



Epilepsy Surgery: A Broken Bridge Between Utility and Utilization

Epilepsy Surgery Trends in the United States, 1990–2008.

Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. *Neurology* 2012;78:1200–1206.

OBJECTIVE: To examine national time trends of resective surgery for the treatment of medically refractory epilepsy before and after Class I evidence demonstrating its efficacy and subsequent practice guidelines recommending early surgical evaluation. **METHODS:** We performed a population-based cohort study with time trends of patients admitted to US hospitals for medically refractory focal epilepsy between 1990 and 2008 who did or did not undergo lobectomy, as reported in the Nationwide Inpatient Sample. **RESULTS:** Weighted data revealed 112,026 hospitalizations for medically refractory focal epilepsy and 6,653 resective surgeries (lobectomies and partial lobectomies) from 1990 to 2008. A trend of increasing hospitalizations over time was not accompanied by an increase in surgeries, producing an overall trend of decreasing surgery rates ($F = 13.6, p < 0.01$). Factors associated with this trend included a decrease in epilepsy hospitalizations at the highest-volume epilepsy centers, and increased hospitalizations to lower-volume hospitals that were found to be less likely to perform surgery. White patients were more likely to have surgery than racial minorities (relative risk [RR], 1.13; 95% confidence interval [CI], 1.10–1.17), and privately insured individuals were more likely to receive lobectomy than those with Medicaid or Medicare (RR, 1.28; 95% CI, 1.25–1.30). **CONCLUSION:** Despite Class I evidence and subsequent practice guidelines, the utilization of lobectomy has not increased from 1990 to 2008. Surgery continues to be heavily underutilized as a treatment for epilepsy, with significant disparities by race and insurance coverage. Patients who are medically refractory after failing 2 antiepileptic medications should be referred to a comprehensive epilepsy center for surgical evaluation.

Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy: A Randomized Trial.

Engel J Jr., McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, Sperling MR, Gardiner I, Erba G, Fried I, Jacobs M, Vinters HV, Mintzer S, Kieburz K. *JAMA* 2012;307:922–930.

CONTEXT: Despite reported success, surgery for pharmacoresistant seizures is often seen as a last resort. Patients are typically referred for surgery after 20 years of seizures, often too late to avoid significant disability and premature death. **OBJECTIVE:** We sought to determine whether surgery soon after failure of 2 antiepileptic drug (AED) trials is superior to continued medical management in controlling seizures and improving quality of life (QOL). **DESIGN, SETTING, AND PARTICIPANTS:** The Early Randomized Surgical Epilepsy Trial (ERSET) is a multicenter, controlled, parallel-group clinical trial performed at 16 US epilepsy surgery centers. The 38 participants (18 men and 20 women; aged ≥ 12 years) had mesial temporal lobe epilepsy (MTLE) and disabling seizures for no more than 2 consecutive years following adequate trials of 2 brand-name AEDs. Eligibility for anteromesial temporal resection (AMTR) was based on a standardized presurgical evaluation protocol. Participants were randomized to continued AED treatment or AMTR 2003–2007, and observed for 2 years. Planned enrollment was 200, but the trial was halted prematurely due to slow accrual. **INTERVENTION:** Receipt of continued AED treatment ($n = 23$) or a standardized AMTR plus AED treatment ($n = 15$). In the medical group, 7 participants underwent AMTR prior to the end of follow-up and 1 participant in the surgical group never received surgery. **MAIN OUTCOME MEASURES:** The primary outcome variable was freedom from disabling seizures during year 2 of follow-up. Secondary outcome variables were health-related QOL (measured primarily by the 2-year change in the Quality of Life in Epilepsy 89 [QOLIE-89] overall T-score), cognitive function, and social adaptation. **RESULTS:** Zero of 23 participants in the medical group and 11 of 15 in the surgical group were seizure free during year 2 of follow-up (odds ratio = ∞ ; 95% CI, 11.8 to ∞ ; $P < .001$). In an intention-to-treat analysis, the mean improvement in QOLIE-89 over-

all T-score was higher in the surgical group than in the medical group but this difference was not statistically significant (12.6 vs 4.0 points; treatment effect = 8.5; 95% CI, -1.0 to 18.1; $P = .08$). When data obtained after surgery from participants in the medical group were excluded, the effect of surgery on QOL was significant (12.8 vs 2.8 points; treatment effect = 9.9; 95% CI, 2.2 to 17.7; $P = .01$). Memory decline (assessed using the Rey Auditory Verbal Learning Test) occurred in 4 participants (36%) after surgery, consistent with rates seen in the literature; but the sample was too small to permit definitive conclusions about treatment group differences in cognitive outcomes. Adverse events included a transient neurologic deficit attributed to a magnetic resonance imaging-identified postoperative stroke in a participant who had surgery and 3 cases of status epilepticus in the medical group. **CONCLUSIONS:** Among patients with newly intractable disabling MTLE, resective surgery plus AED treatment resulted in a lower probability of seizures during year 2 of follow-up than continued AED treatment alone. Given the premature termination of the trial, the results should be interpreted with appropriate caution. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00040326.

Commentary

Surgical resection of brain tissue to treat epilepsy began in the 19th century (1). A number of advances, including electroencephalographic and neuroimaging techniques, have since refined the surgical evaluation, improving its safety and efficacy. Mesial temporal lobe epilepsy (MTLE) is the most common form of medically intractable epilepsy in adolescents and adults, and the most common indication for epilepsy surgery (2). MTLE results in major social and economic burdens (3), in addition to high rates of psychiatric comorbidity, cognitive deterioration, and increased mortality (4, 5). Numerous studies have shown that surgery in patients with medically intractable epilepsy results in high seizure-freedom rates, and that early surgery maximizes the chances of psychologic and social improvements. A randomized controlled trial showed that temporal lobectomy was significantly better than continued medical treatment in achieving seizure freedom (6) and prompted a practice parameter that recommended evaluation for epilepsy surgery as soon as refractoriness to two antiepileptic medications is established (7). Nevertheless, epilepsy surgery continued to be underutilized (8).

The Early Randomized Surgical Epilepsy Trial (ERSET) confirmed the superiority of early anteromesial temporal lobectomy to continued medical therapy in controlling seizures in intractable MTLE. Engel et al. randomized patients older than 12 years with pharmacoresistant MTLE to continued medical therapy versus en bloc anteromesial temporal resection plus continued medical therapy. The primary outcome measure was seizure freedom during the second year of follow-up. Other outcome measures included quality of life, cognitive functioning, and social adaptation, including employment and permission to drive. The trial was stopped by the data and safety monitoring board (DSMB) appointed by the National Institute for Neurological Disorders and Stroke (NINDS) after enrolling only 38 of the planned 200 participants owing to slow subject recruitment. Of these participants, 23 were randomized to the medical arm and 15 to the surgical arm. In the intention-to-treat analysis, 11 of the surgical patients (73%) were seizure-free during year 2 of follow up, compared with 0% in the medical group, yielding an infinite odds ratio.

The surgery also led to improved quality of life. Twelve of 15 subjects (80%) in the surgical group were driving at the end of year 2 of follow-up, compared with only 5 of 23 (22%) in the medical group, but no differences were seen in employment status. Verbal memory and naming deficits were significantly more common in the surgical group. Despite early termination of the trial, the results from the 38 participants demonstrated striking superiority of surgical resection to medical therapy. Since the termination decision was based solely on slow patient enrollment, and not on the unblinded results, inflation of type-I error is unlikely. Indeed, even if the trial was stopped based on the remarkable treatment effect, it is unlikely that the positive bias would have changed the conclusions.

The reasons for the difficulty in recruiting patients for the ERSET trial may intersect with those of underutilization of epilepsy surgery in general. Englot et al. used the Nationwide Inpatient Sample to study trends in epilepsy surgery in the United States between 1990 and 2008. This dataset consists of discharge databases from 20% of all nonfederal U.S. hospitals and identifies diagnoses and procedures using the International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM) codes. The authors identified 20,808 hospitalizations for intractable partial epilepsy across the studied years, and lobectomy was performed during only 1,326 (6.4%) of these hospitalizations. When extrapolated over the United States, weighted data estimated 112,026 hospitalizations over the studied years, including 6,653 (5.9%) with lobectomy. Although hospitalizations for intractable partial epilepsy appeared to double between 1990 and 2008, the number of lobectomies did not increase. Rather, the percentage of hospitalizations for intractable partial epilepsy that included lobectomy decreased from 6.9% between 1990 and 1994 to 4.3% between 2000 and 2004. This was associated with decreased admissions to the 20 highest-volume epilepsy centers that have maintained stable rates of performing lobectomy, and increased admissions to lower-volume hospitals that have a remarkably decreasing trend in performing the procedure. The authors also found that white patients, those with private insurance, and those younger than 30 years, were more likely to undergo lobectomy, an observation that was stable across the study years.



What could explain this extreme underutilization of an effective therapeutic intervention that is known to reverse psychosocial and cognitive deficits and decrease the general burden of the disease? The fear of surgical complications, together with the proliferation of newer-generation antiepileptic drugs, is the most likely primary cause. The fear of surgery should be reversed by adequate education that complications of lobectomy are few (8) and that it can extend the quality-adjusted life expectancy (9). On the other hand, intractable epilepsy is associated with significant disability and increased mortality rates (5). The cost may be another impediment towards the surgical evaluation; Englot et al. found that privately insured patients were more likely to have surgery. However, the cost of long-term medical therapy of intractable epilepsy exceeds that of epilepsy surgery (10).

Certain limitations of the study by Englot et al. are worth mentioning. The authors identified patients with intractable partial epilepsy by using code 345.41 for complex partial seizures, and code 345.51 for simple partial seizures, but these codes are not specific to the lobe of origin. Similarly, for lobectomy, they used the procedure code 01.53, which does not specify which brain lobe is resected. In addition, false-positive and false-negative coding is possible in hospital discharge data. Also, the authors did not exclude patients with secondary diagnoses of syncope or psychogenic seizures, possible causes of provoked seizures such as hypoglycemia, alcohol and drug withdrawal, and brain tumors. Such exclusions would have helped homogenize the studied cohort.

However, these limitations are unlikely to affect the general conclusions, and the study constitutes an alarming wake-up call to remind us that we need to do more to increase the number of epilepsy surgeries and decrease the general burden of the disease. One possible intervention is to organize a robust campaign of physician and patient education that instills useful messages about the safety and efficacy of epilepsy surgery and urges patients to seek referral to an epilepsy center for an epileptologist's opinion if

seizures are not controlled after a year of care by the primary provider or neurologist.

by Mohamad Koubeissi, MD

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