A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

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FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

ABSTRACT

Background Randomized trials of surgery for epilepsy have not been conducted, because of the difficulties involved in designing and implementing feasible studies. The lack of data supporting the therapeutic usefulness of surgery precludes making strong recommendations for patients with epilepsy. We conducted a randomized, controlled trial to assess the efficacy and safety of surgery for temporal-lobe epilepsy.

Methods Eighty patients with temporal-lobe epilepsy were randomly assigned to surgery (40 patients) or treatment with antiepileptic drugs for one year (40 patients). Optimal medical therapy and primary outcomes were assessed by epileptologists who were unaware of the patients’ treatment assignments. The primary outcome was freedom from seizures that impair awareness of self and surroundings. Secondary outcomes were the frequency and severity of seizures, the quality of life, disability, and death.

Results At one year, the cumulative proportion of patients who were free of seizures impairing awareness was 58 percent in the surgical group and 8 percent in the medical group (P<0.001). The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life (P<0.001 for both comparisons) than the patients in the medical group. Four patients (10 percent) had adverse effects of surgery. One patient in the medical group died.

Conclusions In temporal-lobe epilepsy, surgery is superior to prolonged medical therapy. Randomized trials of surgery for epilepsy are feasible and appear to yield precise estimates of treatment effects. (N Engl J Med 2001;345:311-8.)

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*Other members of the study group are listed in the Appendix.
of waiting for years until multiple anticonvulsant drugs have failed. Surgery for temporal-lobe epilepsy, one of the most common syndromes, may not only control seizures but also prevent untimely death. Paradoxically, surgery appears to be grossly underused. It is estimated that only 1500 of the nearly 100,000 eligible patients in the United States undergo such surgical procedures each year. Many clinicians who care for patients with epilepsy are uncertain about the efficacy and safety of costly surgical procedures and still view surgery as a last resort for patients with intractable epilepsy.

The absence of robust evidence supporting the safety and efficacy of surgery for epilepsy figures prominently among the possible reasons for this view. There have been no randomized, controlled trials. All data derive from case series from disparate centers — series that have serious methodologic limitations such as the lack of appropriate controls, the retrospective assembly of cohorts, the unstandardized and unblinded assessment of outcomes, the irregular assessment of negative outcomes and adverse events, and a narrow definition of which outcomes are of interest. Because nonrandomized or inadequately performed trials may unpredictably overestimate or underestimate benefits and risks, developers of practice guidelines for surgery for epilepsy have been unable to make strong recommendations for clinical practice. Finally, comparative studies involving the prospective, longitudinal assessment of the quality of life and psychosocial outcomes have failed to demonstrate a consistent superiority of surgery. We undertook a parallel-group, randomized, controlled trial comparing surgery with medical therapy in patients with temporal-lobe epilepsy.

METHODS

We compared medical treatment with surgical treatment of temporal lobe epilepsy at the London Health Sciences Centre, University of Western Ontario, Canada, between July 1996 and August 2000. The study reflected the standard of care and was approved by the institutional review board.

After receiving explanations of the diagnosis of temporal-lobe epilepsy, the rationales for medical and surgical treatment, the usual procedures for determining patients’ suitability for surgery, and the purpose of the study, all patients whom we enrolled gave written informed consent. At our institution, patients are put on a one-year waiting list before undergoing preoperative investigations. It was explained to patients that randomization results in an equal (50 percent) chance of being assigned to the medical group or to the surgical group. Patients in the medical group were placed on the usual one-year waiting list; then they were admitted for preoperative investigations and, if they were deemed eligible, they underwent surgery within four weeks. The patients in the surgical group underwent preoperative evaluation within 48 hours after randomization and underwent surgery within four weeks if they were deemed eligible. After surgery, they received optimal medical therapy for one year. Patients were told that they could withdraw from the study at any point.

Study Patients

Potential candidates for surgery for temporal-lobe epilepsy whose seizures were poorly controlled with medication were examined by...
and individual requirements, and measured serum anticonvulsant levels when necessary. All patients received similar psychiatric or psychological treatment, as determined by the treating epileptologist and psychologist.

Patients wrote detailed descriptions of all seizure-like events in monthly seizure diaries. Two external epileptologists independently reviewed each diary entry, from which any information identifying the patient had been removed, and reached a consensus on whether or not the event was a seizure. We assessed the severity of seizures and the quality of life with the ictal subscale of the Livermore Seizure Severity Scale (range of scores, 10 to 48, with higher scores indicating greater severity) and the epilepsy-specific Quality of Life in Epilepsy Inventory-89 (QOLIE-89; range of scores, 0 to 100, with higher scores indicating better quality of life), respectively. Psychopathology and depression were assessed with the General Health Questionnaire (range of scores, 0 to 28, with higher scores indicating worse health) and the depression scale of the Center for Epidemiological Studies (CES-D; range of scores, 0 to 60, with higher scores indicating more depressive symptoms), respectively. All of these instruments have demonstrated reliability and validity in assessing patients with epilepsy and were self-administered at baseline and at 3, 6, 9, and 12 months. The research coordinator reviewed all the data for completeness and contacted patients for missing responses before the data were double-entered into the study database.

The primary outcome was freedom from seizures impairing awareness (i.e., complex partial or generalized seizures) at one year. The trial was designed to detect an absolute difference of 34 percent between the proportion of patients in the surgical group who were free of seizures impairing awareness (54 percent) and the portion of those in the medical group who were free of such seizures (20 percent), after correction for the 15 percent of patients in the surgical group who might not be deemed eligible for surgery after they had been assigned to the surgical group.

These conservative estimates were based on reports from nonrandomized studies. We needed to enroll 40 patients per group in order to detect a difference of this magnitude with 90 percent power at a two-sided significance level of 0.05. With a sample this size, the study had 80 percent power to detect a 10-point (±15.5 SD) difference between groups in the mean change in the QOLIE-89 global score (20.0 in the surgical group vs. 10.0 in the medical group).

**Statistical Analysis**

Data were analyzed according to the intention-to-treat principle. Freedom from seizures was determined on the basis of Kaplan–Meier event-free survival curves. The differences between the groups were evaluated with the log-rank test. Cox proportional-hazards regression was used to assess the effect of any imbalances in the baseline demographic and clinical characteristics of the patients on the
RESULTS

Of 92 patients screened, 86 were eligible; 80 agreed to participate, and 40 were randomly assigned to each group. At base line, there were no imbalances in the important demographic and clinical characteristics of the patients in the two groups, such as age, employment status, level of education, duration of epilepsy, type and frequency of seizures, anticonvulsant drugs used, and MRI findings (Table 1). The patients who were randomly assigned to medical treatment had lower quality-of-life scores at base line than those assigned to surgical treatment.

In the surgical group, six patients had recordings from subdural electrodes, and four patients (10 percent) did not undergo surgery. One declined surgery, two were not deemed eligible for surgery because the results on EEG, MRI, and neuropsychological tests did not agree, and one did not have seizures during the investigations conducted in the hospital. A total of 24 patients had operations on the left side, and 12 had operations on the right side. Two patients (5 percent) underwent a surgical procedure that differed slightly from that specified in the protocol. One underwent a selective amygdalohippocampectomy on the dominant side because of a concern about speech and memory, and one had a more extensive resection that was deemed necessary because of the origin of the seizure as revealed by intracranial EEG.

Four patients had adverse effects of surgery. In one patient, a small thalamic infarct developed, causing sensory abnormalities in the left leg; in one, the wound became infected; and in two, there was a decline in verbal memory that interfered with the patients’ occupations at one year. Asymptomatic, superior subquadrantic visual-field defects occurred in 22 patients in the surgical group (55 percent), as expected. No neurologic abnormalities occurred in the patients in the medical group. Depression occurred in seven patients in the surgical group (18 percent) and eight patients in the medical group (20 percent). Transient psychosis developed in one patient in each group.

No patients were lost to follow-up. There were no crossovers from the medical group to the surgical group. One patient in the medical group died (a sudden, unexplained death) 7.5 months into the study. No deaths occurred in the surgical group.

The anticonvulsants were switched or their doses increased in all patients in the medical group, and in 9 (22 percent) in the surgical group. In the medical group, the anticonvulsant was switched once in 19 patients (48 percent), twice in 9 patients (22 percent), three times in 3 patients (8 percent), and four times in 1 patient (2 percent). All doses of anticonvulsants were increased to therapeutic levels or to the maximal tolerated dose.

The cumulative proportions of patients who were free of seizures impairing awareness at one year were 58 percent in the surgical group and 8 percent in the medical group (P<0.001) (Fig. 2A). The proportions who were free of all seizures, including auras, were 38

### Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MEDICAL GROUP (N=40)</th>
<th>SURGICAL GROUP (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>At randomization 34.9±9.9</td>
<td>35.5±9.4</td>
</tr>
<tr>
<td></td>
<td>At the onset of seizures 16.2±10.0</td>
<td>14.3±11.7</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>47.5</td>
<td>57.5</td>
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<tr>
<td>Completed high school (%)</td>
<td>76.0</td>
<td>65.0</td>
</tr>
<tr>
<td>Current employment status (%)</td>
<td>45.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Discharge rate related to epilepsy</td>
<td>37.5</td>
<td>35.0</td>
</tr>
<tr>
<td>Unemployed (%)</td>
<td>17.5</td>
<td>20.0</td>
</tr>
<tr>
<td>History of status epilepticus (%)</td>
<td>12.5</td>
<td>15.0</td>
</tr>
<tr>
<td>CES-D score§</td>
<td>14.9±9.2</td>
<td>17.2±9.3</td>
</tr>
<tr>
<td>QOLIE-89 score‡</td>
<td>52.9±19.2</td>
<td>60.5±15.3</td>
</tr>
<tr>
<td>Average monthly frequency of seizures impairing awareness in year before randomization</td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3.0–14.1</td>
<td>2.4–9.0</td>
</tr>
<tr>
<td>No. of antiepileptic drugs used before randomization</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4–7</td>
<td>4–8</td>
</tr>
<tr>
<td>MRI findings (%)</td>
<td>17.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Normal</td>
<td>17.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Mesiol temporal sclerosis</td>
<td>72.5</td>
<td>70.0</td>
</tr>
<tr>
<td>Low-grade tumor, cortical dysplasia, or vascular malformation</td>
<td>10.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD. QOLIE-89 denotes the Quality of Life in Epilepsy Inventory-89, CES-D the depression scale of the Center for Epidemiological Studies, and MRI magnetic resonance imaging.

†The range of scores is 0 to 28, with higher scores indicating worse health.

‡The range of scores is 0 to 100, with higher scores indicating better quality of life.

§The range of scores is 0 to 60, with higher scores indicating more depressive symptoms. Scores were available for 32 patients in the medical group and 31 patients in the surgical group.
percent in the surgical group and 3 percent in the medical group \((P<0.001)\) (Fig. 2B). Therefore, only 2 patients (95 percent confidence interval, 1.5 to 3) need to undergo surgery (number needed to treat) to render 1 additional patient free of seizures impairing awareness at one year, and 3 patients (95 percent confidence interval, 2 to 5) must undergo surgery to render 1 additional patient free of all seizures at one year. The benefit of surgery persisted after adjustment for all base-line demographic and clinical characteristics, including the quality of life \((P<0.001)\). Twenty-three of the 36 patients who underwent surgery (64 percent) were free of seizures impairing awareness at one year, and 15 of these patients (42 percent) were free of all seizures. The median percentage improvement in the monthly frequency of seizures impairing awareness was 100 percent in the surgical group and 34 percent in the medical group \((P<0.001)\). Approximately 15 percent of the patients in the surgical group continued to have one to four seizures impairing awareness per month, and 10 percent had five or more such seizures (Fig. 3). Among the patients with residual seizures, the mean severity of the seizures was similar in the patients in the medical group and in those in the surgical group (Fig. 4).

The quality of life was better among the patients in
the surgical group than among those in the medical group (P<0.001), and it improved over time in both groups (P=0.003) (Fig. 5). Although there was a trend toward a higher proportion of patients in the surgical group than in the medical group who were employed or attending school at one year (56.4 percent vs. 38.5 percent), this difference did not achieve statistical significance (P=0.11) (Fig. 6).

DISCUSSION

Our results support the superiority of surgery over medical therapy in terms of the control of seizures, the quality of life, and the rates of employment and school attendance among patients with poorly controlled temporal-lobe epilepsy. The absolute benefit of surgery in terms of the rate of freedom from seizures was large (50 percentage points for seizures impairing awareness and 35 percentage points for all seizures) and precise (confidence intervals were narrow). Our intention-to-treat analysis yielded a rate of freedom from seizures impairing awareness in the surgical group of 58 percent. Although this rate is lower than that found in studies assessing the cumulative freedom from seizures from the time of surgery (69 percent in one study and 63 percent in another), the rate of freedom from seizures among the 36 patients who actually underwent surgery was 64 percent.

Although the assessment of outcomes after the trial is ongoing, the comparisons within the trial were limited to one year after surgery. Investigators disagree about the minimal time needed to determine the long-term seizure-related outcome. On the basis of our past experience and that of others, the seizure-related outcome one year after anterior temporal lobectomy seems a reasonable predictor of the subsequent outcome. Significant changes in psychosocial function, employment status, or school attendance may occur more slowly. However, as early as one year after surgery, we observed differences between the groups favoring surgery in terms of the quality of life, employment status, and school attendance. The unexpected death of one patient in the medical group and the absence of deaths in the surgical group support the previous observation of decreased mortality among surgically treated patients.

Surgical morbidity was similar to that reported in case series. Substantial postoperative difficulties with memory developed in 5 percent of our patients and in 1 to 4 percent of those in previous studies. We acknowledge that this complication of surgery is im-

Figure 3. Monthly Rates of Seizures According to Type among Patients in the Medical and Surgical Groups.

Bars represent the percentages of patients in various categories at base line and at monthly intervals after follow-up began (the day after surgery in the surgical group and 25 days after randomization in the medical group). Seizures impairing awareness were complex partial seizures and generalized seizures.
important, but in our opinion, the benefit is worth the risk. Hemiparesis, expected in 2 to 5 percent of patients, did not occur in our study. Finally, depression was equally frequent in both groups and was in keeping with published rates. The results in the medically treated patients substantiate recent reports indicating a low probability of freedom from seizures (10 percent or less) in patients with temporal-lobe epilepsy and in those in whom two or more anticonvulsant drugs have previously failed.

One previous failed attempt at a randomized trial of surgery for epilepsy and commentators’ emphasis on the difficulties inherent in executing such trials have strengthened the view that they are not feasible. The successful performance of this study demonstrates that randomized, controlled trials of surgery for epilepsy are feasible when the methods are adapted to the specific social and health care context of the patients.

For example, pilot studies revealed that neither the patients nor the clinicians in our center would accept randomization after the investigations in the epilepsy monitoring unit had been completed. Therefore, if skilled epileptologists rated the clinical data and the findings of outpatient investigations as highly likely to indicate a unilateral temporal-lobe origin of seizures, patients were randomly assigned to treatment groups before the inpatient investigations had been conducted. This strategy was successful. Only 10 percent of
the patients assigned to the surgical group did not undergo surgery (fewer than our original estimate of 15 percent), and in only two of the patients assigned to the surgical group (5 percent) was surgery not indicated. Thus, in selected patients with temporal-lobe epilepsy, outpatient investigations may accurately predict decisions regarding surgery.39,40

In summary, this study provides robust and precise estimates of the effectiveness and safety of surgery for patients with temporal-lobe epilepsy from any cause. The results substantiate the belief that prolonged trials of anticonvulsant drugs are futile and support the notion that patients with temporal-lobe epilepsy should be evaluated for surgery in order to preclude unnecessary disability and perhaps even death. However, the trial does not address the question of the optimal timing of surgery, particularly whether early surgery for temporal-lobe epilepsy is superior to medical therapy.6

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APPENDIX


REFERENCES