been suggested that neurosurgical treatment can alter the natural history of the disease

ABBREVIATIONS DQ = developmental quotient.

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and that surgery should be offered to reduce the impact of the seizures on the developing brain as soon as technically feasible.^{7,10,16–19} Bolstered by technological innovations and advances in surgical techniques, there has been a growing trend toward surgically treating medically refractory epilepsy in very young children.^{3,10,18,20,21} Reasons for deferring surgery in young children have included technical challenges, a presumed risk of increased complications thought to relate to the child's limited blood volume, and the immaturity of the brain and developing myelination patterns.^{17,22–24} The literature surrounding treatment of these patients is largely composed of small case reports and retrospective case series that have indicated that epilepsy surgery in infants and young children is effective and relatively safe and can result in improved developmental outcomes.^{10,16,25–32}

Here, we present a retrospective series of 38 infants younger than 1 year who underwent surgery at a single program encompassing 2 sites, with long-term follow-up approaching 10 years. We report results such as Engel classification at last follow-up, seizure freedom or reduction posttreatment, and morbidity and mortality. In addition, we conducted a comprehensive and updated literature review on outcomes after epilepsy surgery in infants and young children operated on before the age of 3 years, with a focus on surgical and developmental outcomes, and morbidity and mortality rates. While literature reviews on epilepsy in young children exist,^{28,31} we include a particular focus on data regarding infants.

Methods

Patient Selection

After receiving institutional review board approval, we reviewed the patient charts of infants (< 12 months) from Nicklaus (Miami) Children's Hospital and Jackson Memorial Hospital between December 1994 and October 2018. We performed a retrospective review of patients who presented with infantile seizures that impacted early development and who underwent surgery. All patients were discussed at a multidisciplinary epilepsy conference comprising neurologists, neuropsychologists, and the 2 senior surgeons. Infants selected for surgery were thought to have a good probability of improved seizure outcomes as a result of phase 1 investigations (i.e., video telemetry and MR). Extended EEG and MRI were the primary modes of investigation (prior to invasive monitoring). No phase 2 investigations (i.e., invasive monitoring) were conducted on these patients, as they were only selected for surgery with good correlation from phase 1 tests.

Data Collection

Patient demographics, including current age and sex, and relevant clinicoradiographic information, including diagnosis, age at onset of epilepsy, date of surgery, type of surgical procedure, complications, postoperative seizure frequency, duration of the seizure-free period, date of last follow-up, and Engel class, were collected. All patients in this study were treated with partial or complete hemispherectomy, lobectomy, or lesionectomy.

Postoperative seizure outcome at the 1-year postopera-

TABLE 1. Characteristics of 38 infants undergoing surgery for catastrophic epilepsy

Patient Characteristic	Value
Current age	
Median	17 yrs
Mean (range)	16 yrs & 8 mos (7–23 yrs)
Sex, n (%)	
Male	25 (65.8)
Female	13 (34.2)
Age at epilepsy onset	
Median	11.3 days
Mean (range)	46.5 days (0–317.6 days)
Age at 1st op	
Median	5.9 mos
Mean (range)	5.9 mos (0.9–11.6 mos)
Seizure-free duration	
Median	6.4 yrs
Mean (range)	7.1 yrs (10 days–19.6 yrs)
Engel class at last follow-up	
Median	1
Mean (range)	1.8 (1–4)
Follow-up duration	
Median	7.8 yrs
Mean (range)	9.1 yrs (2 mos–22.3 yrs)

tive mark and duration of the seizure results were the primary outcomes. Seizure freedom was determined to be an absence of any type of seizure after the date of surgery. For the patients with follow-up data available beyond the 1-year postoperative mark, the duration of seizure freedom was defined as either the time between the surgical date and the next subsequent seizure or the time between the surgical date and the most recent follow-up if they remained seizure free. Secondary outcomes included survival rates and postoperative complications.

Statistical Analysis

Results are described as frequencies and percentages. Prism 7 (GraphPad Software) was used for Kaplan-Meier curve production and statistical analysis.

Literature Review

Databases including PubMed and MEDLINE were used for literature search. MeSH terms used in the search included “Epilepsy/di, pa, su” (diagnosis, pathology, surgery), “treatment outcome,” and “infant.” The search was limited to English-language articles with full-text availability from 1990 to April 2019. Citations from key articles were cross-referenced for completeness. Articles were included in our literature review if they included at least 10 cases in which an infant was operated on before the age of 3 years, with functional outcomes that could be correlated. For example, case series that had an age range of 0.5–5 years at time of operation were not included if the functional outcomes of those operated on before the age of 3

TABLE 2. Diagnosis, types of surgical procedures, and seizure outcomes

Patient Characteristic	No. of Patients (%)
Diagnosis	
Cortical dysplasia	12 (31.5)
Hemimegalencephaly	11 (28.9)
Tuberous sclerosis	5 (13.2)
Infarction	3 (7.9)
Ohtahara syndrome	1 (2.6)
Rasmussen's encephalitis	1 (2.6)
Neurocutaneous melanosis	1 (2.6)
Tumor	4 (10.5)
Temporal astrocytoma	1 (2.6)
Hemispheric astrocytoma	1 (2.6)
Poorly differentiated glioma	1 (2.6)
Pleomorphic xanthoastrocytoma	1 (2.6)
Resection type	
Focal resection	13 (34.2)
TLR	7 (18.4)
FLR	5 (13.2)
OLR	1 (2.6)
MLR	8 (21.1)
Hemispherectomy	17 (44.7)
Seizure frequency at 1 yr postop	
Seizure freedom	26 (68.4)
>90% reduction	3 (7.9)
>50–90% reduction	2 (5.3)
<50% reduction	7 (18.4)

FLR = frontal lobe resection; MLR = multilobe resection; OLR = occipital lobe resection; TLR = temporal lobe resection.

years were not clearly delineated. Additional data, including mean age at seizure onset, mean age at operation, diagnosis/pathology, surgical technique, and complications, were extracted. Overall, 13 articles were included.

Results

Patient Demographics, Diagnosis, and Surgical Treatment

Thirty-eight children (25 males and 13 females) presented with early intractable catastrophic childhood epilepsy and underwent surgery at Miami Children's Hospital or Jackson Memorial Hospital and were included in this study (Table 1). Each patient included in the study experienced multiple seizures on a daily basis. The underlying diagnosis in this cohort included cortical dysplasia (n = 12), hemimegalencephaly (n = 11), and tumor (n = 4) (Table 2). In the majority of patients, the onset of epilepsy was within the 1st month of life, with the median onset being 11.3 days (range 0–318 days). Thirty-three of the 38 children were followed up at least 4 years postoperatively, with a mean follow-up duration of 9.1 years (range 2 months–22.3 years). There were no patients in our study who underwent repeat resection.

The most common surgical procedures for this cohort of children with catastrophic epilepsy were hemispherectomy (n = 17) followed by focal resection (n = 13), with resection of the temporal lobe being the most common focal resection. Eight of the 38 children had multilobe resections, and all 11 children diagnosed with hemimegalencephaly underwent a hemispherectomy (Table 3). The median age at the time of surgery was 5.9 months (range 0.9–11.6 months). On average, 7 years of seizure freedom was achieved by surgery (range 10 days–19.6 years).

One-Year Treatment Outcomes

At the 1-year postoperative date, 26 (68.4%) of the 38 children remained seizure free, while 3 (7.9%) children experienced greater than 90% reduction in seizure fre-

TABLE 3. Diagnoses and types of surgical procedures

	Focal Resection				Hemispherotomy	Total
	TLR	FLR	OLR	MLR		
Cortical dysplasia	2	3	1	5	1	12 (31.6)
Hemimegalencephaly					11	11 (28.9)
Tuberous sclerosis	1	2		2		5 (13.2)
Infarction					3	3 (7.9)
Ohtahara syndrome					1	1 (2.6)
Rasmussen's encephalitis				1		1 (2.6)
Neurocutaneous melanosis	1					1 (2.6)
Tumor						
Temporal astrocytoma	1					1 (2.6)
Hemispheric astrocytoma					1	1 (2.6)
Poorly differentiated glioma	1					1 (2.6)
Pleomorphic xanthoastrocytoma	1					1 (2.6)
Total	7 (18.4)	5 (13.2)	1 (2.6)	8 (21.1)	17 (44.7)	

Values represent the number of patients (%).

FIG. 1. A: One-year postoperative seizure outcomes based on surgical technique. **B:** One-year postoperative seizure outcomes based on surgical technique. Figure is available in color online only.

quency, and another 2 experienced a 50%–90% reduction. Seven (18.4%) children experienced less than a 50% reduction in seizure frequency (Table 2). Figure 1A shows the seizure-free outcomes at the 1-year mark based on surgical procedure: the hemispherectomy group had the best seizure outcome ($n = 14/17$ seizure free), followed by the multilobe resection group ($n = 6/8$ seizure free) and the focal resection group ($n = 7/13$ seizure free). In the focal resection group, the patient who underwent occipital lobe resection achieved seizure freedom at 1 year postoperatively. The temporal lobe resection and the frontal lobe resection group achieved 42.9% ($n = 3/7$) and 40% ($n = 2/5$) rates of seizure freedom, respectively.

With regard to pathologic correlation, the children diagnosed with stroke ($n = 3$) and Rasmussen's encephalitis ($n = 1$) were all seizure free 1 year postoperatively. The hemimegalencephaly group had the next best seizure freedom rate at 81.8% ($n = 9/11$), followed by the tuberous sclerosis group at 80% ($n = 4/5$). The corresponding numbers in the tumor group and in the cortical dysplasia group were 75% ($n = 3/4$) and 50% ($n = 6/12$), respectively. The

FIG. 2. A: Long-term seizure outcomes based on surgical technique using Engel classification. **B:** Long-term seizure outcomes based on surgical technique using Engel classification. Figure is available in color online only.

patient with Ohtahara syndrome achieved greater than 90% reduction in seizure frequency, and the patient with neurocutaneous melanosis ($n = 1$) achieved 50%–90% reduction in seizure frequency (Fig. 1B).

Long-Term Treatment Outcomes

To classify long-term postoperative seizure outcomes, the Engel classification was used (Fig. 2). In the hemispherectomy group, 53% ($n = 9/17$) of children had Engel class I outcomes at last follow-up, followed by 37.5% ($n = 3/8$) for the multilobe resection group and 26.7% ($n = 4/13$) for the focal resection group. Within the focal resection cohort, 28.6% ($n = 2/7$) of patients in the temporal lobe resection group and 20% ($n = 1/5$) in the frontal lobe resection group achieved Engel class I outcomes, respectively.

At last follow-up, the percentages of patients with Engel class I outcomes for each of the diagnoses were Rasmussen's encephalitis 100% ($n = 1$), tumors 75% ($n = 3/4$), stroke 33.3% ($n = 1/3$), hemimegalencephaly 45.4% ($n = 5/11$), cortical dysplasia 25% ($n = 3/12$), and tuberous sclerosis 20% ($n = 1/5$). The patients diagnosed with Ohtahara

syndrome ($n = 1$) and neurocutaneous melanosis ($n = 1$) were in Engel class III at last follow-up.

A brief analysis of seizure outcomes based on surgical date indicates a trend toward improved outcomes with later surgeries. There is a myriad of factors that can influence this, including, but not limited to, experience gained, technical advances, and improvements in the perioperative management of epilepsy patients.

Complications and Survival Outcomes

Perioperative morbidity revealed 4 complications: 2 infections and 1 case each of perioperative stroke and immediate reoperation for seizures. All patients who underwent hemispherectomy or multilobar resections had a prophylactic external ventricular drain placed at the time of operation, and no patients went on to develop late hydrocephalus requiring a shunt. The drain was managed and weaned in standard fashion, and no further specific technical changes dedicated to the management of postoperative hydrocephalus were made. The median seizure-free survival among the children who did not remain seizure free was 8.3 years. The median seizure-free survival was greatest for children in the multilobar group (14.6 years), followed by the hemispherectomy group (8.3 years) and the focal resection group (7.3 years). Figure 3 shows the individual Kaplan-Meier curves for all children and broken down by surgical technique.

Discussion

We performed a literature review of papers studying epilepsy surgery in children younger than 3 years. Articles were included in our literature review if they included at least 10 cases in which an infant underwent surgery at or before the age of 3 years with functional outcomes that could be correlated. Data extracted from the articles included the number of cases, mean age at onset of seizure and at time of surgery, diagnosis, surgical technique, surgical outcome, and complications. A total of 13 articles met the inclusion criteria and were included, accounting for 382 cases with an average follow-up duration of 5.2 years.^{7,10,13,15,18,21,25,26,28–32} While this literature search returned a large pooled number of patients, less than 14% were of the same age demographic as our study, that is, infants with epilepsy operated on before the age of 12 months. The studies that focus on epilepsy surgery in these infant patients are further presented in Table 4. The strength of this study as the largest case series of infants younger than 12 months operated on for catastrophic epilepsy is that it shows that operative management of these patients can be safe and effective.

Surgical Outcomes

The percentage of seizure-free outcomes in these series ranged from 47% to 80%, comparing favorably with our results. Surgical techniques ranged from hemispherectomies to focal resections and/or lobectomies. Within the category of hemispherectomies, there was wide heterogeneity in the specific technical procedure performed, whether it be anatomical, functional, or modified anatomical. Sugimoto et al. showed significantly better seizure outcomes in chil-

FIG. 3. Kaplan-Meier curve for seizure freedom in all patients (A) and based on surgical technique (B). Figure is available in color online only.

dren who underwent hemispherectomies than those who underwent focal resections.¹⁵ This correlates with our data, where hemispherectomy patients had better long-term seizure outcomes. However, many of the other studies showed equal outcomes between hemispheric surgeries and focal resections. It is difficult to draw definitive conclusions on whether one type of procedure is superior to the other. In comparison with seizure outcomes of children operated on before the age of 3 years but older than 12 months, there appears to be similar effectiveness and safety.

Developmental Outcomes

Steinbok et al. reported that 55.3% of patients had improved developmental outcomes after surgery, although the exact developmental assessment tools used were not indicated. In their cohort, they found a trend toward improved developmental outcomes in children who became seizure free (60.7%) compared with those with residual seizures (44.8%).³¹ Other studies have used the perioperative developmental quotient (DQ) as a marker of change in development after surgery. Loddenkemper et al. showed a

TABLE 4. Results from literature review on epilepsy surgery in infants and young children

Authors & Year	No. of Patients	Mean Age at Sz Onset (mos)	Mean Age at Op (mos)	Surgical Technique	Diagnosis/Pathology	Engel Class	Complications	Other
Kumar et al., 2015 ^{7*}	25	1.0	4.7	64% hemispherectomy; 34% FR/L	FCD 48%; HME 32%; stroke 8%	I 80%; II/III 8%	Hydrocephalus 20%; infection 4%; death 4%	
Ramantani et al., 2013 ³⁰	30	5.0	20.0	47% hemispherectomy; 53% FR/L	MCD 80%; tumor 10%; stroke 10%	I 70%; II/III 20%	Blood transfusion 87%; hydrocephalus 13%; neuro deficit 17%	
Taussig et al., 2012 ³²	25	5.2	23.0	100% FR	MCD 85%; stroke 7.7%; tumor 7.7%	I 65%; II/III 19%	Neuro deficit 19%; subdural collection 8%	
Dunkley et al., 2011 ²⁶	42	5.0	20.0	64.3% hemispherectomy; 36% FR/L	MCD 74%; SW 12%; tumor/stroke 4.7%	I 47%; II/III 43%	Hydrocephalus 12%	ΔDQ 30→28
Gowda et al., 2010 ^{28*}	15	0.07	3.97	78.5% hemispherectomy; 21.5% FR/L	MCD 53.3%; HME 40%; TS 6.7%	I 53%; II/III 33%	Aseptic meningitis 27%; MCA infarct 7%	
Steinbok et al., 2009 ³¹	116		15.8	34.5% hemispherectomy; 65.5% FR/L	MCD 29.3%; tumors 19%; SW 16.3%	I 62%; II/III 23%	Infection 15%; aseptic meningitis 11%; hydrocephalus 6%	
Loddenkemper et al., 2007 ²⁹	24	12.0	14.0	58.3% hemispherectomy; 41.7% FR/L	MCD 79%; tumor 8.3%; SW 8.3%	I 71%; II/III 29%		ΔDQ 37→49
Lettori et al., 2008 ^{13*}	10	0.66	9.3	100% hemispherectomy	West syndrome 50%; Ohtahara 40%	I 60%; II/III 40%	Hydrocephalus 27%; hemorrhage 9%	ΔDQ 33→32.3
González-Martínez et al., 2005 ¹⁸	18		10.9	100% hemispherectomy	HCD 50%; HME 39%; SW 5%	I 67%; II/III 33%		
Bittar et al., 2002 ²⁵	11	15.5	15.0	63.6% hemispherectomy; 37.3% FR/L	Stroke 27%; HME 18%; tumor 18%	I 73%; II/III 27%		
Sugimoto et al., 1999 ¹⁵	23	4.7	15.3	34.3% hemispherectomy; 65.7% FR/L	FCD 52%; SW 21.7%; tumor 13%	I 52%; II/III 33%		
Duchowny et al., 1998 ¹⁰	31	4.1	18.3	45.2% hemispherectomy; 51.6% FR/L	MCD 68%; tumor 22.6%; stroke 6.5%	I 61%; II/III 19%	Death 6.5%	
Wyllie et al., 1996 ²¹	12	4.03	15.3	41.7% hemispherectomy; 58.3% FR/L		I 50%; II/III 42%	Death 8%	

FCD = focal cortical dysplasia; FR/L = focal resection/lobectomy; HCD = hemispheric cortical dysplasia; HME = hemimegalencephaly; MCA = middle cerebral artery; MCD = malformations of cortical development; neuro = neurological; SW = Sturge-Weber syndrome.

* Series with infants (e.g., patients operated on < 12 months old).

modest statistically significant improvement in DQ, from 37 to 49. Preoperatively, 22 of 24 children in their cohort were developmentally delayed, while postoperatively this number was reduced to 18.²⁹ They also found that a higher preoperative DQ was correlated with a higher DQ after surgery and showed a statistically significant correlation between younger age at surgery and improvement in DQ. In contrast, studies by Dunkley et al. and Lettori et al. showed no significant perioperative change in DQ.^{13,26} Ramantani et al. showed that 75% of children remained in the same developmental status after surgery despite a majority (62%) achieving seizure freedom; the remaining 25% showed a decrease in development.³⁰ There was a high rate of subjective developmental progress among parents of the affected children.

Complications and Mortality

Perioperative morbidity has been reported in up to 27% of infants and young children undergoing epilepsy sur-

gery. In addition, there was a high need for blood transfusions, up to 87% in one case series.³⁰ No patients in our series required intraoperative blood transfusion. The most commonly reported complications were hydrocephalus, infections (including deep, superficial, or meningitis), and neurological deficit. By comparison, our case series had a relatively low complication rate at 10%. None of the patients in our series went on to develop late hydrocephalus requiring shunting. Two patients in our group experienced a perioperative infection: one patient with hemimegalencephaly and another with cortical dysplasia. Neither of these patients underwent invasive encephalography prior to surgery. Postoperative stroke is a rare complication after epilepsy surgery in infants and is reported at a rate less than 1%, while reoperation rates have ranged up to 45%.²⁵ One infant in our series had an occipital infarct after resection of multilobe cortical dysplasia with disconnection of the occipital and parietal lobes but remained developmentally normal at last follow-up. Mortality rates in epilepsy surgery in infants range from 4% to 8%,^{3,7,10} which

compares favorably with our series, and we found that survival rates are good among children who do not remain seizure free, with a median survival of 8.3 years.

Surgical Timing

Our literature review and institutional experience demonstrate that epilepsy surgery in infants and during early childhood is a safe and effective treatment for medically refractory epilepsy. There are theories that postulate the burden of seizure activity on the developing brain during critical phases can have significant, irreversible detriments on developmental outcomes and that definitive treatment should be instituted as soon as possible. Combining our data with the literature on patients operated on before the age of 1 year reveals good surgical outcomes, with seizure freedom rates between 53% and 80%. Ramantani et al. reported an 87% perioperative blood transfusion rate in their series, although it is unclear if this disproportionately affected the 23% of their patients operated on before 1 year of age.³⁰ Kumar et al. reported a 20% hydrocephalus rate, a 4% infection rate, and a 4% mortality rate.⁷ In addition, 1 case was discontinued due to high need for blood transfusion. Gowda et al. reported a postoperative course for 15 patients operated on before the age of 6 months that included 4 cases of aseptic meningitis and 1 case of a middle cerebral artery infarct.²⁸ Our series of 40 patients operated on when they were younger than 1 year revealed a 10% complication rate, with 2 infections, 1 stroke, and 1 reoperation. This supports the fact that operating for epilepsy as soon as technically feasible is a safe and viable option.

Limitations

Our series is limited by the nature of a retrospective series, including selection bias for surgery (only patients who were deemed good candidates for surgery were selected for surgery) and loss of follow-up for some infants. Nevertheless, the follow-up time of nearly 10 years in our series is robust and suggests that surgery for select infants with medically refractory epilepsy is a durable and safe procedure. Additionally, detailed developmental and neuropsychological outcomes for our patients were not assessed. Additional prospective studies evaluating neurodevelopment over time after epilepsy surgery may help predict which etiology will benefit the most from early surgical intervention.

Conclusions

For catastrophic epilepsy in infants, surgery can be a safe and efficacious procedure with the long-term potential of curing seizures in a significant portion of patients. There is evidence to suggest that earlier intervention to remove the seizure burden from the developing brain at critical phases may improve developmental outcomes. The risks of surgery on infants must be weighed against the potential risks of continued epilepsy, which can include developmental delay, long-term hospitalization, coma, and even death. The use of a multidisciplinary team with expertise in treating infants with these conditions is a prerequisite to optimize efficacy and safety in this frail population.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ragheb, Ibrahim, Bhatia. Acquisition of data: Shah, Sur, Achua. Analysis and interpretation of data: Ye, Shah, Sur, Achua, Ibrahim. Drafting the article: Ye, Shah, Sur, Achua, Ibrahim. Critically revising the article: Ragheb, Ye, Shah, Sur, Wang, Ibrahim, Bhatia. Reviewed submitted version of manuscript: Ragheb, Ye, Shah, Sur, Achua, Ibrahim, Bhatia. Approved the final version of the manuscript on behalf of all authors: Ragheb. Statistical analysis: Ragheb, Shah, Sur, Achua, Ibrahim. Administrative/technical/material support: Ragheb, Ibrahim, Bhatia. Study supervision: Ragheb, Bhatia.

Correspondence

John Ragheb: University of Miami, FL. jragheb@med.miami.edu.