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Does Temporal Lobe Resection Cure Seizures in Epileptics?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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The Degree of Master of Science

In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

Objective: The objective of this systematic review is to determine whether or not temporal lobe resection cures seizures in epileptics.

Study Design: Systematic review of three English language, peer-reviewed randomized controlled trials, published between 2001 and 2012

Data Sources: Two randomized controlled trials comparing temporal lobe resection surgery to antiepileptic drugs in the treatment of epileptic seizures, and one randomized controlled trial comparing 3.5 cm temporal lobe resection to 2.5 cm temporal lobe resection in the treatment of epileptic seizures. Studies were obtained by the author through the PubMed database.

Outcomes Measured: Primary outcome measured by the three studies was control of seizures, and additional outcomes measured included quality of life and cognitive function.

Results: The three randomized controlled trials found that temporal lobe resection treatment significantly decreased the frequency and severity of seizures in patients with temporal lobe epilepsy that was refractory to pharmacotherapy. Two of the three studies showed that temporal lobe resection resulted in significantly higher rates of freedom from seizures and significantly higher quality of life as compared to treatment with antiepileptic drugs alone. All three studies showed that surgery poses an increased risk of complications and adverse events, including decline in cognitive function.

Conclusions: Data suggests that temporal lobe resection surgery is more effective than medical therapy alone in decreasing the frequency and severity of seizures in patients with temporal lobe epilepsy that is refractory to pharmacotherapy. Temporal lobe resection is not a definitive cure for seizures in epileptics, but research presented in these three studies shows that surgery is superior to pharmacotherapy alone in controlling seizures. Further research is needed to determine long-term efficacy in seizure reduction post-surgically, as well further assessment of cost and safety of temporal lobe resection.

Key Words: Epilepsy, temporal lobe resection

INTRODUCTION

A seizure is a sudden alteration in behavior, thought, and/or consciousness caused by neuronal dysfunction in the brain.¹ Epileptic seizures specifically are due to electric hypersynchronization of neurons in the cerebral cortex, and these seizures occur independently of provocation by specific events.¹ Epilepsy is characterized by recurrent epileptic seizures (2 or more).¹ Greater than one half of epileptic seizures have no identifiable underlying cause,¹ which makes the treatment of epilepsy difficult because there often is no underlying etiology to be corrected. Although a cause of epilepsy may not be readily identifiable, seizures can often be localized to the specific portion of the brain they are coming from based on interpretation of electroencephalogram (EEG) studies. Of the cases of epilepsy that can be localized, temporal lobe epilepsy is the most common form of the disorder.²

Epilepsy is a serious health problem that affects both men and women of all races, ages, geographic regions, and socioeconomic backgrounds.³ The prevalence of epilepsy is five to ten per 1000 in North America.³ There are currently 2.9 million individuals in the United States diagnosed with epilepsy, accounting for 1% of adults and 0.6% of children.⁴ Many cases of epilepsy are well controlled by pharmacotherapy, but there is still a large percentage of individuals with this disease that do not achieve a seizure-free life. The total indirect and direct cost of epilepsy in the United States annually is \$15.5 billion.⁴ For those with medically controlled epilepsy, the cost is \$2,000 per year, whereas patients with medically uncontrolled pay roughly \$10,000 per year in medical bills.⁵ All epileptic patients average 10 physician visits per year and greater than 30 drug dispensings per year.⁶ Epilepsy is the second most common cause of mental health disability in the United States.³

The typical approach to managing epilepsy includes pharmacotherapy targeted at resolving or decreasing frequency of seizures. This is best done through the use of antiepileptic drugs (AEDs). Some of the most commonly used antiepileptic agents include phenytoin, lamotrigine, carbamazepine, gabapentin, topiramate, and valproate.¹ For some patients, AEDs greatly decrease the frequency of seizures, and sometimes even achieve lifelong freedom from seizures. As many as 20-40% of patients, however, will have seizures that are refractory to AEDs.⁷ Seizures cause patients to have impaired psychosocial functioning and decreased quality of life.⁴ Because there is still such a large percentage of patients with epilepsy whose seizures are not controlled by medication, and because recurrent seizures can cause patients to have a poor quality of life, there has been more and more research in developing other means of treatment for epilepsy.

Of all cases of epilepsy that are refractory to pharmacotherapy, 50-73% are localized temporal lobe epilepsy.² Seizures in temporal lobe epilepsy range from simple partial seizures characterized by auras and preserved awareness, to complex partial seizures with loss of awareness and sometimes convulsions.³ Temporal lobe epilepsy is the form that is most amenable to surgical treatment.⁵ Therefore, much of the new epilepsy research focuses on brain surgery in patients with temporal lobe epilepsy, in attempt to find a treatment for seizures in patients with medically uncontrolled epilepsy.

OBJECTIVE

The objective of this systematic review is to determine whether or not temporal lobe resection cures seizures in epileptics.

METHODS

Criteria used for the selection of studies for this review included randomized controlled trials including persons greater than 12 years old with temporal lobe epilepsy whose seizures were not controlled with AEDs. All studies included an intervention of partial temporal lobe resection surgery with a comparison group of antiepileptic medication. Common outcomes that were evaluated by the three studies were control of seizures, quality of life, and cognitive function. Research was conducted by the author by collecting relevant articles through the PubMed database, using the keywords “temporal lobe resection” and “epilepsy” to find appropriate studies. All articles were published in English in peer-reviewed journals. Studies were selected based on relevance to the clinical question and based on relevance to patients and patient oriented outcomes (POEMs). Inclusion criteria included studies published after the year 2000 that were randomized controlled trails, including a population of patients with temporal lobe epilepsy who have previously failed pharmacotherapy with AEDs. Exclusion criteria included patients under 12 years old, patients with psychosis, substance use disorder, eating disorder, IQ below 70, abnormalities on neuroimaging, and patients who have had previous brain surgery for epilepsy. Statistics reported in these studies were p-values and 95% confidence intervals, and the author calculated numbers needed to treat (NNT), relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to harm (NNH), relative risk increase (RRI), and absolute risk increase (ARI) using dichotomous data found in the studies.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Engle (2012)	RCT	38	≥ 12 yo	Pts 12 yrs and older with mesial temporal lobe epilepsy that have tried and failed at least 2 AEDs	Pts with psychosis, suicidal risk, substance abuse, eating disorders, IQ < 70, non-epileptic seizures, abnormalities on brain MRI	1	Anteromesial temporal lobe resection surgery
Wiebe (2001)	RCT	80	≥ 16 yo	Pts 16 yrs and older with temporal lobe epilepsy whose seizures occur at least monthly and were poorly controlled with AEDs, one of which being phenytoin, carbamazepine, or valproic acid	Pts with psychosis, pseudo-seizures, IQ < 70, CNS disorders, abnormalities on brain MRI, focal temporal spikes or slowing on EEG, pts who have had previous surgery for epilepsy	1	6.0-6.5 cm resection of the anterior lateral non-dominant temporal lobe or 4.0-4.5 cm resection of the dominant temporal lobe
Schramm (2011)	RCT	207	≥ 18 yo	Pts 18 yrs and older with mesial temporal lobe epilepsy that have tried and failed at least 2 AEDs at maximum tolerated doses, seizure duration > 2 yrs, must be available for follow up after 1 yr	Pts with abnormalities on brain MRI, neuropsychological abnormalities, pts who have had previous temporal lobe surgery, seizure duration < 2 yrs	0	3.5 cm temporal lobe resection surgery vs. 2.5 cm temporal lobe resection surgery

OUTCOMES MEASURED

All three studies measured control of seizures, quality of life, and cognitive function. Control of seizures was measured with the ictal subscale of the Liverpool Seizure Severity Scale, through patients' seizure diaries, and through Engel class categories. Quality of life was measured with Quality of Life in Epilepsy Inventory-89 for adults 17 years and older and Quality of Life in Epilepsy-48 for adolescents 16 years and younger, and through records of hours worked per week, number of sick days from school or work, and number of hospitalizations. Cognitive function was measured using clinical neuropsychological measures of visual and auditory attention, motor/speed dexterity, verbal and visuospatial memory, and word finding ability.

RESULTS

The three randomized controlled trials included in this review compared partial temporal lobe resection surgery to the control group of pharmacotherapy with AEDs. One study also compared a 2.5 cm to a 3.5 cm temporal lobe resection.

In the randomized controlled trial by Engle et al⁸, 38 participants age 12 years and older with mesial temporal lobe epilepsy and disabling seizures were randomized into a surgical group and a medical group. The surgical treatment included anteromesial temporal lobe resection performed by experienced neurosurgeons. The comparison group (medical treatment) included use of antiepileptic medication. Prior to this study, all participants must have tried at least two AEDs within the past two years, which failed to control seizures. The primary outcome measured in this study was freedom from disabling seizures at year two of follow-up. Secondary outcomes measured were health-related quality of life and cognitive function. At year two of follow-up,

zero of 23 patients in the medical group were seizure-free, and 11 of 15 patients in the surgical group were seizure free (95% CI, 11.8 to ∞ ; $P < 0.001$)⁸, as portrayed in Table 2. Numbers needed to treat (NNT) was also calculated in Table 2, and it was found that for every two patients with epilepsy that undergo temporal lobe resection surgery, one more person will remain free from seizures as compared to the medical group. Additionally, quality of life was higher in the surgical group than in the medical group, but the difference was not statistically significant (95% CI -1.0 to 18.1; $P = 0.08$).⁸ Four participants in the surgical group experienced memory decline, representing a decline in cognitive function,⁸ but the sample of participants in this study was too small to make definitive conclusions about differences in cognitive outcomes between the two groups.⁸ Additional adverse events included a post-operative stroke leading to transient neurologic deficit in one patient in the surgical group, and three cases of status epilepticus in the medical group.⁸ Based on this information, numbers needed to harm (NNH) was calculated in Table 3. Based on the adverse events that occurred in this study, it was calculated that for every four patients with epilepsy that undergo temporal lobe resection surgery, one more adverse event will occur as compared to the medical group.

Wiebe et al³ conducted a similar study in which 80 participants were randomized into either a surgical group (40 patients) or a medical group (40 patients). The surgical group underwent a 4.0-4.5 cm resection of the temporal lobe if seizures originated from the dominant temporal lobe (based on EEG findings) or a 6.0-6.5 resection of the temporal lobe if seizures originated from the non-dominant temporal lobe. After surgery, patients were started on AEDs. The medical comparison group underwent one year of AED therapy. After one year, experienced epileptologists blindly evaluated patients for the primary outcomes, which was freedom from seizures impairing awareness and freedom from all seizures, and for quality of life. Results

showed that after one year, proportion of patients who were free from seizures impairing awareness was 58% in the surgical group and 8% in the medical group ($p < 0.001$).³ Patients in the surgical group also had a lower incidence of seizures altogether. After one year the proportion of patients who had no seizures in the past year was 38% in the surgical group and 3% in the medical group ($p < 0.001$).³ Table 2 displays NNT for both freedom from seizures impairing awareness and freedom from all seizures. It was found that for every two patients with epilepsy that undergo temporal lobe resection surgery, one more person will remain free from seizures that impair awareness as compared to the medical group, and for every three patients with epilepsy that undergo temporal lobe resection surgery, one more person will remain free from all seizures as compared to the medical group. Patients in the surgical group also had a significantly better quality of life ($p < 0.001$).³

While the study conducted by Wiebe et al³ showed better seizure control in the surgical group as compared to the medical group, there were higher rates of adverse effects in the surgical group. Significant post-operative adverse events (difficulties with memory) developed in 5% of the surgical group as compared to zero in the medical group.³ NNH was calculated in Table 3, showing that for every 20 patients with epilepsy that undergo temporal lobe resection surgery, one more adverse event will occur as compared to the medical group.

The randomized controlled trial conducted by Schramm et al⁹ was slightly different than the other two randomized controlled trials in this review. This study compared two surgical groups rather than a surgical group to a medical group. Two hundred and seven patients were randomized into a surgical group that underwent a 2.5 cm resection of the affected temporal lobe (104 patients) and a surgical group that underwent a 3.5 cm resection of the affected temporal lobe (103 patients). After one year, seizure freedom analysis showed that 74% of patients in the

2.5 cm resection group and 73% of patients in the 3.5 cm resection group were free from seizures. There was no statistical significance between the two groups ($p = 0.843$).⁹ Table 2 further exemplifies the lack of significant difference between these two surgical groups.

Table 2. Percentage of patients free from seizures after one year, relative and absolute risk reduction, and numbers needed to treat

	% Seizure Free (Medical Group)	% Seizure Free (Surgical Group)	p	RRR	ARR	NNT
Engle* (2012)	0	73%	< 0.001	--	73%	2
Wiebe (2001)**	8%	58%	< 0.001	6.25	50%	2
Wiebe (2001)***	3%	38%	< 0.001	11.7	35%	3
Schramm (2011)****	73%	74%	0.843	0.014	1%	100

* Engle et al⁸ assessed freedom from seizures after two years (no assessment at one year)

** Freedom from seizures impairing awareness

*** Freedom from all seizures

**** No medical group in Schramm study; 73% seizure free in medical group column represents 3.5 cm resection group and 74% seizure free in surgical group column represents 2.5 cm resection group

Table 3. Percentage of patients who experienced adverse effects of treatment, relative and absolute risk increase, and numbers needed to harm

	% Harmed (Medical Group)	% Harmed (Surgical Group)	RRI	ARI	NNH
Engle (2012)	9%	33%	2.7	24%	4
Wiebe (2001)	0	5%	--	5%	20

DISCUSSION

All three studies included in this review propose temporal lobe resection surgery as a treatment for patients with temporal lobe epilepsy that has been refractory to treatment with AEDs. Two of these studies (Engle et al⁸ and Wiebe et al²) compared temporal lobe resection surgery to conventional medical treatments of pharmacotherapy with AEDs. Both of these studies showed significantly higher rates of seizure control in the surgical group compared to the medical group ($p < 0.001$). Both studies showed that after one year, surgical groups not only achieved higher rates of seizure freedom, but also had higher rates of quality of life. Contrarily, both of these studies showed that there were greater adverse events including decline in cognitive function in the surgical group compared to the medical group.

Based on the results of the randomized controlled trials by Engle et al⁸ and Wiebe et al², there is strong supporting evidence that temporal lobe resection is more effective in reducing seizures than AED therapy alone. It is important to note that the sample size of patients in each of these studies is relatively small, and a much larger population will need to be studied in order to make any definitive conclusions. It is difficult to study large populations when it comes to performing invasive procedures like resection of a portion of the temporal lobe of the brain. Not only does this surgery pose risks of adverse effects such as lifelong cognitive impairment, but it is also extremely expensive. Patients with epilepsy need to be extensively evaluated before being deemed candidates for surgery, which means enduring numerous costly tests. However, the idea is that patients would have significantly lower rates of seizures post-surgically, and therefore would not have to continue paying the annual medical bills of \$10,000 for uncontrolled epilepsy.⁵ With risks of adverse events, high costs of the testing and procedure, and strict criteria

for eligible patients, it is difficult to include large populations in studies of temporal lobe resection in treatment of seizures in patients with pharmaco-resistant temporal lobe epilepsy.

In the study conducted by Schramm et al⁹, there was no statistical difference between patients who underwent a 2.5 cm temporal lobe resection compared to patients who underwent a 3.5 cm temporal lobe resection. There was, however, a large percentage of patients in each group (74% in the 2.5 cm group and 73% in the 3.5 cm group) who remained seizure-free after one year of surgery, indicating that temporal lobe resection, regardless of the size of resection, is effective in preventing seizures in patients with temporal lobe epilepsy. Schramm et al⁹ concluded that it is adequate resection size rather than larger resection size that helps achieve seizure freedom in patients.

One of the major limitations of all three of these studies is the short time for follow-up. Patients were assessed for seizure activity at one year in the studies by Wiebe et al³ and Schramm et al,⁹ and at two years in the study by Engle et al.⁹ When analyzing whether temporal lobe resection is a cure for epileptic seizures, the follow-up would need to be for a much longer period of time. Given this short time of follow-up, we are not able to assess long-term efficacy, long-term adverse effects, or and changes in the status of patients.

CONCLUSION

The three randomized controlled trials included in this review provide statistically significant evidence that temporal lobe resection is effective in the treatment of seizures in patients with temporal lobe epilepsy that is refractory to treatment with AEDs. While evidence shows that temporal lobe resection greatly decreases the frequency and severity of seizures in patients with temporal lobe epilepsy, surgery is not a definitive cure for seizures in epilepsy.

More extensive research needs to be conducted in order to follow surgical patients for longer periods of time in order to further assess the efficacy of temporal lobe resection in reducing seizures.

It is important to note that temporal lobe resection often comes with complications. Further research needs to be done in order to evaluate the safety of temporal lobe resection surgery. Patients will often need to weigh the risks vs. benefits of undergoing such an intensive procedure. Additionally, not all patients with this condition are candidates for invasive brain surgery. Ongoing research is still warranted concerning the safety, cost, patient qualifications, and efficacy of temporal lobe resection surgery compared to AEDs, but based on the information in these three randomized controlled trials in this review, we can say that temporal lobe resection offers better control of seizures in patients with temporal lobe epilepsy compared to AEDs alone.

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