A Randomized Controlled Trial of Surgery for Medial Temporal Lobe Epilepsy

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Seizures in temporal lobe epilepsy comprise either focal aware or focal unaware seizures, with the latter often including psychic or gustatory phenomena with lost awareness, motor automatisms and (at times) generalized convulsions. At the time of this trial, surgery for such medial temporal lobe epilepsies had shown efficacy, yet it remained under-utilized due to uncertainty regarding its true efficacy and safety. This was in large part due to the lack of sufficient trial data assessing the long-term outcomes of surgery in medial temporal lobe epilepsy. As such, the goal of this trial was to conduct a randomized controlled trial comparing surgery vs. standard anti-epileptic drug (AED) therapy in patients with poorly-controlled medial temporal lobe epilepsy.

Experimental design and statistics: Potential candidates for surgery were those with poorly-controlled temporal lobe epilepsy, with prior brain MRIs and EEGs available. Inclusion criteria included age >16y/o, >1yr of seizures with a strong temporal lobe semiology, and an average seizure frequency of 1/month despite the use of $\geq$2 AEDs. Exclusion criteria included active psychosis, pseudoseizures, IQ score <70, extratemporal lesions causing seizures, or bilateral temporal lobe seizure foci. Eligible patients were then randomized to either surgical or medical treatment. Surgical patients underwent EMU monitoring within 48hrs of randomization for scalp and/or intracranial EEG monitoring to identify temporal lobe seizure origin/lateralization. Following appropriate WADA and neuropsychological testing thereafter, eligible surgical patients then underwent anterior temporal lobe resection within 4wks of randomization (**Fig.1**). Following resection, patients were treated with the same AEDs as before, with dosing adjustments as indicated. Patients assigned to medical treatment were placed on a 1yr waitlist for an EMU admission, and continued on their original AEDs. Both medical and surgical patients were then monitored via follow up assessments every 3 months (for 12 months total) by 3 different epileptologists, for appropriate AED dosing and combination adjustments; treating epileptologists were unaware of treatment group assignments. In between follow ups, all patients were instructed to record descriptions of any seizure-like events, which were later reviewed (blinded) by external epileptologists to determine if such events were consistent with a seizure. Using this and other data, scales assessing seizure severity and epilepsy-related quality of life were quantified for later analysis[1]. The primary outcome included freedom from seizures with impaired awareness at 1yr; seizures were counted from day 1 post-op in the surgical group, and from day 25 post-randomization in the medical group. Data were analyzed via an intention-to-treat protocol, with Kaplan-Meier event-free survival curves for the primary outcome, and analysis of covariance models for QOL scores.

Results: A total of 92 patients were screened of which 86 were eligible; 80 patients agreed to participate with 40 randomized to the medical and 40 to the surgical arm of the study. In the surgical group, 4 patients did not undergo surgery[2] and one patient in the medical group died unexpectedly. Otherwise, baseline patient characteristics between the two study groups were similar (**Table 1**) other than lower QOL scores in the medical group. In terms of the primary outcome (via intention to treat protocol), the proportion of patients free from unaware seizures was 8% in the medical group vs. 58% in the surgical group ($p < 0.001$, NNT of 2; **Fig. 2A**), with 38% of the surgical group vs. 3% of the medical group being free from ALL seizures ($p < 0.001$, NNT of 3; **Fig. 2B**). Of the 36 of patients who actually

[1] Liverpool Seizure Severity Scale (high scores = high severity), Quality of Life in Epilepsy Inventory-89 (QOLIE-89, high scores = better).

[2] One declined, two were not eligible per EEG/MRI data, and one did not have seizures during monitoring.

underwent surgery, the rate of 1yr, impaired-aware seizure freedom was still 64%, and only 15% of the surgical group continued to have 1-4 seizures/month (seizure severity equivalent to that of the medical group, **Fig. 3 & 4**). Finally, QOL scores were also significantly better in the surgical vs. medical group (**Fig. 5**). Otherwise, ASEs of surgery included a small thalamic infarct in one, a wound infection in one, a decline in verbal memory in two, and expected superior quadrantic VF deficits in 55%.

Conclusions: Overall, data from this study strongly supported temporal lobe resection for better seizure control and improved quality of life in patients with poorly-controlled, temporal lobe epilepsy: the rate of freedom from impaired-awareness seizures was 58%. In addition, data from the medical group continued to support the low probability of seizure freedom in temporal-lobe epilepsy, and suggested that long trials of multiple AEDs may be futile in temporal lobe epilepsy. Notably, the surgical morbidity in this study was very low and similar to that of smaller case series, and the single unexplained death in the medical group supported reduced mortality in surgically-treated patients. Finally, it is worth noting that outpatient investigations seemed to accurately predict a unilateral, temporal-lobe seizure origin before EMU investigations began, suggesting that outpatient evaluations are very likely to correctly predict decisions regarding surgical candidacy. More recent trials have suggested that early surgery, after failure of 2 AED trials, may be optimal.

Additional reading, if interested:

1) Engel, J.E. et. al., Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy. JAMA (2012). 307 (9): 922-930.

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