ABSTRACT: Background: Although randomized controlled trials (RCTs) are the gold standard for evaluating therapeutic interventions, surgical RCTs are particularly challenging and few have been done in the field of epilepsy surgery. We assess the level of RCT activity in epilepsy surgery and propose feasible alternatives to develop sustainable research initiatives in this area. Methods: We undertook a systematic review of the world literature to assess the level of RCT activity in epilepsy surgery. Previous personal experience with RCTs in epilepsy surgery and examples of successful Canadian multicentre research networks were reviewed to propose initiatives for sustainable, valid research in epilepsy surgery. Results: We identified 12 RCTs in epilepsy surgery, including 692 patients, of whom 416 were involved in vagus nerve stimulation, 16 in various brain electrostimulation procedures, 180 in comparisons of different surgical techniques, and 80 in a comparison of medical versus surgical therapy. Most studies were of short duration (median = 3 months, range 3-12 months). In the area of resective surgery, only temporal lobe epilepsy has been subjected to any type of RCT comparison. All RCTs have been done within the last 13 years. There were no multicentre Canadian surgical studies. Conclusions: The adoption of RCTs in epilepsy surgery has been slow and difficult worldwide. Because of its universal health care system and its well established epilepsy surgery centres, Canada is in a strong position to create a national epilepsy surgery research initiative capable of undertaking high quality, sustainable research in epilepsy surgery.

Over the years, clinicians have wrestled with the optimum methods to deal with bias and confounders in clinical research. Among the many types of biases, two can dramatically influence the study results and are particularly important in assessing the effect of surgical interventions. Selection bias refers to the process by which participants are not selected equally for the treatment and the control groups, resulting in groups with different prognostic variables. The best way to avoid selection bias is through concealed randomization, a process by which each study participant has an equal chance of being allocated to the experimental or to the control group. The second type of bias pertains to outcome assessment. This entails a risk of treating patients or assessing outcomes differently, based on expectation and preconceptions of the treating and the evaluating

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individuals. The optimum way to deal with outcome assessment bias is through blinding or masking of study participants, treating clinicians, outcome assessors and data entry personnel. Some researchers estimate that inadequate concealment of randomization may result in an over estimation of benefit of up to 40%, and that lack of adequate blinding may over estimate results by 17%. Recently, minimization has been used as a statistical method to ensure similarity of groups based on predefined prognostic criteria.

The methodology of clinical research in epilepsy surgery has evolved substantially in the last 15 years. Observational surgical studies have adopted increasingly rigorous methods of data gathering and reporting. Although few surgical studies have controls, modern reports have strengthened their validity, and centres around the world document very similar surgical results. Randomized controlled trials (RCT) however, remain sparse despite the large number of surgical interventions and devices used in the treatment of epilepsy. The challenges imposed by RCTs of surgical interventions, particularly in epilepsy, have been reviewed. Most notably these include willingness of patients and clinicians to allocate patients to surgery at random, issues with equipoise (insufficient uncertainty about the risk and benefit of alternate treatments), and difficulties with blinding or masking study participants. Although some neurosurgical studies have used sham brain operations, especially in the treatment of movement disorders, heated ethical debate precludes its widespread adoption.

In this review, we systematically appraise the RCT addressing aspects of surgical procedures or devices in the treatment of epilepsy, or aspects of management of medical issues in relation to surgical interventions in epilepsy. Lastly we propose feasible initiatives to develop and sustain high quality surgical research in epilepsy in Canada.

METHODS

We performed an extensive literature search using Medline and the Cochrane Database, spanning the years 1966 to 2005, using MeSH terms and text words involving epilepsy, surgery, surgical treatment, vagus nerve stimulation, deep brain stimulation, hippocampal stimulation, responsive neurostimulation, cerebellar stimulation, neurosurgery, and limiting it to humans and “RCTs”. We also searched references of relevant papers. Studies were included if they were RCTs describing the efficacy of therapeutic surgical procedures, surgical devices, or medical management around surgical interventions in epilepsy. Results were tabulated and summary statistics were derived from each study. When possible, we calculated the number needed to treat (NNT), which refers to the number of patients that need to undergo the procedure for one additional patient to benefit. In addition, we provide a brief description of the trials’ methodology, duration of treatment, and interpretation of results.

RESULTS

A total of 16 reports deal with randomized controlled studies addressing aspects of surgical procedures or devices in the treatment of epilepsy, or with aspects of management of medical issues in relation to surgical interventions. Of these, twelve are actual reports of surgical RCTs, two are reports of failed surgical RCT attempts, and two are RCTs of medical perioperative care.

Early Attempts at Surgical RCTs

Two of the studies are descriptions of early, unsuccessful attempts at randomized trials of resective brain surgery for epilepsy. As early as 1963, Ommaya described the results of temporal lobectomy in 106 patients and craniotomy without lobectomy in 25 patients in whom intraoperative electrocorticography led to the decision not to resect brain tissue. The results were strikingly similar in both groups. Substantial improvement occurred in 55% of patients with resections and in 59% of those without resections. Furthermore, those without resection had “better adjustment.” Ommaya goes on to propose that this justifies performing a controlled clinical trial, which never took place. In the second report, Dusheiff et al described their unsuccessful attempt at implementing an initially funded RCT of temporal lobe epilepsy surgery in Pittsburgh, citing as causes for failure the inability to recruit patients and to maintain funding for a slow recruiting trial.

RCT of Perioperative Care

Two studies address aspects of clinical management directly related to epilepsy surgery. In 1992, Kuzniecky et al reported a small randomized trial of 40 patients who, following temporal lobectomy, were allocated to treatment with carbamazepine alone, or continuation with anticonvulsant polytherapy. After one year, no significant differences were observed in the number or types of seizures, but more patients experienced side effects in the polytherapy group (30%) than in the monotherapy group (10%). In the second study, Sahi et al compared dexmethylasone versus placebo to treat pain, nausea and systemic symptoms in patients following subdural electrode implantation. They found a trend towards improvement in pain, nausea, and meningismus as well as lower temperature in those receiving dexmethylasone for 72 hours. However, the results were not statistically significant.

RCTs of Vagus Nerve Stimulation

The remaining 12 studies tested actual surgical interventions or surgical devices in a randomized controlled fashion (Table 1). Five of these assessed the efficacy of vagus nerve stimulation in 416 patients with refractory partial seizures with or without secondary generalization. Three studies tested low versus high intensity stimulation and one tested fast versus slow stimulation algorithms, and one assessed three different duty cycles. All studies had a short duration of follow-up not exceeding three months (Tables 1 and 2).

RCTs of Deep Brain Stimulation

Three studies have evaluated the effect of electrical brain stimulation in patients with refractory epilepsy (Table 1). One study, describes randomized trials in four individual patients (n-of-1) undergoing unilateral hippocampal stimulation, which was turned on and off at random in three treatment pairs. Although not significant, the results suggested a beneficial trend
with hippocampal stimulation, and no adverse effect on memory or cognitive function. Another study reports the results of a pilot analysis of bilateral centro-median thalamic stimulation in seven patients in a randomized, three-month crossover, double-blind, controlled study involving patients with generalized seizures. No significant differences were found in seizure control during the randomized controlled phase, but three patients experienced a 50% reduction in seizure frequency. In the third study, Velasco et al.\textsuperscript{19} report the results of a pilot analysis of bilateral cerebellar superomedial electrical stimulation in five patients with medically refractory generalized tonic clonic seizures, randomized to stimulator on (n=3) or stimulator off (n=2). Seizures were reduced to 33% of baseline frequency with stimulation, as compared to no seizure reduction in those without stimulation. Unblinded stimulation for 24 months in some patients showed continued benefit. Electrodes had to be removed in one patient because of an infection (Table 2).

### RCTs Comparing Surgical Approaches

Of the five remaining studies, four compare different surgical resective techniques (Table 1). Wyler et al.\textsuperscript{21} randomized 70 patients to partial hippocampectomy to the level of the cerebral peduncle or to total hippocampectomy to the level of the superior colliculus. Seizure freedom was achieved by 69% of patients with hippocampal stimulation, and no adverse effect on memory or cognitive function. Another study reports the results of a pilot analysis of bilateral centro-median thalamic stimulation in seven patients in a randomized, three-month crossover, double-blind, controlled study involving patients with generalized seizures. No significant differences were found in seizure control during the randomized controlled phase, but three patients experienced a 50% reduction in seizure frequency. In the third study, Velasco et al.\textsuperscript{19} report the results of a pilot analysis of bilateral cerebellar superomedial electrical stimulation in five patients with medically refractory generalized tonic clonic seizures, randomized to stimulator on (n=3) or stimulator off (n=2). Seizures were reduced to 33% of baseline frequency with stimulation, as compared to no seizure reduction in those without stimulation. Unblinded stimulation for 24 months in some patients showed continued benefit. Electrodes had to be removed in one patient because of an infection (Table 2).

### RCTs of Medical vs Surgical Therapy

Only one study has compared the efficacy and safety of temporal lobe resection versus medical therapy. Wiebe et al.\textsuperscript{24} randomized 80 patients with temporal lobe epilepsy to anterior temporal lobectomy versus optimum medical treatment using a parallel group, RCT with masked outcome assessment at one year. In an intention to treat analysis, the cumulative proportion of patients who were free of disabling seizures was 58% in the surgical group and 8% in the medical group (Table 2).
Table 2: Surgical Randomized Trials in Epilepsy - Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Main Outcome</th>
<th>Main Results (%)</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VNS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VNS Study Group, 199517</td>
<td>114</td>
<td>50% sz reduction</td>
<td>31 high/18 low</td>
<td>NNT=6 One myocardial infarction</td>
</tr>
<tr>
<td>Handforth, 199811</td>
<td>196</td>
<td>50% sz reduction</td>
<td>23 high/16 low</td>
<td>NNT=14 Better global outcome, no complications</td>
</tr>
<tr>
<td>Schermann, 200112</td>
<td>17</td>
<td>Mean % sz reduction</td>
<td>71 high/6 low</td>
<td>NS No complications</td>
</tr>
<tr>
<td>DeGiorgio, 200516</td>
<td>28</td>
<td>50% sz reduction</td>
<td>No differences</td>
<td>NS One patient with vocal cord paralysis</td>
</tr>
<tr>
<td>Amar, 199811</td>
<td>17</td>
<td>Mean % sz reduction</td>
<td>No differences</td>
<td>NS</td>
</tr>
<tr>
<td>Schermann, 200112</td>
<td>28</td>
<td>50% sz reduction</td>
<td>No differences</td>
<td>NS</td>
</tr>
<tr>
<td>DeGiorgio, 200516</td>
<td>61</td>
<td>50% sz reduction</td>
<td>No differences</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Brain Stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher, 199218 (Thalamic)</td>
<td>7</td>
<td>Mean % sz reduction</td>
<td>30% ON/8% OFF</td>
<td>NS Intense stimulation induced SW</td>
</tr>
<tr>
<td>Velasco, 200519 (Cerebellar)</td>
<td>5</td>
<td>Mean % sz reduction</td>
<td>67% ON/7% OFF</td>
<td>p=0.02 Infection &amp; removal in 1 patient</td>
</tr>
<tr>
<td>Tellez-Zenteno, 200620 (Hippocampal)</td>
<td>4</td>
<td>Median % sz reduction</td>
<td>26% ON/46% worse OFF</td>
<td>NS No cognitive changes</td>
</tr>
<tr>
<td><strong>Surgical Techniques</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyler, 199531 (Hippocampal resection)</td>
<td>70</td>
<td>% sz free</td>
<td>69% large/38% small</td>
<td>NNT=4 No cognitive effects</td>
</tr>
<tr>
<td>Hermann, 199922 (Superior temporal gyrus)</td>
<td>30</td>
<td>Language function</td>
<td>No differences</td>
<td>NS Older age predicted speech dysfunction</td>
</tr>
<tr>
<td>Lutz, 200421 (Selective AH)</td>
<td>80</td>
<td>Cognitive function</td>
<td>No differences</td>
<td>NS Fluency worse with Transsylvian</td>
</tr>
<tr>
<td><strong>Surgical vs Medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weibe, 200124 (Temporal lobectomy)</td>
<td>80</td>
<td>% sz free</td>
<td>58% surgery/8% medical</td>
<td>NNT=2 Surgery had better QOL, but 10% complication rate. One death in medical group</td>
</tr>
</tbody>
</table>

VNS – vagus nerve stimulation, sz – seizure, NS – not significant, NNT – number needed to treat, SW – spike wave, AH – selective amygdalohippocampectomy, QOL – quality of life

life was superior in the surgical group, 10% of patients had surgical adverse effects, and one patient died in the medical group. Finally, Engel et al25 recently initiated a study randomizing patients with early intractable temporal lobe epilepsy to surgical or medical therapy. Recruitment to this multicenter trial has been problematic and has resulted in discontinuation of the study.

WHERE DO WE GO NEXT?

Randomized controlled trials are unquestionably the gold standard to test new interventions, but such trials remain difficult to perform when evaluating epilepsy surgical techniques, and single centres are unable to undertake timely RCTs with adequate sample sizes. A glance at efforts in this area during the last decade identifies few successes and also some casualties.2 Most recently, the NIH-funded, multicentre ERSET study (Early Randomized Surgical Epilepsy Trial) was stopped because of unacceptably low enrollment rates.25 To avoid the treacherous road of the epilepsy surgery RCT, other researchers have opted for non-randomized, non-controlled prospective designs.26 We suggest that for high quality epilepsy surgery research to move forward the following aspects need to be addressed.

**Early identification of surgical candidates**

Surgical superiority has been demonstrated for chronically pharmaco-resistant patients suffering from temporal lobe epilepsy through an RCT,24 and the American Academy of Neurology’s has crystallized this into clinical practice guidelines.3 However, no surgical RCTs have been performed in extratemporal lobe epilepsy or early after diagnosis of localization related epilepsy. Experience with unsuccessful attempts at early surgery RCTs has taught us that knowledge about the course of illness of various surgically amenable epilepsies would go a long way towards defining eligibility criteria for enrolling patients in surgical
RCTs. Time to intractability, severity of epilepsy and identification of early predictors of pharmacoresistance play a defining role in planning and executing surgical epilepsy RCTs. Although reports of surgical cohorts often document a lag of more than 20 years between epilepsy diagnosis and surgical intervention,\textsuperscript{24,27} it has become clear that not all patients remain medically refractory during this entire period. In a multicentre adult surgical cohort, Berg et al\textsuperscript{28} reported a median latency of nine years from diagnosis of epilepsy to intractability (failure of >2 antiepileptic drugs). Conceivably, patients and clinicians would not consider epilepsy surgery as long as there is a reasonable response to medications. Questions about which patients become medically refractory, at what point in time and what impact epilepsy has on their physical and psychosocial function need to be explored to allow for adequate RCT planning and implementation. A better understanding of patients’ and clinicians’ attitudes and knowledge regarding epilepsy surgery is equally important. For example, even after a surgical RCT proved conclusively that surgery was superior to medical therapy, some clinicians expressed a staunch view that surgery was barbaric and unwarranted.\textsuperscript{15} Evidently, knowledge transfer and education are important in the referral process of patients to epilepsy surgery centres.

**Building the research infrastructure**

A network of epilepsy surgery centres that collaborate to collectively design and implement surgical RCTs is essential. Not only would this allow for the faster recruitment of sufficient numbers of patients, but it would also serve other important research functions. The concept is not novel and has yielded spectacular results in other areas. Consider the example of the Canadian Critical Care Trials Group (CCCTG).\textsuperscript{29} This non-profit organization not only fosters, but actively develops and implements investigator initiated trials. With a solid history of success, the CCCTG has a simple structure, consisting of a chair, and executive and administrative committees, with a broad mix of members, whose function is to provide scientific and administrative support to the membership, and aid in grant and manuscript preparation. Members contribute a modest fee which helps support the organization. Any CCCTG member can develop protocols throughout the year. Draft protocols are circulated to the membership prior to review in biannual meetings. Detailed discussions at meetings involve aspects of relevance, methodology, implementation, statistics and ethics, all of which lead to iterative protocol refinement. Each protocol is reviewed for membership in the CCCTG and if accepted, undergoes a thorough evaluation of which lead to iterative protocol refinement. Each protocol is circulated to the membership prior to review in biannual meetings. Detailed discussions at meetings involve aspects of relevance, methodology, implementation, statistics and ethics, all of which lead to iterative protocol refinement. Each protocol is voted for membership in the CCCTG and if accepted, undergoes further internal peer-review, prior to submitting for external peer-reviewed funding.\textsuperscript{29} Moreover, this research network can also assist in organizing research projects aimed at answering questions about risk factors, which typically require cohort-based studies.\textsuperscript{30} and it can assist in developing quality improvement tools for monitoring patient participation in RCTs.\textsuperscript{31} Groups such as the CCCTG typically develop and adhere to policies regarding study management methods, ethics and authorship.\textsuperscript{29} By fulfilling these functions, and working within existing Canadian epilepsy organizations, a “Canadian Epilepsy Surgery Study Group” (CESSG) could become a strong vehicle for epilepsy surgery research.

**Establishing research priorities**

The broad range of research questions involving epilepsy surgery requires different study designs. For interventions, RCTs are the ideal vehicle, whereas exploration of risk factors, determinants of prognosis, and analyses of diagnostic accuracy require adequately designed cohort studies. Accordingly, the exploration of different clinical questions entails a gradient of clinical importance and also gradations of feasibility and ease of implementation. Prioritizing research efforts ensures that high-yield, feasible studies move forward, and it also increases the likelihood of obtaining peer-reviewed funding. As epilepsy surgery research agendas evolve, more wide-ranging prioritizing strategies may become necessary. For example, consensus methods have been used successfully to establish national research priorities in critical care in the United Kingdom.\textsuperscript{32} One of the main functions of an epilepsy surgery study group would be to prioritize research initiatives brought forward by its membership, and to help refine initial ideas into mature protocols with higher impact and likelihood of implementation. An example of epilepsy surgery research areas, categorized in terms of their expected complexity and feasibility is given in Table 3.

**A Canadian Epilepsy Surgery Study Group makes sense**

The portability, relative homogeneity and universality of the Canadian health care system permit an easier organization of homogeneous research groups than is possible in for profit or mixed health care systems. Patients with epilepsy in Canada can receive a high level of epilepsy care in their own province or by referral to specialized centres in other provinces. The Canadian community of clinicians specializing in epilepsy and epilepsy surgery is relatively small and follows well known practice patterns. A 2004 Canadian survey of epilepsy resources revealed that 74 neurologists (provincial range 0 to 22, median 8) and 23 neurosurgeons (provincial range 0-6, median 4) focus their practice on epilepsy. Although numbers change rapidly, there are approximately 20 epilepsy centres in Canada involved in presurgical evaluation and epilepsy surgery (median 3 per province). Although the availability of sophisticated technology such as radiosurgery, stereotactic and functional surgery, magnetoencephalography (MEG), positron emission tomography (PET) scanning and fMRI varies from centre to centre, standard diagnostic and surgical tools are common to all centres, and relative homogeneity of epilepsy care exists across the country. Finally, one cannot overemphasize the importance of a strong tradition in epilepsy surgery research in Canada, which provides a firm foundation for ongoing and future research initiatives. Consider for example, that after the United States, Canada contributes the largest number of manuscripts to Epilepsia, the world’s flagship journal for epilepsy related publications (personal communication, editorial board). If significant interest exists in establishing a trials network through a Canadian Epilepsy Surgery Study Group exists in the epilepsy community, reasonable next steps would be to assemble a task force to work out a specific roadmap, to launch the study group in the context of specific research protocols, and to make certain that the study group works in concert with existing Canadian epilepsy research efforts.

In conclusion, our analysis confirms that RCTs in the field of epilepsy surgery are rare, yet critical in determining optimal care.
for patients with pharmacoresistant epilepsy. We also highlight the importance of approaching epilepsy surgery research collectively in Canada. This would allow addressing crucial unanswered questions, such as understanding the course of illness of various forms of epilepsy, predicting pharmacoresistance, identifying surgical candidates early on, and performing adequately sized surgical RCTs. Ability and opportunity exist to move forward. Establishing a trials network through a Canadian Epilepsy Surgery Study Group would enable future collaborative multicentre research efforts and allow the pursuit of high quality, sustainable research in epilepsy surgery.

**Table 3: Sample research topics amenable to multicentre studies in Canada, and expected level of implementation difficulty**

<table>
<thead>
<tr>
<th>Example of Research Topic</th>
<th>Expected level of study difficulty (low, medium, high)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous versus sample EEG reading in select persurgical cases</td>
<td>Low</td>
</tr>
<tr>
<td>Role of Ambulatory EEG in select presurgical cases</td>
<td>Low</td>
</tr>
<tr>
<td>Use of antiepileptic drugs post-surgery</td>
<td>Low</td>
</tr>
<tr>
<td>Role of various symptomatic treatments for patients undergoing intracranial monitoring</td>
<td>Low</td>
</tr>
<tr>
<td>Role of alternative therapies for symptom control or for seizure control for those not deemed to be surgical candidates</td>
<td>Medium</td>
</tr>
<tr>
<td>Prolonged outpatient versus continuous inpatient recordings in TLE patients</td>
<td>Medium</td>
</tr>
<tr>
<td>Comparison of surgical techniques for specific clinical entities</td>
<td>Medium</td>
</tr>
<tr>
<td>Role of various neuroimaging techniques</td>
<td>Medium</td>
</tr>
<tr>
<td>Role of brain stimulation for various epilepsies</td>
<td>Medium-High</td>
</tr>
<tr>
<td>Role of intracranial monitoring in uncertain cases</td>
<td>Medium-High</td>
</tr>
<tr>
<td>Role of structured psychosocial intervention in improving surgical outcomes</td>
<td>Medium-High</td>
</tr>
<tr>
<td>Role of new surgical techniques (gamma knife, stereotactic ablation, etc.)</td>
<td>Medium-High</td>
</tr>
<tr>
<td>Selective amygdalohippocampectomy vs anterior temporal lobectomy</td>
<td>High</td>
</tr>
<tr>
<td>Medical vs surgical therapy for extratemporal epilepsy</td>
<td>High</td>
</tr>
<tr>
<td>Role of surgery for specific structural abnormalities</td>
<td>High</td>
</tr>
</tbody>
</table>

* Level of difficulty is based on expected sample size requirements and logistic aspects.

**References**


