

Factors influencing medication adherence after epilepsy surgery

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ABSTRACT – Aim. In drug-responsive epilepsy patients, treatment non-compliance is a major factor in seizure recurrence, but adherence to prescribed regimens following epilepsy surgery has not been examined. We measured adherence to prescribed antiepileptic drugs (AEDs) after epilepsy surgery and investigated factors influencing treatment non-compliance.

Methods. Postsurgical epilepsy patients ($n=214$) were monitored for 18.1 ± 8.1 months. Adherence was measured using the Medication Possession Ratio (MPR) self-report questionnaire, with $MPR < 0.8$ defined as non-adherence.

Results. According to the MPR, 58 patients (27.1%) were non-adherent after surgery. There were no differences in demographic and clinical variables, such as age ($p=0.057$, $t=-1.925$), duration of illness ($p=0.597$, $t=0.530$), gender ratio ($p=0.714$, $\chi^2=0.134$), and place of residence (urban vs. rural; $p=0.874$, $\chi^2=0.025$), between adherent and non-adherent patients. Moreover, adherence was not related to surgical outcome as evaluated by the Engel classification ($p=0.635$, $\chi^2=1.628$) or to the types of AEDs after surgery ($p=0.165$, $\chi^2=6.530$). The most common reasons for non-adherence were seizure-free status for an extended period (26.5%), forgetfulness (19.1%), and an inability to buy the drugs locally (18.6%).

Conclusion. Adherence to AEDs is improved after epilepsy surgery compared to presurgical estimates, but is still a common and serious problem. Targeted postsurgical management programs and communication strategies are necessary to improve adherence to AEDs after epilepsy surgery.

Key words: epilepsy surgery, adherence, antiepileptic drugs, treatment outcome, follow-up studies

Epilepsy is a common and widespread neurological disorder afflicting people of all ages and socioeconomic classes (De Boer, 2002). The vast majority of patients are treated with antiepileptic drugs (AEDs), and approximately 70% can become seizure-free with AEDs alone (Eatock and Baker, 2007). Approximately one third of patients,

however, continue to experience seizures despite multiple AEDs prescribed at appropriate doses (Hui *et al.*, 2007). For these drug-refractory epilepsy patients, surgery has been demonstrated to be a safe and effective treatment, and surgically treated patients achieve significantly higher rates of seizure-free status compared to

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drug-refractory patients who have not been treated surgically (Yasuda *et al.*, 2006). Indeed, long-term seizure-free rates after epilepsy surgery range from 55% to 80% depending on definitions used and follow-up duration (Elsharkawy *et al.*, 2011; Hauptman *et al.*, 2012).

Postoperative seizure freedom is associated not only with completeness of surgical resection but also with the postoperative medication regimen (Moeller *et al.*, 2009). Medication is crucial after surgery, particularly the combination and doses of AEDs (Moeller *et al.*, 2009).

Adherence to AED therapy is critical for effective epilepsy management (Faught, 2012), and non-adherence may be the most important cause of poorly controlled epilepsy (Manjunath *et al.*, 2009). Non-adherence to AEDs is high in epilepsy patients (Hovinga *et al.*, 2008) and studies have demonstrated a higher prevalence of seizures (21-45%) in those who did not adhere to their AED regimens (Davis *et al.*, 2008).

While many studies have investigated the most effective AED regimens after epilepsy surgery, no study has addressed AED adherence in this group. In this report, we used the Medication Possession Ratio to assess the extent of medication adherence and investigated the causes of non-compliance.

Materials and methods

Subjects

This was a retrospective cohort study of subjects from the Military General Hospital of Beijing People's Liberation Army. Inclusion criteria were:

- clearly diagnosed refractory epilepsy, defined as persistence of seizures after adequately applied treatment with two or more appropriate AEDs (Kwan *et al.*, 2009);
- epilepsy surgery after a standard preoperative evaluation from October 2010 to June 2013;
- follow-up for more than three months.

Exclusion criteria were:

- incomplete demographic and clinical information;
- loss during follow-up;
- or seizures associated with a malignant tumour.

Postoperative follow-up and outcome classification

Demographic and clinical characteristics were collected before surgery which included gender, age at seizure onset, age at surgery, duration of epilepsy, and monthly seizure frequency prior to surgery. All patients were monitored postoperatively by clinic visits or telephone interview every three months. If the

seizures were not well controlled, the dosage of AEDs was adjusted or new AEDs were added slowly. If the seizures were well controlled and not associated with any epileptiform discharges based on postoperative electroencephalogram (EEG), AED tapering was administered more than 24 months after surgery. During follow-up, the drug regimen was noted and all patients were asked the same questions about the adherence to the AED regimen.

Adherence was measured using the widely accepted and well documented Medication Possession Ratio (MPR) (Andrade *et al.*, 2006). The MPR is measured as an average over a patient's entire observation period by dividing the total daily supply of medication by the number of days in the observation period (Manjunath *et al.*, 2009). The MPR was measured by self-report. The regimen we prescribed was one tablet twice a day, with a total of 60 tablets a month. If patients reported that they took 30 one month, we recorded an MPR of 0.5. Patients with an MPR of at least 0.8 were classified as adherent and those with an MPR of less than 0.8 as non-adherent. The MPR threshold of 0.8 to define adherence has been widely used in many therapeutic areas, including neurological conditions (Grosset *et al.*, 2005a; Grosset *et al.*, 2005b).

Surgical outcome was rated according to Engel's classification:

- Class I (no seizures, auras only, or seizures only upon drug withdrawal);
- Class II (three or fewer seizures per year);
- Class III (worthwhile improvement, but more than three seizures per year);
- Class IV (no worthwhile improvement after surgery).

Analyses

All statistical analyses were conducted using SAS Version 16.0. Continuous variables are expressed as mean \pm SD and categorical variables by proportions. Chi-squared and Student's *t* tests were used to compare group proportions and means, respectively. Significance was defined as an $\alpha < 0.05$.

Results

Patient characteristics

A total of 234 patients treated surgically for intractable epilepsy met the inclusion criteria for this study, of whom 20 patients (8.5%) were excluded from analysis because of insufficient follow-up information. Finally, we retrospectively studied 214 patients, 146 males and 68 females. The mean age at the time of surgery was 24.1 ± 9.5 years (range: 5-54 years). The mean duration of epilepsy before

surgery was 11.7 ± 8.5 years (range: 1-43 years). The average duration of follow-up after surgery was 18.1 ± 8.1 months (range: 3-34 months). The majority of patients (74.8%) were rural dwellers. There were no permanent complications in the surgical cohort.

Of the 214 patients included, 98 (45.8%) were treated by standard temporal lobectomy only. Other resection sites were the frontal lobe (38 patients; 17.8%), temporal lobe (14; 6.5%), occipital lobe (28; 13.1%), parietal lobe (10; 4.7%), multiple lobes (16; 7.5%), and other regions (10; 4.7%) such as the insula and corpus callosum.

The average number of different AEDs prescribed after surgery was 1.7 ± 0.6 and at the end of follow-up was 1.6 ± 0.8 . The average number of tablets taken daily after surgery was 6.6 ± 2.7 and at the end of follow-up was 6.2 ± 3.5 . The majority of patients (186; 86.9%) took their AEDs twice daily, while 22 (10.3%) took them three times a day, and six (2.8%) once a day. Seizures recurred in 12 (5.6%) of all patients.

According to Engel's classification, the surgical outcomes were as follows: 102 (47.7%) in class I, 40 (18.7%) in class II, 42 (19.6%) in class III, and 30 (14.0%) in class IV.

Rates of non-adherence to AEDs

In our study, 58 patients (27.1%) reported non-adherence ($MPR < 0.8$) and 156 (72.9%) reported adherence, with 138 (64.5%) reporting that they never missed a dose.

There was no significant difference in age ($p = 0.057$, $t = -1.925$) or duration of illness ($p = 0.597$, $t = 0.530$) between adherent and non-adherent groups. The proportion of adherent patients did not differ between males and females ($p = 0.714$, $\chi^2 = 0.134$), urban and rural dwellers ($p = 0.874$, $\chi^2 = 0.025$), or among subgroups defined by Engel classification ($p = 0.635$, $\chi^2 = 1.628$) or AED type ($p = 0.165$, $\chi^2 = 6.530$). There was significant difference according to the number of tablets taken daily ($p = 0.028$, $t = -2.230$). There was no significant correlation between adherence and seizure recurrence ($p = 0.404$, $\chi^2 = 0.696$). The dosing frequency was twice per day for nearly all patients, therefore we did not assess the relationship between adherence and dosing frequency.

Factors associated with non-adherence

The most common reasons for non-adherence were seizure-free status (26.5%), forgetfulness (19.1%), inability to buy drugs locally (18.6%), fear of adverse drug effects (14.7%), disappointment with AED efficacy when seizures recurred after surgery (8.8%), not understanding the regimen change advised by a physician (8.8%), and other reasons (5.9%) such as pregnancy and the high cost of AEDs.

Discussion

Adherence to AED therapy is critical for effective epilepsy management both before and after surgery. Non-adherence prior to surgery is common in both developing and developed countries. Approximately 29-58% of patients in the United States do not adhere to their prescribed AED regimens (Davis *et al.*, 2008; Hovinga *et al.*, 2008). Other estimates of non-adherence are 59% in the United Kingdom (Jones *et al.*, 2006), 64% in Arab countries (Sweileh *et al.*, 2011) and 48.1% in China (Liu *et al.*, 2013).

This is the first study to specifically measure adherence to AEDs after epilepsy surgery. In presurgical or drug-responsive patients, no demographic differences, such as gender ratio or age, were found between adherent and non-adherent groups (Hovinga *et al.*, 2008) and treatment effectiveness was not the primary factor affecting adherence (Liu *et al.*, 2013). These same results were observed in postsurgical patients. In China, people living in rural or urban areas may differ substantially in the level of education and economic status, but the area of residence did not affect adherence, thus we assume that neither educational background nor economic status affected adherence. In general, the duration of treatment does affect medication adherence, with acute illnesses associated with higher compliance compared to chronic illnesses (Gascon *et al.*, 2004; Dhanireddy *et al.*, 2005). In fact, disease duration was the only factor affecting adherence in our previous study of presurgical patients (Liu *et al.*, 2013). After surgery, however, the duration of treatment was not related to adherence. Several studies have found no significant relationship between the number of different AEDs used before surgery and medication adherence (Patel and Taylor, 2002; Grant *et al.*, 2003), and we found this same result after surgery.

In this study, 72.9% of patients were adherent to AEDs and 64.5% reported never missing a dose, compliance rates markedly higher than reported previously in Chinese epilepsy patients (Liu *et al.*, 2013). In previous studies of non-surgical patients, a poor patient-prescriber relationship was a strong factor affecting patient compliance (Moore *et al.*, 2004; Gonzalez *et al.*, 2005). Surgery may offer a means of empowerment, which facilitates treatment adherence.

Nearly all studies on presurgical patients have found that forgetfulness is the most common reason for non-adherence (reported by 52.4-87.5% of patients) (Dowse and Futter, 1991; Hovinga *et al.*, 2008; Liu *et al.*, 2013). In our study, forgetfulness was the second most common reason given. This result was surprising as there was no specific intervention to reduce forgetfulness. In developing countries like China, the disease places a heavy economic burden (Liu *et al.*, 2012), and the deci-

sion to undergo expensive surgery is very difficult and may be the patient's last hope for effective seizure control. Knowing that non-compliance will likely reduce treatment success, patients may make every effort to take their medicine on time.

Although adherence improved after surgery, several new reasons arose that should be the focus of postsurgical follow-up programs, such as a presumption that medication is no longer necessary (due to temporary seizure-free status), fear of adverse drug effects, disappointment with AEDs if seizures recur, and misunderstanding the new drug regimen. All these reasons may stem from a basic lack of appreciation of the importance of strict postoperative medication adherence. Thus, physicians should provide closer postoperative monitoring (in the clinic or by telephone) and clearly emphasize the importance of adherence.

The inability to purchase the prescribed drugs was the primary reason cited by 18.6% of patients, compared to only 1.9% before surgery (Liu *et al.*, 2013). We speculate that this may be partly due to the prescription of newer AEDs, such as oxcarbazepine and levetiracetam, which are more difficult to buy in smaller cities. To circumvent this problem, treating physicians should consider prescribing AEDs that are more readily available or remind patients to purchase sufficient quantities at discharge or when the opportunity arises.

Some studies concluded that early AED withdrawal does not affect long-term seizure outcome or cure (Jin *et al.*, 2008; Boshuisen *et al.*, 2012). In Canada, 50% of physicians advocated a minimum seizure-free period of more than one year after epilepsy surgery before withdrawing AEDs (Tellez-Zenteno JF *et al.*, 2012). The majority of epileptologists initiated an AED taper at six months after surgery in the US (Swisher and Sinha, 2012). There are differing views on whether to continue AEDs after surgery and for how long (Cole and Wiebe, 2008). We found no significant relationship between adherence and surgical outcome according to the Engel classification, a result suggesting that earlier drug withdrawal does not significantly affect outcome. Our study has a few limitations. First, the number of patients studied was relatively small. Second, the MPR threshold (0.8) may affect outcome, and the relationship between compliance at this specific level and recurrence risk is unclear. Third, there is a risk of response bias because this study was based on self-report.

Conclusion

Adherence to AEDs is improved after epilepsy surgery compared to presurgical estimates, but is still a common and serious problem. Targeted postsurgical

management programs and communication strategies are necessary to improve adherence to AEDs after epilepsy surgery. □

Disclosures.

None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF



- (1) Adherence to AED therapy is critical for effective epilepsy management, however, non-adherence is high in epilepsy patients. Can patients adhere to their AED regimen after epilepsy surgery?
- (2) Poor adherence to AEDs may be the most important cause of poorly controlled epilepsy. Is there any correlation between the outcome of surgery and drug adherence?
- (3) Why do patients with epilepsy not follow the doctor's advice to take AEDs after surgery?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".