

ORIGINAL ARTICLE

Surgery for Drug-Resistant Epilepsy in Children

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ABSTRACT

BACKGROUND

Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials.

METHODS

In this single-center trial, we randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). The patients in the medical-therapy group were assigned to a waiting list for surgery. The primary outcome was freedom from seizures at 12 months. Secondary outcomes were the score on the Hague Seizure Severity scale, the Binet–Kamat intelligence quotient, the social quotient on the Vineland Social Maturity Scale, and scores on the Child Behavior Checklist and the Pediatric Quality of Life Inventory.

RESULTS

At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group ($P<0.001$). Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to the score on the Hague Seizure Severity scale (difference, 19.4; 95% confidence interval [CI], 15.8 to 23.1; $P<0.001$), on the Child Behavior Checklist (difference, 13.1; 95% CI, 10.7 to 15.6; $P<0.001$), on the Pediatric Quality of Life Inventory (difference, 21.9; 95% CI, 16.4 to 27.6; $P<0.001$), and on the Vineland Social Maturity Scale (difference, 4.7; 95% CI, 0.4 to 9.1; $P=0.03$), but not on the Binet–Kamat intelligence quotient (difference, 2.5; 95% CI, -0.1 to 5.1; $P=0.06$). Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%).

CONCLUSIONS

In this single-center trial, children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months. Surgery resulted in anticipated neurologic deficits related to the region of brain resection. (Funded by the Indian Council of Medical Research and others; Clinical Trial Registry–India number, CTRI/2010/091/000525.)

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CHILDREN AND ADOLESCENTS WITH drug-resistant epilepsy are at increased risk for poor long-term intellectual and psychosocial outcomes, along with a poor health-related quality of life.^{1,3} In this form of recalcitrant epilepsy, appropriate surgical management is often undertaken with the goal of reducing or stopping seizures, but there is limited evidence from randomized trials showing the benefit in this age group.

The region of the cerebrum that is subjected to surgery depends on the localization of the origin of seizures in the cerebral cortex and the functional importance of the surrounding brain tissue. These factors are determined on presurgical evaluation, including simultaneously acquired video electroencephalographic (video EEG) recordings and structural and functional imaging of the brain. The type of surgery is dependent on the underlying cause of epilepsy and may include resection of the mesial temporal lobe or other regions of the cerebral cortex, excision of a focal lesion or developmental malformation, sectioning of the corpus callosum (corpus callosotomy), disconnection of a part of the cerebral cortex, or disconnection of an entire hemisphere (hemispherotomy). Some of these procedures necessarily result in neurologic deficits.

Two randomized trials of temporal lobectomy for drug-resistant epilepsy included only adults.^{4,5} A Cochrane review of epilepsy surgery included only four trials that had more than 30 participants, and these trials involved patients in all age groups.⁶ Three of these trials compared different surgical techniques or compared different extents of surgical resection, but only one⁴ randomly assigned patients to surgical and medical groups. A meta-analysis of uncontrolled studies that compared seizure outcomes of surgeries in children showed that 74% of those with brain lesions and 45% of those without lesions had become seizure-free at the 1-year follow-up.⁷ In a retrospective analysis involving 142 children who had undergone surgery for drug-resistant epilepsy at a mean age of 9.8 years between 2000 and 2011 at our center, 79.3% were free from disabling seizures after a mean follow-up of approximately 4 years.⁸ To follow up on these results, we performed a trial involving children and adolescents with drug-resistant epilepsy to compare epilepsy surgery with continued medical therapy alone in patients on a waiting list for surgery.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial was conducted from November 2010 through March 2015 at the All India Institute of Medical Sciences in New Delhi, which is the referral center for epilepsy surgery in northern India. The trial was approved by the institutional ethics committee; written informed consent was provided by parents or legally authorized representatives of the children. An independent data and safety monitoring board reviewed the records of the recruited patients for adverse events at annual meetings. The trial was funded by the Indian Council of Medical Research and the Department of Biotechnology, Government of India. The trial was initiated by the last author, and all the authors contributed to its design. The first and second authors wrote the first draft of the manuscript, and all the authors reviewed the manuscript and vouch for adherence of the trial to the protocol (available with the full text of this article at NEJM.org) and for the completeness and accuracy of the data.

PRESURGICAL EVALUATION AND SURGICAL INTERVENTION

Patients were evaluated with long-term video EEG monitoring with the use of scalp electrodes in the standard 10–20 system of electrode placement and with 3-Tesla magnetic resonance imaging (MRI) that included an epilepsy protocol. This protocol involved the use of T₁-weighted sagittal three-dimensional (3D) and 3D FLAIR (fluid-attenuated inversion recovery) sequences with a slice thickness of less than 1 mm without an intervening gap, coronal T₂-weighted and FLAIR sequences with a 2.5-mm slice thickness without a gap (perpendicular to the hippocampus), and axial susceptibility-weighted images.

Drug-resistant epilepsy was defined as the failure of adequate trials of two appropriately chosen antiepileptic drug schedules with acceptable side effects.⁹ Patients who had no definite localization of seizures on video EEG, those who had no concordance of the EEG results and a lesion on MRI, and those who had no lesion, more than one lesion, or lesions with poorly defined margins on imaging underwent ictal and interictal single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), or magnetoencephalography (MEG) as part of the presurgical evaluation.¹⁰

Each patient was discussed at the weekly multidisciplinary epilepsy surgery case conference attended by neurologists, neurosurgeons, neuroradiologists, and nuclear medicine specialists; the assessments of neuropsychologists and psychiatrists were taken into consideration before surgery to evaluate coexisting psychiatric conditions and corroborate the localization of epilepsy and resulting deficits. Patients with concordance of video EEG localization of the region of onset of the seizure (ictal-onset zone) and the location of the lesion on MRI underwent resection of that region of cortex or of the lesion or malformed cortex; those with multiple, subtle, or no lesions underwent resection of the region that was concordant between video EEG results and localization on PET, SPECT, or MEG. Patients who had multiple seizure types (including drop attacks) and multiple bilateral lesions and seizure foci underwent corpus callosotomy. Patients who had extensive lesions confined to one hemisphere with significant weakness of limbs (weak pincer grip or worse) opposite to the involved hemisphere underwent hemispherotomy.

Patients were not included in the trial if there was no consensus regarding the location of an epileptic focus and were excluded if there were metabolic abnormalities (genetic or acquired) or cardiac, renal, or any other systemic illness or a history of status epilepticus. In all the patients in the surgery group, postsurgery MRI was performed with a high-field 1.5 Tesla system in the operating room to ensure the adequacy of the planned excision.

RANDOMIZATION AND BLINDING

Randomization was performed with the use of computer-generated, nonstratified sequences, and assignments were prepared in sequentially numbered, sealed, opaque envelopes by persons not involved in the trial. Patients who were assigned to the surgery group underwent the procedure within a month after randomization; those who were assigned to the medical-therapy group remained on the waiting list, with surgery planned for 1 year or longer after randomization, which represented the standard of care at our center, since the waiting list is typically 12 months or longer. All the patients continued to receive antiepileptic drugs, and changes were made by the treating clinicians as necessary to manage seizures. In the surgery group, patients who became

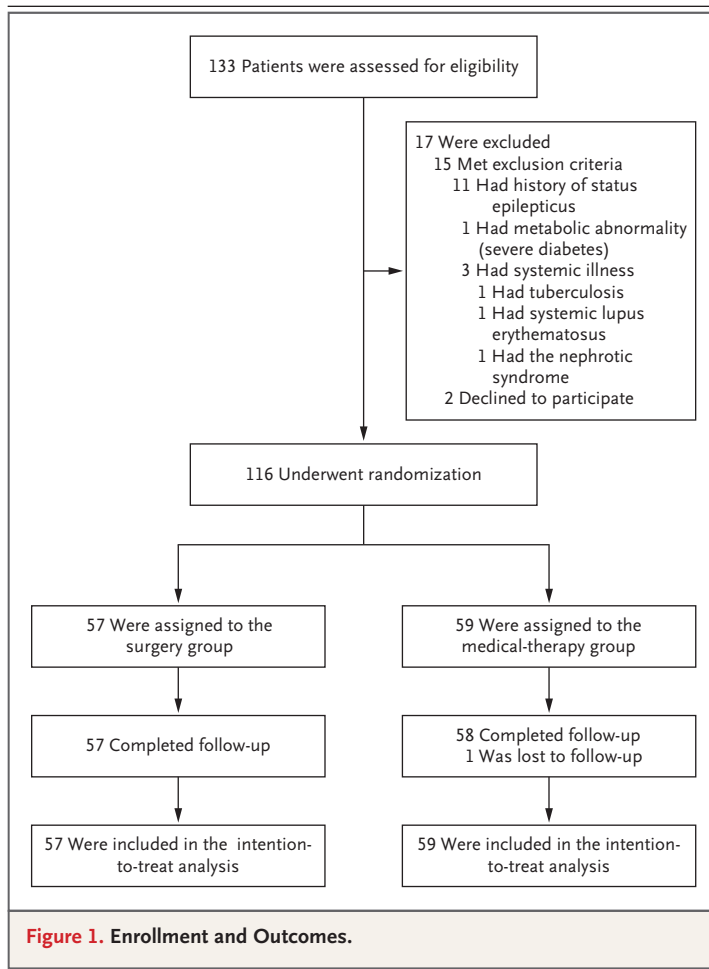
seizure-free underwent tapering of antiepileptic drugs, starting 1 year after surgery.

OUTCOMES

The primary outcome was freedom from seizures, which was defined as class 1 (no seizures or auras) on the International League Against Epilepsy scale¹¹ at 12 months. Other categories on the scale are as follows: auras only with no other seizures (class 2), 1 to 3 seizure days per year (class 3), from 4 seizure days per year to a number of seizure days that represents a 50% reduction in the number of days from baseline (class 4), from less than a 50% reduction in the number of seizure days to a 100% increase in the number of seizure days from baseline (class 5), and more than a 100% increase in the number of seizure days from baseline (class 6).

Secondary outcomes, which were evaluated at 12 months after the date of surgery or randomization and were compared with baseline scores, included any occurrence of seizures, the score on the Hague Seizure Severity scale (ranging from 13 to 54, with higher scores indicating greater severity), the Binet-Kamat intelligence quotient or the social quotient on the Vineland Social Maturity Scale (normal range, 85 to 110 on both scales, with higher scores indicating higher levels of function), the T score on the Child Behavior Checklist (normal score, <60; borderline, 60 to 63; and clinically impaired, >63), and the score on the Pediatric Quality of Life Inventory (ranging from 0 to 100, with higher scores indicating a better quality of life). The Binet-Kamat test was administered to children with adequate verbal responses, and the Vineland Social Maturity Scale was administered to children younger than 2 years of age and to older children whose verbal response was inadequate for the completion of the Binet-Kamat test. (Details regarding the evaluation scales and testing procedures are provided in Section 1 in the Supplementary Appendix, available at NEJM.org.)

The primary outcome measure of freedom from seizures was assessed in a blinded manner on the basis of seizure diaries, as reported by telephone at 6 months and 12 months (see Section 2 in the Supplementary Appendix) and verified from seizure diaries. Diaries were coded with unique identification numbers and sent to the assessor by a person uninvolved in the trial. Secondary outcomes of seizure occurrence during the 12-month period and psychosocial measures



were assessed by the treating epileptologist and psychologist (both of whom were aware of study-group assignments) during clinical visits and with the use of the seizure diary. All the patients were seen at the epilepsy clinic every 3 months or more frequently as required for clinical care.

ADVERSE EVENTS

Adverse events that were classified as serious were assessed in a blinded manner during a telephone checklist discussion. (Details are provided in Section 2 in the Supplementary Appendix.) Serious adverse events included death, hospital admission or prolongation of an existing hospital stay, and events that resulted in persistent or substantial disability or incapacity or that were considered to be life-threatening.¹² All other adverse events were recorded as nonserious.

STATISTICAL ANALYSIS

Power calculations were based on the results of the study by Widjaja et al., in which the seizure-free rate after surgery was 60%.¹³ We calculated that the enrollment of 116 patients would provide a power of 90% to determine an absolute between-group difference of 40 percentage points in the rate of freedom from seizures (and a superiority margin of 15% in the surgery group) at 12 months at a two-sided alpha level of 5% and assuming that 5% of the patients would be lost to follow-up.

We used the chi-square test and Fisher's exact test to compare categorical characteristics at baseline; we used Student's t-test to compare normally distributed continuous variables and the Wilcoxon rank-sum test to compare nonparametric continuous data. Intention-to-treat analyses were performed for both primary and secondary outcomes. Patients who did not complete follow-up at 12 months were not considered to be seizure-free in the primary analysis; for the secondary outcomes, the last observation was carried forward.

The primary outcome of complete freedom from seizures at 12 months was analyzed with the use of the z-test and was reported as the difference in proportions and relative risk with 95% confidence intervals. We used the Kaplan–Meier method and log-rank test to analyze the secondary outcome of seizure during the 12-month period and a Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals. We used Student's t-test to analyze other secondary outcomes and the paired t-test to analyze the change from baseline to last follow-up. A P value of less than 0.05 was considered to indicate statistical significance. All the statistical analyses were performed with the use of Stata software, version 11.0.

RESULTS

PATIENTS

A total of 133 children underwent screening; 2 of the children were eligible but did not provide informed consent and 116 met the inclusion criteria (57 in the surgery group and 59 in the medical-therapy group) (Fig. 1). One patient in the medical-therapy group did not return for the last follow-up visit. There were no significant

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Surgery Group (N = 57)	Medical-Therapy Group (N = 59)
Median age (range) — yr	9.0 (0.8–17.0)	10.0 (2.0–17.0)
Female sex — no. (%)	23 (40)	19 (32)
Family history of epilepsy — no. (%)	3 (5)	6 (10)
Median age at onset of seizures (range) — yr†	1.5 (0.1–9.0)	3.0 (0.1–10.0)
Median duration of epilepsy (range) — yr	4.9 (0.4–16.3)	5.0 (0.5–16.0)
Type of seizures — no. (%)		
Focal	43 (75)	43 (73)
Secondary generalized	14 (25)	16 (27)
Frequency of seizures 6 mo before randomization		
≥1 Per day	48 (84)	40 (68)
≥1 Per week	5 (9)	10 (17)
≥1 Per mo	4 (7)	6 (10)
≥1 Per 3 mo	0	3 (5)
Median number of previous antiepileptic medications (range)	3 (2–6)	3 (2–6)
Score on Hague Seizure Severity scale‡	37.9±4.2	37.4±4.3
Intelligence quotient on Binet–Kamat test§	63.9±19.3	62.8±21.4
Social quotient on Vineland Social Maturity Scale§	38.6±24.2	41.8±20.9
Total score on Child Behavior Checklist¶	69.5±6.3	67.8±5.1
Total score on Pediatric Quality of Life Inventory	53.4±15.4	53.2±16.4

* Plus-minus values are means ±SD. There were no significant differences between the groups.

† The earliest onset was between 2 and 4 days after birth.

‡ Scores on the Hague Seizure Severity scale range from 13 to 54, with higher scores indicating greater seizure severity.

§ Average scores on the tests of intelligence quotient and social quotient range from 85 to 110, with higher scores indicating higher levels. Intelligence quotient was tested in 30 patients in the surgery group and 33 in the medical-therapy group; social quotient was tested in 27 patients in the surgery group and 26 in the medical-therapy group.

¶ The normal T score on the Child Behavior Checklist is less than 60, with higher scores indicating greater behavioral problems.

|| Scores on the Pediatric Quality of Life Inventory range from 0 to 100, with higher scores indicating a better quality of life.

differences in the baseline characteristics between the two groups (Table 1). The following surgical procedures were carried out: temporal lobe resections in 14 patients, resection of lesion in a lobe other than temporal in 12, hemispherotomy in 15, corpus callosotomy in 10, and disconnection or resection of hypothalamic hamartoma in 6. (Details regarding the surgical procedures are provided in the Supplementary Appendix, Section 1, Tables S7 and S8.)

PRIMARY OUTCOME

At 12 months, complete freedom from seizures was reported in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group (absolute difference, 70.4 percentage points; 95% confidence interval [CI], 57.8 to 83.1; $P < 0.001$)

(Table 2). The relative risk of seizure recurrence was 4.09 (95% CI, 2.52 to 6.62) in the medical-therapy group as compared with the surgery group.

At the last follow-up, all the patients who had undergone temporal lobectomy or hypothalamic hamartoma surgeries were seizure-free. Of those who had undergone extratemporal resection or hemispherotomy, 11 of 12 patients (92%) and 13 of 15 (87%), respectively, had complete freedom from seizures (Supplementary Appendix, Section 1, Table S2). In the medical-therapy group, 2 of 15 patients (13%) who were on the waiting list for a temporal lobectomy were seizure-free at 12 months, along with 1 of 19 patients (5%) who were on a waiting list for an extratemporal resection and 1 of 16 (6%) who were waiting

Table 2. Primary and Secondary Outcomes at 1 Year.*

Outcome	Surgery Group (N=57)	Medical-Therapy Group (N=59)	Absolute Difference		Difference in Change from Baseline	
			Value (95% CI)	P Value	Value (95% CI)	P Value
Primary outcome: freedom from seizures — no. (%)	44 (77)	4 (7)	70.4 (57.8 to 83.1)†	<0.001	NA	NA
Secondary outcomes						
Score on Hague Seizure Severity scale	15.4±5.5	34.3±11.8	18.9 (15.5 to 22.3)	<0.001	19.4 (15.8 to 23.1)	<0.001
Intelligence quotient on Binet–Kamat test	62.7±18.5	58.9±22.1	3.7 (–6.6 to 14.0)	0.47	2.5 (–0.1 to 5.1)	0.06
Social quotient on Vineland Social Maturity Scale	41.5±23.1	39.9±19.7	1.6 (–10.3 to 13.4)	0.79	4.7 (0.4 to 9.1)	0.03
Total score on Child Behavior Checklist	57.2±6.7	68.6±7.6	11.4 (8.8 to 14.0)	<0.001	13.1 (10.7 to 15.6)	<0.001
Total score on Pediatric Quality of Life Inventory	76.1±13.1	53.9±18.5	22.1 (16.2 to 28.1)	<0.001	21.9 (16.4 to 27.6)	<0.001

* Plus-minus values are means ±SD. NA denotes not applicable.

† The absolute between-group difference for the primary outcome is provided in percentage points.

for a corpus callosotomy; among those with a planned hemispherotomy or intervention for hypothalamic hamartoma, none of the patients were seizure-free (Supplementary Appendix, Section 1, Table S3).

SECONDARY OUTCOMES

Estimates of the probability of being seizure-free at 12 months on Kaplan–Meier analysis were 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% CI, 4.6 to 8.2; $P<0.001$) (Fig. 2). (Although 77% of the patients in the surgery group were seizure-free at the 12-month follow-up, the postoperative seizures that had occurred during the first 6 months were included in the Kaplan–Meier analysis.) The reduction from baseline in the score on the Hague Seizure Severity scale at 1 year was significantly greater in the surgery group than in the medical-therapy group (between-group difference in the change from baseline, 19.4; 95% CI, 15.8 to 23.1; $P<0.001$) (Table 2). The Binet–Kamat test was administered to 63 patients (30 in the surgery group and 33 in the medical-therapy group). The reduction from baseline in the mean ($\pm$ SD) intelligence quotient was not significant in the surgery group (-1.3 ± 6.5 , $P=0.29$) and was significant in the medical-therapy group (-3.8 ± 3.6 , $P<0.001$); however, the between-group difference in change from baseline to 12 months was not significant (difference, 2.5; 95% CI, -0.1 to 5.1 ; $P=0.06$). The Vineland Social Maturity Scale test was administered to 53 children (27 in the surgery group and 26 in the medical-therapy group). There was no significant change from baseline in the mean social quotient in either group (2.9 ± 7.9 in the surgery group, $P=0.07$; and -1.8 ± 7.7 in the medical-therapy group, $P=0.24$), but the between-group difference in the change from baseline significantly favored the surgery group (difference, 4.7; 95% CI, 0.4 to 9.1; $P=0.03$) (Table 2).

At 12 months, the change from baseline in the mean T score on the Child Behavior Checklist was significant in the surgery group (-12.3 ± 6.2 , $P<0.001$) but not in the medical-therapy group (-0.86 ± 7.2 , $P=0.36$), which resulted in a significant between-group difference that favored the surgery group (difference, 13.1; 95% CI, 10.7 to 15.6; $P<0.001$). On the Pediatric Quality of Life Inventory, the mean total score increased sig-

nificantly in the surgery group (22.7 ± 14.3 ; 95% CI, 18.9 to 26.5; $P < 0.001$) but not in the medical-therapy group (0.70 ± 16.0 ; 95% CI, 3.5 to 4.9; $P = 0.74$), which also resulted in a significant between-group difference in the change from baseline that favored the surgery group (difference, 21.9; 95% CI, 16.4 to 27.6; $P < 0.001$). (Details regarding the subscales on the Child Behavior Checklist and Pediatric Quality of Life Inventory at baseline and 12 months are provided in the Supplementary Appendix, Section 1, Tables S5 and S6.)

ADVERSE EVENTS

There were no deaths in either group. Serious adverse events occurred in 19 patients (33%) in the surgery group and none in the medical-therapy group. These events included monoparesis in 2 patients who had undergone temporal lobectomy or resection of parietal focal cortical dysplasia, hemiparesis in 15 patients who had undergone hemispherotomy, and generalized hypotonia and language deficits in 1 patient each who had undergone frontal lobectomy. Of the 17 patients with monoparesis or hemiparesis, 15 (with the exclusion of 2 of those with hemiparesis) were able to move all major joints against gravity or better at 12 months. In the child with generalized hypotonia and the one with language deficits after surgery, both reached baseline levels of motor and language functions, respectively, at 12 months. In the medical-therapy group, 10 had physical injuries associated with seizures (cuts, burns, and fractures), 1 had an adverse event associated with an antiepileptic drug, and autistic features developed in another. (Details regarding adverse events are provided in the Supplementary Appendix, Section 1, Tables S7 and S9.)

DISCUSSION

In this single-center, randomized, controlled trial, seizure outcomes 1 year after epilepsy surgery were significantly better than after continued medical therapy alone. Of the 57 patients who underwent surgery, 44 (77%) became seizure-free and 13 (23%) had ongoing seizures of varying degrees (class 2 to class 5 on the International League Against Epilepsy scale) (Supplementary Appendix, Section 1, Tables S1 and S2). In comparison, 93% of those receiving medical therapy

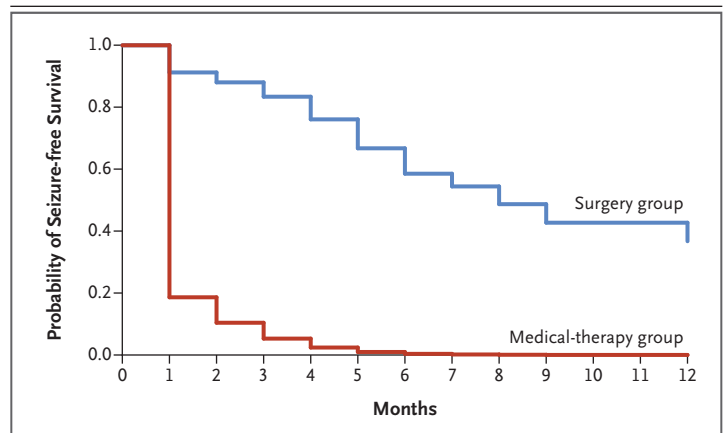


Figure 2. Probability of Seizure-free Survival at 1 Year.

Shown are Kaplan–Meier estimates of the probability of being seizure-free at 1 year in the two study groups. The rate of seizure-free survival was 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% confidence interval, 4.6 to 8.2; $P < 0.001$).

alone continued to have seizures. In the surgery group, 21 patients (37%) were completely seizure-free during the entire 12-month period, whereas during the first weeks after surgery, the other 23 patients continued to have seizures; these episodes subsequently decreased in frequency, a feature that has been observed in other series of epilepsy surgery.¹⁴ A substantial proportion of the children in the surgery group had anticipated major postoperative motor, sensory, or cognitive deficits that were related to the area of the brain that was resected or disconnected.

Complete freedom from seizures occurred in all the patients in our trial who had undergone temporal lobectomy, as compared with only 38% of those who had undergone the same surgery in another randomized trial of epilepsy surgery that included only adults with a longer duration of epilepsy than the children in our trial. The difference in ages and duration of epilepsy between the two trials may explain the difference in results.⁴

The between-group difference in the change from baseline to 12 months in the mean intelligence quotient was not significant in our trial, and it is possible that the 12-month interval of observation was too brief to observe a change in this measure. The improvements that were observed in other cognitive, behavioral, and quality-of-life scores in the surgery group may have been due to a reduction in the frequency of

seizures; conversely, the deterioration in these measures in the medical-therapy group may be attributed to a continuation of seizures, which has been associated with poor cognitive functioning in children.¹⁵⁻²⁴ In two nonrandomized trials, overall quality-of-life scores were significantly better among children who had undergone epilepsy surgery than among those who had received only medical therapy after 2 years or more of follow-up.^{25,26} An observational study comparing surgical versus medical treatment in children with epileptic encephalopathy in infancy and early childhood showed that surgery resulted in better seizure control and a better developmental quotient than did medical therapy.²⁷

Our trial has some limitations. First, we included patients undergoing many types of epilepsy surgeries that were directed at several underlying pathological causes of seizures. However, the patients who were included in the trial reflect the populations encountered at a referral center for pediatric epilepsy. Second, there was an overrepresentation of hypothalamic hamartomas in our trial as compared with some other series. And third, our statistical analysis plan called for an outdated approach of last observation carried forward for missing data of secondary outcomes, although the effect was relatively minor, since information was missing in only one patient.

Serious adverse events due to the surgery in-

cluded major motor, sensory, and cognitive deficits that were related to the area of the brain that was resected or disconnected. Despite these deficits, quality-of-life measures were significantly better in the surgery group, possibly because of better seizure control.

In conclusion, surgery in children with drug-resistant epilepsy resulted in higher rates of cessation of seizures at 1 year and better scores on some measures of behavior and quality of life than continued medical therapy alone. Some patients in the surgery group had anticipated serious neurologic consequences, including hemiparesis, some of which improved over time.

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