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Management of antiepileptic drugs following epilepsy surgery: A meta-analysis

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Summary
Objective: No consensus exists regarding the management of antiepileptic drugs (AEDs) after successful epilepsy surgery (ES). We performed a meta-analysis with the most relevant evidence in this topic. Our aim was to provide evidence-based estimates of results on AEDs discontinuation after ES.
Methods: We searched MEDLINE and Embase using Medical Subject Headings and keywords related to AEDs discontinuation after ES. Two reviewers independently applied the following inclusion criteria: original published research that directly compared seizure outcomes in patients having or not AEDs discontinuation after ES. Two investigators independently extracted data, resolving disagreements through discussion. A random and fixed-effect model was used to derive a pooled odds ratio (OR) for either seizure recurrence in both groups.
Results: Of 257 abstracts initially identified by the search, 57 were reviewed as full text. Sixteen articles fulfilled eligibility criteria and described outcomes in 1456 patients with AEDs discontinuation and 685 patients with no discontinuation. The odds of having seizure recurrence after AEDs discontinuation was 0.39 times lower in patients with attempted discontinuation after surgery (OR 0.39, CI 95% 0.300—0.507, $p < 0.001$). Most likely the difference is related with a selected population where discontinuation was attempted.
Significance: Seizure recurrence was higher for patients without AED modification than for the withdrawal group. Patients with seizure recurrence after discontinuation can be managed easily after re-start of medications. The discontinuation of medications should be done in good candidates and the decision should be individualized taking into account clinical, electrographical, imaging and histopathological variables.

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Introduction

The safety and efficacy of epilepsy surgery (ES) for temporal lobe epilepsy (TLE) has been well established in two randomized clinical trials (RCTs) (Engel et al., 2012; Wiebe et al., 2001), as well as their sustained beneficial effects in the long-term, such as prolonged seizure freedom (Téllez-Zenteno et al., 2005), lower mortality, improved psychosocial and memory outcomes (Téllez-Zenteno et al., 2007), and improved quality of life (Mohammed et al., 2012). Potential reduction and eventual withdrawal of antiepileptic drugs (AEDs) is one of the most difficult therapeutic challenges after successful ES. There are legitimate reasons to stop AEDs after ES, including avoiding undesirable long-term toxicity, to reduce cognitive adverse effects of AEDs, to reduce costs and to remove daily treatment that serves as a major affirmation of the sick role in patients (Cole and Wiebe, 2008). Compared with other surgical outcomes such as the seizure outcome, few studies have been published regarding the management of AEDs after ES and current recommendations are based largely on local experience at different centers. The selection of candidates for AEDs withdrawal is complex and we do not have uniform criteria across epileptologists and epilepsy centers.

According to three medical surveys (Berg et al., 2007; Swisher and Sinha, 2013; Téllez-Zenteno et al., 2012) of clinical practice regarding AEDs withdrawal, the majority of US and Canadian epileptologists and neurologists prefer to wait between six months to two years before any change in medication. AEDs levels, electroencephalogram (EEG), and a magnetic resonance imaging (MRI), are typically done before stopping AEDs (Berg et al., 2007; Swisher and Sinha, 2013; Téllez-Zenteno et al., 2012). The most important factors considered by epileptologists in North America were the following: focal pathology, complete postoperative seizure freedom, complete resection of a well-defined epileptic lesion, lack of postoperative epileptiform discharges on EEG, a patient's desire to stop medications and a temporal localization for the surgery (Berg et al., 2007; Téllez-Zenteno et al., 2012). Although successful AEDs withdrawal has been associated with improvements in scales of general satisfaction and quality of life, some studies have shown controversial information.

We performed a systematic review and meta-analysis of the evidence comparing seizure recurrence in patients with and without AEDs discontinuation after successful ES. Our aim was to provide clinicians with a scientifically valid and coherent summary of the best current evidence, and to provide a best estimate of seizure recurrence rates in patients with and without AEDs discontinuation after ES.

Methods

Data source

A medical librarian performed a comprehensive literature search of the Medline®, Embase®, Index Medicus®, and Cochrane databases from January 1980 to July 2013 that incorporated Medical Subject Headings and text words for literature on the management of AEDs after ES (Literature search strategy in Appendix A). We also searched bibliographies of reviews, original articles and book chapters, and consulted experts about other studies. We included studies if they contained original research involving patients, irrespective of age and regardless of language or country of origin.

Study selection and classification

Two reviewers independently applied the following study inclusion criteria: (a) Original published research with $\geq$30 patients of any age undergoing resective ES; (b) reports that directly compared seizure outcome in patients having or not AEDs discontinuation after successful ES; (c) description of number of patients having each intervention; (d) quantitative description of seizure outcomes in patients with and without AED discontinuation, thus allowing for direct comparisons, and (e) seizure outcomes reported after at least one year of follow-up since surgery. We considered all outcomes in children and adults. Children were considered less than 16 years old. We excluded studies with not consistent data or any overlapping patient populations from the same center. We selected the most recent publication for inclusion if studies were duplicate reports from the same population. For this study we used the term ''controlled studies'' to describe studies where a comparison was done among patients where discontinuation was attempted after ES vs. not attempted. The outcomes explored included: postoperative seizure outcome using the Engel's classification; time to start the discontinuation of AEDs; time to achieve discontinuation; seizure recurrence in both groups, and seizure freedom rate after the re-start of medications.

Data gathering and extraction

We reviewed full texts in duplicate and selected those that met our inclusion criteria for meta-analysis. Data extracted from eligible studies included year of publication, country in which the study was conducted, study type (e.g., controlled/non-controlled), study design (e.g., case and control, cohort, etc.), number of participants and timing and method of discontinuation. Demographic data included sex distribution, mean age at seizure onset, mean age at ES, epilepsy etiology, time interval from surgery to start of AED discontinuation (ten months was selected as a cutoff for ''early'' vs. ''late'' drug tapering), time to achieve discontinuation and duration of total follow-up. Surgical data included Engel's classification of seizure outcome, surgical resection type, and area of resection. Two reviewers independently abstracted all data, resolving disagreements through discussion and included a senior author where necessary. An attempt was made to assess risk factors for seizure recurrence in some studies (Al-Kaylani et al., 2007; Berg et al., 2006; Boshuisen et al., 2012; Hoppe et al., 2006; Kuzniecky et al., 1992; Lachhwani et al., 2008; Lee et al., 2008; Menon et al., 2012; Murro et al., 1991; Park et al., 2010; Rathore et al., 2011; Schiller et al., 2000).