



Antiepileptic Medications after Extratemporal Epilepsy Surgery: When Do We Stop?

Feasibility of Antiepileptic Drug Withdrawal Following Extratemporal Resective Epilepsy Surgery.

Menon R, Rathore C, Sarma SP, Radhakrishnan K. *Neurology* 2012;79:770–776.

OBJECTIVE: To identify the rate of successful antiepileptic drug (AED) withdrawal after resective surgery and the predictors of postwithdrawal seizure recurrence in patients with extratemporal epilepsy. **METHODS:** We retrospectively analyzed the postoperative AED profile of 106 consecutive patients who had completed 2 or more years after resections involving frontal, parietal, and occipital lobes for AED-resistant epilepsy. To identify the potential predictors of seizure recurrence, we compared the attributes of recurred and nonrecurred groups by univariate and multivariate analyses. **RESULTS:** We attempted AED withdrawal in 94 (88.7%) patients. Forty-four (41.5%) patients had seizure recurrence while reducing AED, of which 14 (31.8%) did not become seizure-free subsequently. On multivariate analysis, an abnormal postoperative EEG and longer preoperative duration of epilepsy predicted seizure recurrence, while early postoperative seizures and presence of gliosis or dysplasia were additional predictors on univariate analysis. At mean follow-up duration of 4.6 years, 63 (59.4%) patients were seizure-free. The cumulative probability of achieving complete AED-free status was 20% at fourth year, 34% at sixth year, 40% at eighth year, and 52% at 10th year after surgery. **CONCLUSIONS:** Following resective extratemporal epilepsy surgery, AED can be successfully discontinued in only in a minority of patients. One-third of patients who recur fail to regain seizure control upon AED reintroduction. Longer duration of epilepsy prior to surgery, abnormal postoperative EEG, early postoperative seizures, and focal gliosis or dysplasia as substrate predispose to seizure recurrence. This information will be helpful in making rational decisions on AED withdrawal following extratemporal resective epilepsy surgery.

Commentary

Epilepsy surgery has been increasingly advocated because numerous studies report its superiority to continued antiepileptic drug (AED) trials in controlling seizures in patients with drug-resistant partial epilepsy (1). These studies often report surgical outcome without specifying the post-operative AED regimens, and little evidence exists to inform rational postoperative AED management. Discontinuation of AEDs, if possible, is desirable due to the cost, adverse events, and the continued stigma of the epilepsy label. Decisions regarding discontinuation or simplification of AED regimens in postsurgical patients are often influenced by patient preference (2) and uncertain clinical indicators that are largely inferred from retrospective studies. However, these studies may sometimes offer discordant conclusions; for example, some reports associate AED withdrawal with a higher risk of seizure relapse (3), while others find no such association (4, 5). Similarly, some studies suggest that early postoperative seizures predict eventual relapse of epilepsy (6), while others find no such predictive value (7). A recent survey found that the majority of epileptologists

discontinue AEDs no earlier than a year of postoperative seizure freedom (2), although previous studies found no association between the timing of AED discontinuation and seizure relapse (3, 5). Despite prospective trials of postoperative AED withdrawal after temporal lobectomy (4), there remains a large void in our knowledge of AED management after extratemporal lobe epilepsy (ETLE) surgery.

Menon et al. (8) recently published a retrospective analysis that aimed at identifying predictors of seizure recurrence upon AED withdrawal after ETLE surgery. They included 106 consecutive cases, 104 of which had abnormal brain MRIs. Consistent with practice at most epilepsy centers, the authors tailored the extent of resection based on MRI and intraoperative gross pathologic findings, as well as intracranial recordings and brain mapping when indicated. Postoperatively, they initiated AED withdrawal after 3 months of seizure freedom in patients who received AED polytherapy, one medication at a time, and after one year in those who received a single AED.

Of the 106 patients included, AED withdrawal was attempted in 94 (88.7%), and seizure recurrence occurred in 46.8% of these. Of the subjects who relapsed, 31.8% became intractable. Thus, almost half of postsurgical ETLE patients who underwent withdrawal experienced seizure recurrence, and almost one-third of these remained refractory after reinstitution of AEDs. These rates are higher than previously



reported rates after temporal lobectomy (4, 5, 9). Univariate analysis identified older age, epilepsy duration, abnormal postoperative EEG, early postoperative seizures, and dysplasias or gliosis as predictors of seizure recurrence. However, only abnormal EEG (odds ratio 3.12, 95% confidence interval 1.20–8.08) and pre-surgical duration of epilepsy (odds ratio 1.07, 95% confidence interval 1.01–1.14) were retained in multivariate analysis.

The Menon et al. (8) study, with its large sample size, provides important information on AED management after ETLE surgery that will greatly assist in the counseling of patients. For example, in patients with normal postoperative EEG, chances of seizure recurrence were 26% with a five-year history of seizures and 33% with a 10-year history of seizures. These figures nearly doubled in patients who had epileptiform discharges postoperatively. In addition, the study indirectly corroborates known evidence about the superiority of early epilepsy surgery in improving the outcome (1). As in other studies of surgical outcome in epilepsy, the findings also remind us of the necessity of revising the definition of the epileptogenic zone itself. This zone is defined as the brain region whose interruption or resection will result in seizure freedom (10), a definition that does not specify whether the postoperative validation is achieved with or without AEDs.

The retrospective nature of the Menon et al. (8) analysis is partially ameliorated by including consecutive subjects and by using a standardized AED discontinuation schedule in all subjects. However, a number of questions remain unanswered and await a prospective controlled study. A major question is whether certain AED withdrawal schedules truly increase the chances of seizure recurrence or lead to eventual refractoriness—and in what subset of patients (3, 4). Like many other observational studies, the study could not answer this question due to lack of a control group maintained on AEDs. Additionally, the authors did not resolve other issues of discordant findings in previous retrospective studies, such as the role of the duration of post-operative seizure freedom in seizure recurrence before or after AED withdrawal (2, 5).

A prospective study in ETLE will provide more reliable answers to some of these questions but will need to overcome unique difficulties. The conduction of prospective studies of postsurgical AED management in TLE were likely facilitated by the high prevalence of TLE and temporal lobectomy, as well as the relative homogeneity of the lobectomy procedure across most epilepsy centers. A prospective study in ETLE will need to consider the heterogeneity of ETLE related to the lobes of origin, etiologies, and surgical techniques. In addition, future studies will need to address in what subset of patients should AED tapering be attempted, when it should start, and on what schedule. They will also need to 1) document whether seizures recur during the AED taper or after complete AED discontinu-

ation, 2) clarify the frequency and duration of post-operative EEGs that might yield a meaningful predictive value, and 3) possibly characterize the efficacy of different AEDs, at what doses (or serum levels) in controlling certain epilepsies post-surgically. These questions will undoubtedly require many studies for definitive answers. Moreover, a more complete knowledge about AED management after surgery must parallel our evolving knowledge of the pathophysiology and genetics of epilepsy itself.

by Mohamad Koubeissi, MD

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