Outcomes after Epilepsy Surgery

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ABSTRACT: Epilepsy surgery is a highly effective and durable treatment for specific types of drug resistant epilepsy such as temporal lobe epilepsy. Assessment of outcomes is essential in epilepsy surgery, which is an irreversible intervention for a chronic condition. Excellent short-term results of resective epilepsy surgery have been established. In the last years more information regarding long term outcomes have been published. This article reviews the best available evidence about the best measures to assess outcomes and the most important evidence. The outcomes reviewed in this article are the following: seizure outcome, social and psychiatric outcomes, complications and mortality

RÉSUMÉ: Résultats de la chirurgie de l'épilepsie. La chirurgie de l'épilepsie est un traitement très efficace et durable de certains types bien spécifiques d'épilepsies pharmacorésistantes telle l'épilepsie du lobe temporal. L'évaluation des résultats est essentiel dans la chirurgie de l'épilepsie, une intervention irréversible effectuée pour traiter une maladie chronique. Les excellents résultats à court terme de la résection chirurgicale sont bien connus. Au cours des dernières années, des informations supplémentaires sur les résultats à long terme ont été publiés. Cet article revoit les meilleures données disponibles concernant les meilleures méthodes d'évaluation des résultats et les données les plus importantes. Nous revoyons les résultats suivants : l'effet sur les crises, l'impact social et psychiatrique, les complications et la mortalité.

Drug resistant epilepsy, a chronic condition with long-term consequences, is often treated with surgery, which produces permanent structural changes and has long-lasting effects. Epilepsy surgery is a highly effective and durable treatment for specific types of refractory epilepsy such as temporal lobe epilepsy[1,2]. The definition of outcomes is the most important aspect to assess the prognosis of a specific medical condition. After epilepsy surgery there are different outcomes of interest and some of them are not easy to measure[3]. This review analyzed some outcome measures and the most recent information regarding the following outcomes: seizure outcome, social and psychiatric outcomes, cognitive outcomes, complications of epilepsy surgery and mortality.

Seizure outcome

Seizures after surgery are the most important outcomes explored in clinical studies[3]. The short-term efficacy and safety of epilepsy surgery for temporal lobe epilepsy have been established through a large number of cohort studies and one randomized controlled trial (RCT)[1]. In the only RCT patients with temporal lobe epilepsy were randomly assigned to medical or surgical treatment. At the end of one year, 58% of patients in the surgical group were free of disabling seizures, compared with only 8% in the medical group. In 2003 Engel et al[4] synthesized the evidence about epilepsy surgery with an intermediate duration of follow-up (one to five years) in a meta-analysis of 32 studies involving 2250 patients. In the aggregate, 65% of patients with anteromesial temporal resections were seizure free, while 21% improved and 14% did not improve. In another systematic review of temporal lobe resections, seizure free rates varied widely (33%-93%), with a median of 70%. Tellez-Zenteno et al[5], synthesized the evidence about long-term outcomes (five years or longer) of epilepsy surgery. The median proportion of seizure free patients in the long-term was 66 (CI_{95} 62-70) for temporal lobe resections, 34% (CI_{95} 28-40) for extratemporal resections in general, 27% (CI_{95} 23-30) for frontal lobe resections, 46% (CI_{95} 35-57) for parietal and occipital lobe resections, 16% (CI_{95} 8-24) for multiple subpial transections, and 35% (CI_{95} 26-44) for callosotomy (patients free of seizures causing falls).

Overall long-term outcomes were consistently similar to those of short-term studies, including those from the RCT. Even though studies do not use a single seizure scale, the studies show similar results making the seizure outcome as one of the most stables outcome to measure. The available evidence supports the notion that the benefits of surgery in general are durable.

Quality of life

The term quality of life (QUOL) is used to evaluate the general well-being of individuals and societies[6]. The chronic

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nature of epilepsy, the resistance to antiepileptic drugs of some types of epilepsy, and the stigmata of the disease impact all aspects of QUOL[6].

Several instruments have been introduced over the years to measure QUOL. A review performed by Leone in 2005[7] identified 21 instruments. The Washington Psychosocial Seizure Inventory (WPSI) was the most commonly used instrument. However, it was not specifically designed to assess the broad construct of HRQOL. Of the remaining 20 instruments, five of them (the Liverpool Battery, the ESI-55 and the QOLIE-89, QOLIE -31 and QOLIE -10) accounted for 68% of the used instruments.

In a recent meta-analysis, Seiam et al[8] analyzed the main determinants of quality of life before and after epilepsy surgery. 39 studies involving 3,373 patients were included. Ninety-one percent of the studies showed improvement in quality of life measures after epilepsy surgery. Only three studies did not show positive changes and was probably related with reduced sample sizes and other methodological problems. The meta-analysis demonstrated that seizure outcome is by far the most important predictor of patient-centered QOL after surgery. Quality of life improvement is five times lower if seizures only improve, rather than remit altogether. The main preoperative determinants of QUOL were poor preoperative psychological function, negative affect (neuroticism), unrealistic or unmet expectations of surgical results. The main postoperative determinant of QUOL were seizure improvement, being employed, high patient satisfaction, less AED effects, poor psychological function, verbal memory problems, having physical comorbidities and seizure severity.

Antiepileptic Drugs

Epilepsy surgery is a highly effective treatment for specific types of refractory epilepsy and once seizure freedom is achieved many patients and clinicians have to ponder whether to taper or discontinue antiepileptic drugs (AEDs).

Schmidt and Löscher[9] reviewed the use of antiepileptic drugs (AEDs) after temporal lobe epilepsy surgery with short and long term follow up, emphasizing the proportion of "cured" patients (seizure free and off AEDs). Approximately one-third of patients were cured, one third were controlled on AEDs and one third continued to have disabling seizures on AEDs. Tellez-Zenteno et al[10] performed a second meta-analysis of long term surgical outcomes exploring the use of AEDs. Their findings were somewhat less favorable than those of Schmidt[9]. For all types of surgery, in the long term 22% (CI_{95} 18-23) were cured and 20% (CI_{95} 18-23) were off AEDs (with or without seizures), while 41% (CI_{95} 18-23) were on monotherapy and 31% (CI_{95} 18-23) were on polytherapy. Outcomes with regard to AEDs varied by type of surgery; in temporal lobe surgery 20% (CI_{95} 17-23) were cured, 14% (CI_{95} 11-17) were free of AEDs, 50% (CI_{95} 45-55) were on monotherapy and 33% (CI_{95} 29-38) were on polytherapy.

In general published data regarding AEDS after epilepsy surgery has to be interpreted as a representation of particular practice patterns in selected groups of patients, and that practices vary widely because there are currently no standards of practice or evidence guides to decrease or discontinue AEDs after surgery. In a survey of 151 epileptologists in the US[11], 62% believed that patients should remain on AEDs for ≥2 years before considering discontinuation, but actual practice was not explored. Finally, the factors commonly held to as clinical predictors of successful AED withdrawal are being brought into question. A second survey was performed on pediatric and adult epileptologists in Canada[12]. The minimum seizure free period required after epilepsy surgery before withdrawing AEDs, varied substantially among responders: >6 months in 10%, 6-11 months in 21%, >1 year in 50%, >2 years in 12%, >2 years in 3%. The most important factors influencing the decision to withdraw AEDs were an EEG with no epileptiform activity after surgery (71%), patients' preferences (78%) and the presence of unilateral mesial temporal sclerosis (70%). The most important factors against reduction were patients' wishes to resume driving (67%), focal (65%) or generalized (78%) epileptiform activity in the EEG after surgery, persistent isolated auras (78%), any seizures after discharge (81%), and presurgical multifocal/bilateral/diffuse findings (78%).

Controlled studies assessing AED use are few and results vary. For example, Schiller et al[13] retrospectively evaluated seizure outcomes pertaining to AEDs following successful epilepsy surgery. Seizures recurred in 26% at five years in those who discontinued AEDs, compared with 7% in those who did not discontinue AEDs. By contrast, in a prospective controlled study by Berg et al[11], paradoxically, seizures recurred in 32% of those who decreased or stopped AEDs, and in 45% of those who did not, a statistically significant difference. The most important predictor of seizure freedom, regardless of AED use, was immediate remission after surgery.

Recently Rathore et al[14], analyzed the safety of medication withdrawal after successful epilepsy surgery in 310 patients. Discontinuation was performed in 83% of patients. There was seizure recurrence in 24.8% while reducing medications. From the group of patients where recurrence of seizures was seen, 92.3% became seizure free after re-starting the medication. The authors concluded that AED withdrawal was safe and seizures after withdrawal were easy to manage.

A randomized controlled trial (RCT) is necessary to obtain robust evidence that can guide clinical decisions. Because many variables influence AED changes after successful surgery, and because patient and clinicians often have strong views and preferences in this regard, a number of questions need to be explored before launching an RCT.

Mortality

Mortality is the ultimate outcome in epilepsy and one that concerns physicians and patients greatly[15]. Studies in selected populations, as well as from the community consistently have demonstrated an increased risk of death in epilepsy. In hospitals or epilepsy centers, standardized mortality ratios (SMR) range from 1.9 to 3.6[16]. In population based studies the SMR ranges from 1.6 to 4.1[17].

Few studies have analyzed mortality after epilepsy surgery. In the short-term a potential decrease in mortality has been reported. Salanova et al[18] found that patients with persistent seizures following temporal lobe surgery had an SMR of 7.4, as compared with 1.7 (similar to the general population) in those who became seizure free. In a systematic review Tellez-Zenteno et al[10] identified few studies assessing mortality in the long term

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(>5 years of follow up). Studies comparing mortality in surgical vs. non-surgical patients showed inconclusive results. Two found no differences[19,20], and one found a reduction of mortality in surgically treated patients[21]. Hennessy et al[22], found that epilepsy surgery reduced mortality but not quite to the rate expected in the general population.

Recently published studies show the same divergence of results. A recent study Seymour et al[23] assessed mortality in a cohort of 306 patients with temporal epilepsy who underwent epilepsy surgery. The standard mortality ratios were not decreased by surgery and remained above the standard population. This study was in contrast with the study of Bell at al[24]. In this study the mortality rates of two cohorts of patients were assessed (surgical v. medical group). The surgical group had lower rates than the medical group. Patients that achieved seizure freedom after the operation had lower mortality rates than patients who continued having seizures. The authors concluded that successful epilepsy surgery is associated with a reduced risk of premature mortality.

The divergence of results may be explained by differences in methodology and study populations. For example, studies use different metrics to assess mortality rates and, most importantly, seizure outcomes, resulting in dissimilar and non-comparable populations. Although, studies show inconsistent findings, in the last few years more studies have demonstrated that mortality rates can be improved in surgical patients if they are rendered seizure free after surgery. On the other hand studies calculating SMR against local or general populations have shown that even when patients reach a seizure free status, this status does not normalize their risk of death.

Cognitive Function

Chronic epilepsy is often accompanied by cognitive changes and by alterations of processes related to functional reorganization and behavioral compensation. Poor cognitive function is generally associated with early onset and long duration of epilepsy, and with poor seizure control[25]. Yet, patients who may benefit from epilepsy surgery might be deterred from it because of concerns of postoperative cognitive decline.

A recent meta-analysis summarizes the information about cognitive changes after epilepsy surgery[26]. Regarding intelligence the meta-analysis showed that after temporal and extratemporal resections there is a low rate of average gains and losses across studies, with 11% loss and 16% gain for combined left and right groups. Verbal IQ losses and gains were similar (14% and 12% respectively) for combined left and right surgeries. Finally, performance IQ losses and gains were marginally lower (7 and 9%).

Regarding memory, the same meta-analysis reported results for only studies including temporal resections[26]. In left-operated patients, the average rate of verbal memory decline was 44%, versus 20% in right-sided patients. Gains in verbal memory were relatively rare (7% in left, 14% in right). For visual memory, risk or loss was similar for both right and left surgery (23% and 21% respectively). Gains in visual memory were slightly less frequent, with an average rate of 15% in left-sided patients and 10% in right sided patients.

Regarding language outcomes, an average rate of naming decline of 34% was found for left-sided temporal surgery. No significant gains were identified and one study reported decline in receptive comprehension after left temporal surgery (4%).

Verbal fluency was reduced on average in 10% of left-sided patients compared to 27% with gains, which suggest a potential benefit from surgery. Right-sided surgery was associated with a relatively similar rate of loss and gains (21% and 16% respectively). Executive functioning was not modified significantly by temporal lobe surgery. Few studies examined attention and their combined data indicated that few patients decline post-surgery (6% and 2% for left and right surgery) and a small number reporting improvements (10% and 15% for left and right surgery, respectively).

Few studies in the meta-analysis explored self-reported subjective changes in cognition. There was a low rate of loss overall (9%) and a higher mean rate of reported gains (18%), regardless of the operated side. Finally, some controlled studies suggest that non operated patients have significantly more cognitive decline over the time[27].

In summary, left temporal resections have a higher risk of postoperative verbal memory impairment and seizure freedom may entail better memory outcomes. Naming was reduced after left-side resections. Data on attention indicated that few patients reporting declines post-surgery. Interestingly self-reported cognitive declines after epilepsy surgery were relatively uncommon.

Social Aspects

People with refractory partial epilepsy suffer from significant psychosocial predicaments. Inability to drive, employment restrictions, family function, life satisfaction, stigmata, and general worsening of quality of life accompanied by health deterioration are some of the difficulties faced by these patients[3].

A recent meta-analysis reported a variety of social outcomes after epilepsy surgery[28]. Regarding employment, 10 to 40% (median 15%) of patients improved their employment situation after epilepsy surgery. This improvement was seen mainly in studies where surgical candidates were compared with medical treatment controls. Full time students before surgery had the best employment outcomes after surgery. Employment outcomes were poorer in those who were older at the time of the surgery. Employment improvement was dependent upon seizure freedom in many studies. Improvement in driving status was noted in 7-65% (median 48%) of patients depending upon the study. The ability to drive was dependent on seizure free status after surgery. Driving outcomes were worse in older patients.

Income after surgery was explored in the same meta-analysis[28]. Unfortunately the assessment of outcomes was different among studies without the possibility to perform a pooled analysis. Some well-known controlled studies comparing surgical vs. medical groups have shown modest improvements of income and the main changes occurred in patients who are seizure-free after surgery. In general the studies show no changes of income in medical groups or in patients who continue having seizures. The same trend applies to education outcomes after epilepsy surgery, where the gains are modest and only in patients that are rendered seizure-free post-operatively.

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Independence also was explored in the meta-analysis and the gains reported in studies are variable but very significant[28]. Studies measuring independence rates before surgery and after surgery have shown an improvement that can go from 48-68 to 85-88%. Social relationships and interactions can also be improved by surgery. Patients can get involved in a relationship or getting married after surgery in rates that go from 27 to 60%. In the same way as income and education, the outcomes are better in patients who are rendered seizure free.

Psychiatric outcomes

A recent meta-analysis explored psychiatric outcomes after epilepsy surgery[29]. The pre-operative base rate of depressive symptoms in surgical patients was high, between 24 to 38%. The majority of studies reported an improvement of depression after surgery. Studies including medical groups as controls showed that medical groups had significantly higher rates of depression after surgery. Some studies explored de novo depression after surgery, reporting rates from 4 to 18.2%. Seizure freedom was identified in many studies as an important predictor for improvement of depression after surgery.

In the same meta-analysis anxiety had a high baseline prevalence before surgery (48%)[28]. Similar to depression, most of the studies demonstrated reduced prevalence of anxiety postsurgery. The percentage of patients with anxiety after surgery was twice the percentage of patients showing reliable worsening of anxiety postsurgery (13-23 improved vs. 4-6 worsened anxiety). Although the majority of studies showed improvement, there are some negative studies showing similar rates of anxiety before and after surgery[29]. Some studies have reported de novo anxiety after surgery and the rates go from 6.9 to 13%.

Regarding overall psychological disorders the meta-analysis demonstrated that the majority of studies reported an improvement of general psychological adjustment, distress and overall performance of psychiatric disorders[29]. Few of them show no improvement or mixed results. In general studies suggest that a previous history of psychiatric disorders is a risk factor for development and continuation of psychiatric disorders after surgery. This factor can be enlarged with the continuation of seizures after surgery.

Complications of epilepsy surgery

Complications after epilepsy surgery are outcoms that have not been explored systematically in many studies. A systematic review of studies reporting minor and major complications after epilepsy surgery was published in the RAND study[30]. Minor complications were defined as those which completely resolved within three months of surgery while major complications persisted beyond that time frame. In patients who had resective surgery, minor medical complications were reported in 5.1% of patients, most common being CSF leak, aseptic meningitis, bacterial infection and intracranial hematomas. Major medical complications were identified in 1.5% of cases. Overall, taking into account all kind of procedures, minor neurological complications occurred in 10.9% of patients and major neurological complications were noted in 4.7% of patients. Perioperative mortality was uncommon after epilepsy surgery, occurring in only 0.4% of TL patients (1.2% ET). The study demonstrated that the majority of complications result in temporary impairment for patients with good recovery. Permanent and major neurological complications associated with the most common epilepsy surgical procedure, temporal lobe resection, are low. The study concludes that the most common epilepsy procedures are safe should alleviate some of the fears and misconceptions regarding epilepsy surgery.

Conclusions

At present, seizures are by far the most frequently reported outcomes, but data on other outcomes are more recognized. Overall, studies with long term follow-up show that the short term results of epilepsy surgery are enduring; about 60% of patients with temporal epilepsy and from 35% to 40% of those with extratemporal epilepsy achieve long-term seizure freedom after epilepsy surgery.

Although the evidence on the impact of epilepsy surgery on mortality is inconclusive, recent data support a reduction in the risk of death if patients are rendered seizure free with surgery.

Decline in verbal memory occurs frequently after left temporal lobe resections, better memory outcomes occur in seizure free patients, and memory decline has been described in non-operated patients with intractable epilepsy. Attention and intelligence is not affected by epilepsy surgery.

The majority of studies have reported positive social outcomes after epilepsy surgery such as income, education, independence. Although the majority of studies are positive, the outcomes are significantly better in patients that rendered seizure free after surgery.

Some studies have shown an improvement on psychiatric comorbidity after epilepsy surgery, specifically depression and anxiety, although some controlled studies have not shown differences suggesting that methodological issues in studies are relevant. The presence of psychiatric disorders before surgery is by far the most important predictor for development of psychiatric disorders after epilepsy surgery.

Finally, major and permanent complications related with the most common surgical procedures are low reinforcing the safety of the intervention.

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