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Early versus late antiepileptic drug withdrawal following temporal lobectomy

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ABSTRACT

Purpose: To compare the seizure outcome following early and late complete antiepileptic drug (AED) withdrawal following anterior temporal lobectomy (ATL) for mesial temporal lobe epilepsy (MTLE).
Method: All the patients who were seizure free for one year following ATL were offered early or late AED withdrawal. AEDs were discontinued starting at one year in those who opted for early withdrawal. Patients who opted for late withdrawal were continued on single AED for three years following surgery before attempting complete discontinuation.
Results: Of the 135 study patients, 65 opted for early AED withdrawal and 70 for late withdrawal. The mean postoperative follow-up duration was 10.4 ± 1.3 (Range, 8–12) years. At three years following surgery, seizure recurrence occurred in 23 (35.4 %) patients in the early withdrawal group and in 10 (14.3 %) patients in late withdrawal group (p = 0.005; relative risk [RR], 2.48; 95 % confidence interval [CI], 1.28–4.80). At last follow-up, 27 (41.5 %) patients in the early withdrawal group and 26 (37.1 %) in late withdrawal group had recurrence (p = 0.60; RR, 1.12, 95 % CI, 0.74–1.70). At last followup, 80 (59.3 %) patients were off AEDs. During the terminal one year, 123 (91 %) patients were seizure free, similar in the two groups.
Conclusions: This nonrandomized controlled study suggests that early complete AED withdrawal starting one year following ATL is associated with a higher risk of early seizure recurrence. However, long term seizure outcome is similar in early and late AED withdrawal groups.

1. Introduction

Freedom from antiepileptic drugs (AEDs) is an important goal of epilepsy surgery and patients usually consider themselves cured only when the AEDs are completely withdrawn [1,2]. Although this issue of AED withdrawal following epilepsy surgery is very important to patients, there is relative dearth of data about the AED usage following epilepsy surgery. The practice of AED withdrawal varies across the centers and clinicians remain sharply divided in their practice of AED management following epilepsy surgery [3–5]. While many centers attempt early AED withdrawal, other centers continue AEDs indefinitely. Whether and when to withdraw AEDs following successful epilepsy surgery remain important questions with little data available to guide the clinical practice and formulate uniform guidelines.

Recent studies have shown that AEDs can be successfully withdrawn in 30–50 % patients following anterior temporal lobectomy (ATL) [6–14]. Still, the exact timing of initiating AED withdrawal and the long-term outcome of the patients who undergo AED withdrawal is not certain. It is not certain whether early AED withdrawal following surgery increases the chances of seizure recurrence compared to patients who either undergo late AED withdrawal or who are maintained on AED therapy indefinitely.

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In two previous studies from our centre involving patients operated from 1995 to 2005, we reported that AEDs could be successfully withdrawn in 53 % patients who have undergone ATL for mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) [9,14]. Over the years with increasing experience, there have been some changes in the AED withdrawal practices at our centre. Until 2005, our practice was to attempt complete AED withdrawal in all patients who have remained seizure free for three months following ATL. From 2006 onwards, selected patients with MTLE who have remained seizure free for one year were offered complete AED withdrawal after explaining pros and cons. AEDs were tapered and completely stopped in those who opted for withdrawal while those who opted to continue the AEDs were maintained on one AED till three years of follow-up. The aim of the present study is to compare the seizure outcome of these patients who have undergone early and complete AED withdrawal with those patients who had late AED withdrawal.

2. Methods

This study was carried out at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India. We have previously published our methods of patient selection for ATL and our protocol of postoperative AED management [9,14,15]. For this study, we included patients who had undergone ATL from February 2006 to December 2009 and had completed minimum eight years of postoperative follow-up. Patients with unilateral hippocampal sclerosis on MRI and/or histopathology and those with well circumscribed lesions confined to mesial temporal structures (not extending lateral to the collateral sulcus) were offered complete AED withdrawal if they remained seizure free for one year.. All patients with lesions other than hippocampal sclerosis were offered AED discontinuation only if they had complete resection confirmed by postoperative MRI. Patients with normal MRI, bilateral hippocampal sclerosis, dual pathology, lesions involving lateral temporal lobe, and those who have undergone predominant neocortical temporal resection were maintained on one AED for three years following surgery and hence were not included for this study. Similarly, the patients who had seizure recurrence during the first year following surgery and patients who required continued AED use for psychosis were also excluded from this analysis. In children less than 12 years, AED were completely discontinued if they remained seizure free for one year and hence these children were not included in this analysis.

Our presurgical evaluation protocol consists of detailed clinical history, long-term Video-EEG monitoring for interictal and ictal EEG data, 1.5 T high resolution magnetic resonance imaging (MRI), and neuropsychological evaluation, as described previously [16–18]. For VEEG monitoring, we used 10–20 system of electrode placement with additional anterior temporal (T1 and T2) electrodes. Sphenoidal electrodes were used in those patients with bilateral temporal interictal epileptiform discharges (IEDs) and nonlateralized ictal EEG. Ninety percent or more of IEDs lateralized to one temporal lobe were considered as unilateral IEDs. All the cases were discussed in the multidisciplinary patient management conference and decisions for ATL were taken if there was a concordance between clinical and Video-EEG recorded semiology, interictal and ictal EEG data, and MRI abnormality. Majority of the patients were selected on the basis of concordant noninvasive data. Few patients with discordant or nonlocalizing noninvasive data were selected for ATL after bilateral hippocampal depth electrode monitoring. All the patients were subjected to standard ATL during which neocortical resection was followed by microsurgical resection of the amygdala and complete resection of the hippocampus and the parahippocampal gyrus. Patients undergoing nondominant temporal lobe resection had excision of 4 cm of the superior and middle temporal gyrus and 5–6 cm of the inferior temporal gyrus or up to the vein of Labbe. In patients undergoing dominant lobectomy, superior temporal gyrus was kept intact and the middle and inferior gyri were excised 4–5 cm or up to the vein of Labbe.

2.1. Postoperative follow-up and AED management

All the patients were evaluated at three months and one year following surgery and subsequently at yearly intervals till AEDs were completely withdrawn. Subsequently those patients who had difficulty in yearly visits were followed up through postal or telephonic interview. Last followup was obtained through a telephonic interview. Antiepileptic drug tapering was started at three months in all seizure free patients if they were taking more than one drug. At one year of follow-up, all the eligible patients fulfilling the criteria described above were given the option of complete AED withdrawal. In those patients who opted for complete AED withdrawal, all drugs were tapered and stopped sequentially (early withdrawal group). Those patients who opted for continued AED therapy were maintained on the existing dose of one primary drug till three years of follow-up (late withdrawal group). In this group also, all other drugs except one primary drug, were gradually tapered and stopped. At three years, all the patients in the late withdrawal group were also advised AED withdrawal. Antiepileptic drugs were withdrawn every monthly at a standard rate in all the patients. The usual rate of withdrawal for each drug was as follows: phenytoin, 50 mg; carbamazepine, 100 mg; phenobarbitone, 15 mg; oxcarbazepine, 150 mg; lamotrigine, 25 mg; zonisamide, 50 mg; clobazam, 2.5 mg; clonazepam, 0.25 mg; topiramate, 25 mg; and levetiracetam, 250 mg. Dates of starting withdrawal and complete discontinuation were noted for each drug. Patients were instructed to contact in case of seizure recurrence and the dates of seizure recurrence were noted. Following seizure recurrence, patients were advised to continue the last effective dose of AEDs and patients were managed on individual basis. EEG was done at each followup up to three years and all the EEG were reviewed and recorded for this study.

2.2. Outcome and statistical analysis

We classified the seizure outcome as seizure free (free of all seizure and auras corresponding to Engel class IA outcome) and non-seizure free groups. We compared the number of patients who had a recurrence in the early withdrawal group as compared to late withdrawal group at three years of follow-up and at last follow-up. We also compared the seizure outcome during the terminal one year of follow-up among the two groups. We compared the various clinical and electrophysiological characteristics between patients who had seizure recurrence to those who did not have seizure recurrence during the entire period of follow-up. Fisher's exact test was used for comparing categorical variables and student's *t*-test was used for comparing continuous variables. All analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. and a p value of less than 0.05 was considered significant.

3. Results

During the study period, 261 patients underwent anterior temporal lobe resection. Of these, 135 patients fulfilled the inclusion criteria. The rest 126 patients were not included in the analysis because of following reasons: 29 patients were less than 12 years of age, 38 patients had lesions involving temporal neocortex, 20 patients had either bilateral hippocampal changes or predominant neocortical pathology, 10 patients had dual pathology, three patients underwent selective amygdalohippocamectomy, 15 patients had seizure recurrence by one year of follow-up, and 11 patients did not have adequate three years of followup.

Thus the study population consisted of 135 patients older than 12 years of age who underwent ATL from February 2006 to December 2009 and were seizure free for one year following surgery and who either had hippocampal sclerosis or other lesions medial to the collateral sulcus. Of these, 117 had hippocampal sclerosis on MRI and histopathology while rest of the 18 patients had circumscribed lesions

Table 1
Baseline characteristics of two groups.

Characteristic	Early withdrawal (n = 65)	Late withdrawal (n = 70)	P value
Age at surgery, years (mean ± SD)	27.7 ± 9.4	27.2 ± 9.4	0.454
Sex ratio (Male:Female)	36:29	43:27	0.490
Age at onset, years (mean ± SD)	11.5 ± 7.6	11.2 ± 7.7	0.576
Duration of epilepsy, years (mean ± SD)	16.2 ± 8.1	16.1 ± 8.9	0.810
Febrile seizures, n(%)	36 (55.4)	42 (60)	0.485
Hippocampal sclerosis, n(%)	56 (86.2)	61 (87.1)	1.000
Side of surgery (Left:Right)	35:30	42:28	0.491
Bitemporal and extratemporal IEDs, n(%)	18 (27.7)	17 (24.3)	0.697
Secondary generalized seizures, n(%)	34 (52.3)	35 (50)	0.864
Seizure clustering, n(%)	22 (33.8)	22 (31.4)	0.855

IEDs - Interictal epileptiform discharges.

(four cavernoma; 14 low grade neoplasm) confined to the mesial temporal lobe. For the whole group, 49 patients (36.3 %) had no initial precipitating injury, 76 patients (56.3 %) had febrile seizures while 10 patients (7.4 %) had other forms of initial precipitating injury including febrile status epilepticus and meningo-encephalitis. Among the hippocampal sclerosis group, 74 patients (63.2 %) had febrile seizures as initial precipitating injury.

Of the 135 patients, 65 patients opted for AED withdrawal (early withdrawal group) while 70 patients opted for AED continuation (late withdrawal group). The baseline characteristics of these patients have been compared in Table 1. There were no differences in the baseline characteristics among the two groups. The mean postoperative follow-up duration was 10.4 ± 1.3 years (range, 8–12 years). The mean postoperative follow-up duration was 10.4 ± 1.2 years in the early withdrawal group and 10.4 ± 1.3 years in the late withdrawal group (p = 0.60). The median time for complete AED discontinuation was two years (range, 1.75–2.35) in the early withdrawal group and 4.8 years (range, 3.85–5.5) in the late withdrawal group (p = 0.0001).

At the time of surgery, 12 patients were on single AED, 113 patients were on duotherapy and 10 patients were taking more than two AEDs. In all patients who were taking two or more drugs, AED withdrawal was started at three months. Hence all, except 12 patients who were on single drug, were already initiated on AED withdrawal by one year of follow-up. At three years of follow-up, seizure recurrence occurred in 23 (35.4 %) patients in the early withdrawal group and in 10 (14.3 %) patients in the late withdrawal group (p = 0.005; Relative risk, 2.48; 95 % confidence interval, 1.28–4.80; Fig. 1). At last follow-up, a total of 53 (39.3 %) patients had seizure recurrence, 27 (41.5 %) patients in the early withdrawal group and 26 (37.1 %) in late withdrawal group (p = 0.60; Relative risk, 1.12, 95 % confidence interval, 0.74–1.70). At last follow-up, AED were completely stopped in 80 (58.5 %) patients, 38 (58.4 %) patients in the early withdrawal group and 42 (60 %) patients in the late withdrawal group (p = 0.36). Of the rest, 46 (34 %) patients were on single AED, and 9 (7 %) were on two AEDs.

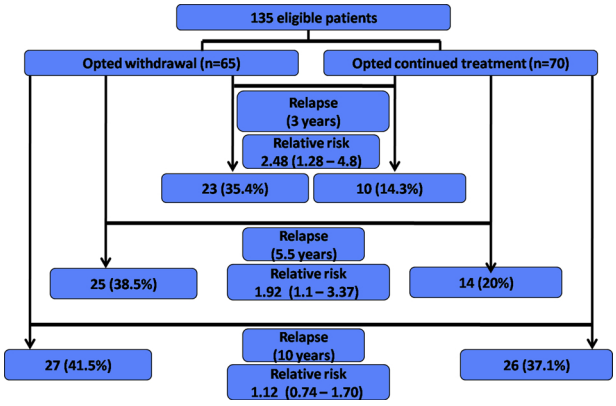

Fig. 1. The chart showing the seizure relapse rates between the two groups at three years, 5.5 years and at last followup.

In the early withdrawal group, 16 patients had recurrence after completely stopping AEDs while 11 patients had recurrence on reducing the last AED. In the late withdrawal group, nine patients had recurrence while being maintained on single AED, seven patients had recurrence while reducing the last AED and ten patients had recurrence after completely stopping AEDs.

During the terminal one year, 123 (91 %) patients were seizure free, similar in the two groups. Of the 53 patients with seizure recurrence, 41 (77 %) again became seizure free after adjusting AED doses while 12 patients, five in the early withdrawal group and seven in the late withdrawal group, had seizures during the terminal one year of follow-up. All these 12 patients had seizure recurrence while withdrawing the last drug. None of the patients who had seizure recurrence after complete AED discontinuation had persistent seizures.

3.1. Predictors of seizure recurrence

We compared the characteristics of patients who had seizure recurrence to those who did not have seizure recurrence at last follow-up (Table 2). As patients with hippocampal sclerosis formed the largest group, we restricted this analysis to hippocampal sclerosis group to maintain uniformity. Absence of febrile seizures and late onset of habitual seizures were associated with a significantly higher risk of seizure recurrence on AED withdrawal in this highly selected group of patients. None of the other variables were significantly different between two groups.

Table 2
Comparison of patients with hippocampal sclerosis with and without seizure recurrence on AED withdrawal.

Characteristic	No recurrence (n = 71)	Recurrence (n = 46)	P value
Age at surgery, years (mean ± SD)	26.7 ± 9.0	29.3 ± 8.9	0.183
Age at onset, years (mean ± SD)	9.8 ± 6.6	14.1 ± 8.6	0.045
Duration of epilepsy, years (mean ± SD)	16.9 ± 8.8	16.3 ± 7.7	0.821
Age at IPI, years (mean ± SD)	1.4 ± 1.3	1.8 ± 1.5	0.226
Febrile seizures, n(%)	54 (76.1)	20 (43.5)	0.001
Seizure clustering, n(%)	22 (31.0)	14 (30.4)	1.000
Generalized seizures, n(%)	32 (45.1)	24 (52.2)	0.570
Bilateral temporal IEDs, n(%)	15 (21.1)	14 (30.4)	0.279
Rhythmic, well defined, unilateral temporal ictal pattern, n(%)	55 (77.5)	34 (73.9)	0.664
IEDs on postoperative EEG			
3 months	17 (23.9)	9 (19.6)	0.653
One year	14 (19.7)	7 (15.2)	0.626
Two year	10 (14.1)	6 (13.1)	1.000

AED - Antiepileptic drugs; IED - Interictal discharges; IPI - Initial precipitating injury.

4. Discussion

Our results show that, in this highly selected group of patients with MTLE with hippocampal sclerosis or other mesial temporal lesions, AEDs can be withdrawn in 58 % patients by 10 years following ATL. Moreover, an early and complete AED withdrawal before three years is associated with a 2.5 times higher risk of early seizure recurrence as compared to patients who are maintained on single AED up to three years following surgery. However, as our results show, late AED withdrawal after three years does not offer protection against seizure recurrence during or after late AED withdrawal. Our results also show that early AED withdrawal is safe and final seizure outcome is not different in patients who undergo early or late AED withdrawal. Inclusion of a uniform group of patients and long and meticulous followup are major strengths of our study.

Patients included in this study represents highly selected group of patients who are traditionally considered to have a very good seizure outcome following ATL as confirmed by 91 % seizure freedom during the terminal one year. All patients had either hippocampal sclerosis on pathology or circumscribed lesions confined to mesial temporal lobes and were seizure free for one year following surgery. As compared to our previous protocol, we offered more rapid withdrawal in these selected patients as we believed that these patients have lower risk of seizure recurrence on AED withdrawal while in all other patients we opted for a more conservative approach. Even in these patients, seizure recurrence was noted in 40 % patients which is similar to the previously reported rates in unselected patients including our own earlier studies [6–14].

In this nonrandomized controlled study, our results suggest that AEDs does have protective effect against seizure recurrence following ATL. Higher rate of early recurrences in early withdrawal group and the temporal association of recurrences with AED withdrawal further confirm the protective effect of AEDs against seizure recurrence. These results further corroborate the previously reported preliminary findings. A study from Mayo Clinic, which mainly consisted of patients who underwent temporal resections, reported that seizure recurrence rate after AED withdrawal was 14 % while it was 3 % in patients who did not undergo AED withdrawal [8]. Another study which reported the outcome of pediatric epilepsy surgeries before and after 1997 noted better outcomes in post-1997 patients, which was largely credited to the less aggressive AED withdrawal policy after 1997 [19].

However, our results also indicate that late AED withdrawal after three years of ATL does not offer long-term protection against seizure recurrence on eventual AED withdrawal. The long term risk of seizure recurrence at 10 years was similar in patients who underwent early or late AED withdrawal. Similarly, there is no difference in the terminal seizure outcome in patients who undergo early or late AED withdrawal. These results are similar to a recent retrospective study in pediatric patients which concluded that early AED withdrawal merely helps to identify the people who require long-term AEDs without affecting long-term outcome [20]. Thus at the group level, late AED withdrawal does not appear to offer any definite long-term advantage over early withdrawal and offering complete withdrawal after one year of seizure freedom appears quite safe. Still, early AED withdrawal increases the risk of early seizure recurrence. Even a single seizure recurrence after surgery can be emotionally devastating for the adult patients with active social and professional life who otherwise consider themselves as cured. Single seizure can also lead to loss of driving privileges, in the interim period, before the seizure control is again achieved. However, it is also true that many patients want to stop AEDs following surgery [1,2]. In this scenario, our results can be used for counseling the patients and making evidence based and individualized decisions of AED withdrawal in postoperative period following ATL. Sometimes, continuing patients on one AED may offer a better tradeoff between the risk of seizure recurrence and side effects associated with high AED load. It is important to discuss the chances of stopping AEDs and risk of seizure recurrence with AED withdrawal during the pre-operative counseling.

Our results show that absence of febrile seizures and a relatively late age of onset of habitual seizures in patients with MTLE–HS are associated with a higher risk of seizure recurrence on AED withdrawal. Absence of febrile seizures as a risk factor for seizure recurrence on AED withdrawal following ATL has been reported in a recent study [14]. Presence of febrile seizures is a useful diagnostic clue for HS and MTLE–HS patients with febrile seizures usually have better seizure outcome following ATL as compared to those with no febrile seizures [21,22]. MTLE–HS is a heterogeneous disorder with varied pathophysiology and those patients with febrile seizures might represent more classical cases of hippocampal sclerosis with epileptogenic zone confined to anterior temporal lobe and a high likelihood of complete resection following ATL. These patients also have seizure onset around late first decade and early second decade. Hence those patients with a relatively early or late age of onset might represent a separate subgroup of patients with MTLE-HS with some part of epileptogenic zones being outside the boundaries of standard temporal lobectomy. However, based on our group analysis results, it is not possible to suggest a cut-off for the age of onset which can be associated with a lower risk of seizure recurrence. Other factors such as the presence of bilateral interictal discharges, presence of secondarily generalized seizures, and presence of interictal discharges on postoperative EEG were not predictive of seizure recurrence on AED withdrawal. This may be due to the small number of patients who had recurrences following AED withdrawal. At the same time, these all factors are associated with a higher risk of seizure recurrence even without AED withdrawal and it is possible that these patients were already excluded from our patient population by seizure recurrence within first year [15,23,24].

The terminal one year seizure freedom of 91 % and AED withdrawal rate of 58 % is highest among the studies involving adult patients [23–25]. This again highlights that post-ATL outcome is very good in well selected patients. However, this is also one of the limitations of this study as the results cannot be generalized to all the patients who undergo ATL. We also started AED withdrawal at three months but included only those patients who were seizure free at one year. Hence, a few patients who had seizure recurrences before one year and after initiating AED withdrawal were not included in this study. Our study has other important limitations. Although patients were stratified in two groups and were counseled by one neurologist, this is not a randomized study. Hence the unintentional bias introduced as a part of routine clinical practice and pre-withdrawal counseling might have influenced the patient's decision making. However, the baseline characteristics were similar between the groups. Even if bias was there, it was always towards the side of caution where patients with a perceived higher risk of seizure recurrence might have been counseled to continue AEDs rather than to withdraw AEDs. Hence, we feel that this is unlikely to change the results to a great extent. Although all the patients with hippocampal sclerosis underwent uniform surgery, we did not ascertain the completeness of resection in these patients by postoperative MRI mainly due to the affordability issues. Lastly, patients in late withdrawal group had lesser followup duration following AED discontinuation as compared to patients in early withdrawal group. However, we feel that a followup of five years after the last AED change in late withdrawal group is sufficient to capture all likely recurrences as most of the recurrences are likely to occur within two years of AED discontinuation.

5. Conclusions

Our results show that early and complete AED withdrawal starting at one year following temporal lobectomy is associated with a higher risk of early seizure recurrence as compared to the patients who are maintained on AEDs. However, delaying the withdrawal up to three years following surgery does not offer protection against eventual seizure recurrence and chances of seizure recurrence and long term

prognosis following early and delayed withdrawal are similar. Thus our results confirm that early AED withdrawal starting one year following ATL is safe and does not affect the long-term seizure outcome in adult patients following anterior temporal lobectomy. These results will be helpful in making informed decisions about AED withdrawal following successful epilepsy surgery.

Declaration of Competing Interest

None of the authors have any conflict of interest related to this work.

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