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Effect of reduction of antiepileptic drugs in patients with drug-refractory epilepsy☆,☆☆

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ABSTRACT

Purpose: The present study was conducted with the aim of evaluating the effects of reducing the number of antiepileptic drugs (AEDs) administered to patients with drug-refractory epilepsy (DRE) during their admission and document any change in seizure frequency in subsequent follow up.
Methods: A total of 962 patients with DRE who were admitted to the neurology wards waiting for connection to video EEG were recruited for this prospective study. After their admission to the neurology ward, modifications in the number and dosage of AEDs were done with a target of a maximum of three AEDs in every patient. Drug tapering was done using a standardized protocol. The primary outcome was the change in seizure frequency in the follow-up period of 6 months. Secondary outcome measures were the adverse event profile (AEP) and the quality of life (QOL).
Results: Of the 1134 patients screened, 962 patients gave consent to participate in the study. The mean number of AEDs received by each patient was 4.24. After the tapering following a standardized protocol each patient received a mean of 2.65 AEDs per patient. In 82.70% patients with DRE, there was either a reduction or no change in seizure frequency in the subsequent 6 months follow up. There was a significant reduction in the AEP score after the reduction in the number of AEDs ($P = 0.001$).
Conclusion: Our study proves that optimization of reduction of the number of AED's in patients with DRE leads to reduction or no change in seizure frequency with a significant decrease in adverse effects.

1. Introduction

Despite recent advances in neuropharmacology, around 20–30% of persons with epilepsy (PWE) have DRE. Most of them are on multiple AEDs with the hope of achieving good seizure control [1]. Although there is evidence that there is a decreased chance of seizure control after failure of an adequate trial of first-line AEDs, polytherapy is rampant in clinical practice.

Polytherapy increases the side effects of medications through drug–drug interactions, impacts cognition, mood, and overall behavior in PWE. It also leads to reduced compliance and makes monitoring more difficult. Moreover, some AEDs are known to aggravate pre-existing seizures and trigger new seizure types [15].

There is evidence from previous studies that reduction of one or more AED is possible without an increase in seizure frequency in patients with DRE [2,3,14].

Uncontrolled epilepsy leads to an increase risk of death, cognitive and behavioral dysfunction and socioeconomic disadvantage. All attempts should be made to make the patient seizure free, but not at the cost of a poor QOL. The present study aims to evaluate the effects of reducing the number of AEDs administered to patients with DRE during their stay in the neurology ward and the likelihood of decrease and non-increase in seizure frequency in subsequent 6 month follow up.

2. Methods

A total of 1134 patients of DRE who were being evaluated in the EMU from 2003 to 2012 were identified and were screened for the study. Out of them 962 were recruited for this prospective study

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after informed written consent. The study was approved by the institute ethical committee. Informed consent was sought from the patient or and caregiver after explaining the details of the study in the language the patient could understand, by an epilepsy fellow. Patients and or their caregivers were also explained the possible risk of increase in seizure frequency during the study. Out of the 172 patients who declined to the study, 124 did so due to their inability to come for a timely follow up (As they were residing in remote rural areas) and 48 declined after they were explained the possible risk of increase in seizure frequency during the study. DRE was defined as failure of adequate trials of two tolerated and appropriately selected and used AED schedules (in combination) to achieve sustained seizure freedom.

Inclusion criteria consisted of patients with DRE being treated with at least three or more AEDs with seizure frequency of at least 1 per month. Frequency of seizures was determined as an average of the previous 6 months. PWE with catastrophic epilepsies like Rasmussen encephalitis, malignant brain tumors and severe central nervous system infections like fungal infections, prion diseases, progressive multifocal leukoencephalopathy were excluded.

Patients were enrolled into the study after admission to neurology wards while they were waiting for connection to VEEG either for characterization of seizure type or as a work up for epilepsy surgery. Clinical, demographic, diagnostic evaluation and treatment-related details were recorded in all patients after an interview in a structured proforma. Details regarding the age of onset of seizures, the semiology of seizures, frequency of seizures, any history of status epilepticus was recorded. Treatment details included the number of AEDs prior to the monitoring, their combinations, dose adequacy, AED levels and side-effect profile. After their admission AED's were tapered gradually. The tapering of AEDs was done after admission in neurology wards prior to transfer to the EMU. A slow tapering protocol was done after reviewing the history and response to each AED- in situations where a definite history of response to a particular AED was seen, then that AED was not tapered. Those AEDs which were enzyme inducing and had produced no response were tapered first. In situations where it was not clear if there was any AED which has produced a response an enzyme inducing AED/those AEDs which were producing an adverse effect were tapered first. Dosage of tapering was only 25% of the dosage of AED per day. Phenobarbitone was reduced at a slower rate of 10% of the dosage. Benzodiazepines were not tapered so as to not provoke withdrawal seizures. After the patients underwent VEEG recording and an adequate number of seizures were recorded, the AED's were restarted. Modifications in the number and dosage of AEDs were done and the target was to keep the patient on a maximum of three AEDs. These would be the ones to which the patient had good response as per routinely maintained seizure charts and diaries and caregivers information. The choice of drugs was based on the treating epileptologists (MT) review, to be either that which was producing maximum side effects or was ineffective. Serum drug levels were done in all patients and drug dosage titration was done according to the drug levels. The primary outcome was the change in seizure frequency in the follow-up period of 6 months after reduction of the number of AEDs. Seizure frequency was determined from a seizure diary completed by the patient or caregiver, which was reviewed at routine monthly clinic visits. Secondary outcome measures were the AEP and the QOL. Adverse effects (AEs) were identified by the AEP questionnaire comprising of 21 questions. The AEP score has been widely used in epilepsy research [4–8]. The frequency of occurrence of each AE in the previous 4 weeks was rated on a 4-point digital scale (4 = frequent, 3 = sometimes, 2 = rarely and 1 = no occurrence). The total score, as a sum of the individual AED rating, indicates the total burden of AED's adverse effect. The patient AEP score was calculated at baseline and again after 6 months of the reduction of an AED.

We used Hindi translation of QOLIE-10, which is a self-administered questionnaire. It comprises of 10 questions about health and daily activities, one question about how much distress the person feels about problems and worries related to epilepsy and a review of what is most bothersome. The responses of the questionnaire were recorded. We also determined Cronbach's alpha, a marker of reliability to indicate how closely related a set of items are as a group. A relative coefficient of 0.7 or higher is considered acceptable in most situations. We found a reliability coefficient of 0.94. Further, all domains of QOL correlated well with each other indicating that these domains were interlinked. The follow-up assessment was done by a neurologist (VA) and pharmacologist (RJ) blinded to the patient treatment protocol. The seizure frequency and AEP score at 6-month follow up was compared to the baseline frequency.

3. Results

3.1. Subject characteristics

Of the 962 patients, 595 (61.8%) were males and 367 (39%) were females. The mean age at the time of presentation was 19.97 ± 11.37 years. Most of the patients (884, 93.84%) were under 40 years and 270 patients (28.66%) were under 10 years of age. The mean duration of epilepsy was 7.21 years (range: 1–28 years) and in most the duration of epilepsy was under 10 years (762 patients, 80.89%). The mean age of onset of epilepsy was 12.76 years with a range of 0.6–59 years. The etiology and seizure types are tabulated in Table 1.

3.2. Seizure frequency after reducing the number of AED

The mean number of AEDs received by each patient was 4.24 with a range of 3–6 AEDs. Most of the patients (58.38%) were receiving 4 AEDs while only 15 patients (1.59%) were on 6 AEDs. The average duration of stay of patients in the EMU was 5.4 ± 2.1 days. The total duration of stay of patients in hospital was 11.2 ± 3.2 days. After the tapering each patient received 2–3 AEDs with a mean of 2.65 AED per patient. The number of patients exposed to an individual AED has been depicted in Table 2.

Table 1
Etiology and seizure types.

Etiology	Number
Etiology of seizures	
Mesial temporal sclerosis	226 (24.0%)
Perinatal hypoxia	225 (23.9%)
Cortical dysplasia	198 (21.0%)
DNETs	56 (5.9%)
Gliosis secondary to infarction	45 (4.7%)
Post traumatic gliosis	43 (4.5%)
Gangliogliomas	41 (4.3%)
Post Infectious	32 (3.3%)
No substrate	96 (10.2%)
Types of seizures	
Focal dyscognitive seizures	607 (63.1%)
Focal motor seizures	34 (0.3%)
Focal sensory	6 (0.6%)
Focal progressing to bilateral convulsive-	28 (2.9%)
Drop attacks	192 (2.0%)
Myoclonus	23 (2.3%)
Multiple seizure types	31 (3.2%)
Reflex epilepsy (sound, touch, eating)	21 (2.1%)
Generalized tonic	16 (1.7%)
Clonic	1 (0.1%)
PNES plus focal seizures	3 (0.3%)

Table 2
Exposure of individual AED to number of patients.

	Drugs	Number of patients
1	Phenytoin	634
2	Valproate	523
3	Carbamazepine	646
4	Oxcarbamazepine	120
5	Levitiracetam	213
7	Topiramate	42
8	Clobazam	109
9	Phenobarbitone	121

Table 3
Percentage of patients with either no change or decrease in seizure frequency in follow up.

Follow up period	Percentage of patients with no change or decrease in seizure frequency in follow up after tapering of AED's (%)
1 month	72.3
3 months	79.0
6 months	82.70

Out of 962 patients recruited for the study, 20 were lost to follow up and 942 could be followed up after 6 months. The percentage of patients with either no change or decrease in seizure frequency at 6 months follow up was 82.70%. Table 3 shows the percentage of patients with either no change or a decrease in seizure frequency at different follow up periods. Cox regression analysis was done to calculate predictors of decrease in seizure frequency on reduction of number of AED's. The significant negative predictors of decrease in seizure frequency after tapering the number of AED's included a history of status epilepticus, younger age of onset of epilepsy, presence of mental retardation and findings of perinatal hypoxia on MRI.

Two patients had status epilepticus in the first month after tapering of drugs and one had status in the second month. In 82.70% of our patients there was a reduction or no change in seizure frequency in the subsequent 6 months follow up. In 56% patients, there was a decrease in seizure frequency after reduction of number of AEDs. The mean reduction of seizures per patient was 0.50 which was highly significant (P value <0.001, 95% CI 0.39–0.61). Out of the 942 patients, 17 had an increase in seizure frequency with a mean seizure frequency of 3.5 prior to the change in AED number to 4.5 after the tapering of AED's. History of prior episodes of status epilepticus was found to be a significant negative predictor for the reduction of seizure frequency after decrease in the number of AEDs. Out of 17 patients who had worsening of seizures after reduction of AEDs and the history of status epilepticus was present in 15 patients (88.23%).

None of the patients had epilepsy surgery during the study period. This is because of an average waiting period of at least 12 months for surgery in our hospital after the evaluation in the EMU. Of the 942 patients 718 subsequently underwent epilepsy surgery after discussion in our weekly presurgical case conference.

3.3. Adverse effect profiles

The adverse effects encountered before tapering the AEDs and after 6 months of tapering of number of AEDs have been depicted in Fig. 1. Drowsiness, ataxia and double vision were found to be significantly decreased at 6 months following reduction of the AEDs (50.73%, 49.57% and 65%, respectively). The mean AEP score at baseline was 64.2 ± 8.3. The AEP score after reduction in the number of AED's at 6 months follow up decreased to 40.4 ± 7.8. There was a significant reduction in the AEP score before and after reduction of number of AEDs ($P = 0.001$). We categorized AEP scores into 5 subgroups 21–30, 31–40, 41–50,51–60 and >60. We calculated the percentage of patients having AEP scores in different categories at the initial assessment and after 6 months follow up of tapering of AED's (Fig. 2).

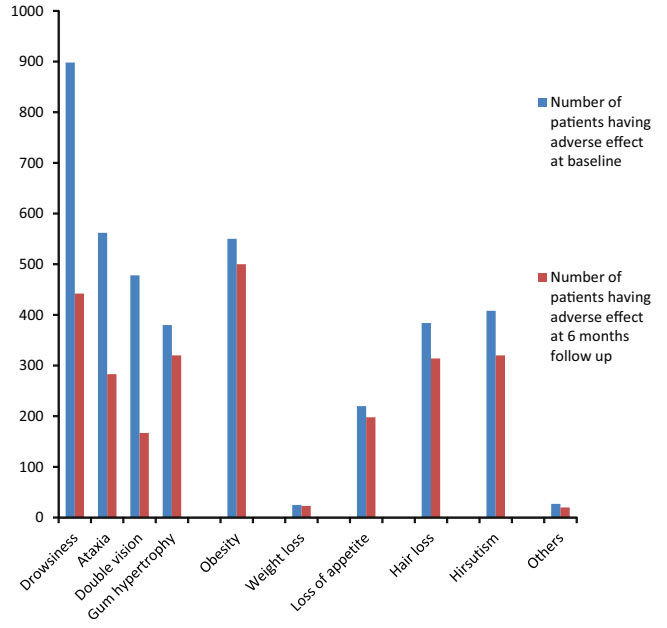

Fig. 1. Different adverse effects at initial assessment and after 6 months of follow up.

3.4. Quality of life

The mean total QOLIE-10 score at baseline was 56 ± 19 and at 6 months after a reduction in the number of AEDs was 62 ± 14 and this was not statistically significant. The ratings of QOL on all parameters were almost comparable for patients on two AEDs as well as on three AEDs.

4. Discussion

We enrolled 962 consecutive patients of DRE, admitted for evaluation in the EMU who were on at least three or more AEDs. The number of AEDs in these patients was reduced to a maximum of 3 during their stay in the neurology wards. They were subsequently followed up for next 6 months. In 82.70% of our patients there was either a reduction or no change in seizure frequency observed after decreasing the number of AEDs. There

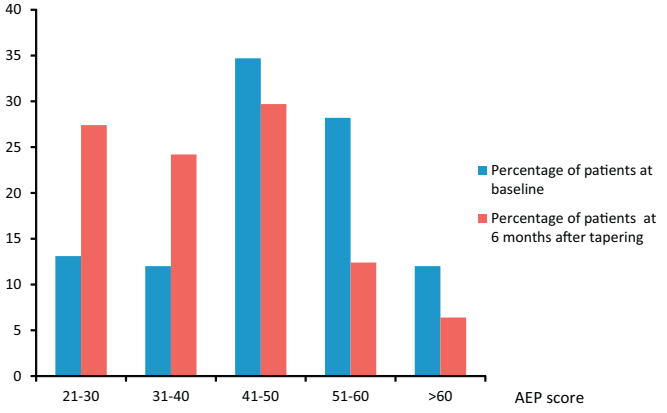

Fig. 2. Percentage of patients in various categories of AEP scores at initial assessment and after 6 months of follow up of tapering of AED's.

was decrease in seizure frequency in 56% of patients after reduction of the number of AEDs. The mean reduction of seizure per patient was 0.50 which was statistically significant (P value <0.001, 95% CI 0.39–0.61). Adverse effects which included drowsiness, ataxia and double vision were found to be significantly decreased 6 months after reduction of the AEDs (50.73%, 49.57% and 65%, respectively). There was a significant reduction in the AEP score before and after reduction of number of AEDs ($P = 0.001$).

Matsuura prospectively evaluated the effect of polytherapy reduction on patient satisfaction and subjective seizure severity in patients with chronic epilepsy [9]. AEDs were withdrawn using a 1-year reduction schedule. In the cohort of 80 patients with chronic epilepsy, there was reduction of seizure frequency in 9 patients. Seizure frequency remained stable in 69 out of 80 patients even after reduction of AEDs. They also found that no patient had an increase in seizure frequency after withdrawal of sedative groups of the AEDs. QOL was assessed by the authors on the side effect and life satisfaction (SEALS), which is a self-reported questionnaire developed by Brown and Tomlinson for use in community surveys to evaluate side effects of AED [10]. After reduction of number of AEDs, total SEALS score improved and also the temper sub score improved. The total SEALS score and temper sub score were not affected by the type of epilepsy or change in seizure frequency. The authors concluded that the improvement in QOL score used was probably due to the reduction in the adverse effects of the AEDs. In contrast, our study did not find a significant improvement in the QOLIE-10 scores after a reduction in the number of AEDs. This could be probably because of the short duration of follow-up period. The other reason could be that as most of our patients had a very low educational background and the questionnaire was self-administered. This could have led to them not understanding the scoring system. Assistance in the form of an epilepsy nurse explaining the scoring system may have brought out different results. The scale used to measure QOL was also different compared to the one used by Matsuura.

Albright and Bruni conducted a study and attempted to reduce the number of AEDs in 90 patients with epilepsy (Albright [13] and Bruni 1982). In 72 patients (80%), the mean number of drugs administered were reduced from 2.75 to 1.49. 39 (54%) of these patients were converted to monotherapy. Patients were followed up for a minimum of 16 months after reduction of polypharmacy and were found to have either no change or an improvement in seizure control. The authors also noted a significant decrease in AEP. The variable predicting failure in reducing polypharmacy was the presence of multiple concurrent seizure types. In the present study, patients were on a larger number of AEDs to begin with, but even then a similar trend of no change or reduction in seizure frequency was noted after a 6-month follow up.

In a retrospective chart review by Richardson et al. [16], 35 patients of DRE who had been shifted from polytherapy to monotherapy were identified and followed for at least 12 months. Out of 35 patients, none had worsening of their seizure frequency. A significant proportion of patients (40%) became seizure-free. Out of 35 patients, 28 (80%) had a 50% or greater reduction in seizure frequency. None of the 35 patients had worsening of seizure frequency. QOL on monotherapy was better as compared with polypharmacy in a number of domains: memory loss, concern over medication long-term effects, difficulty in taking the medications, trouble with leisure time activities, and overall state of health [16]. In contrast to Richardson et al., our study design was prospective in nature and the assessor of final outcome was blinded to the treatment protocol thus decreasing the chances of bias. In our study, 56% patients had a decrease in seizure frequency after reduction of number of AEDs The plausible explanation could be that our cohort had a more refractory variety of DRE (mean seizure frequency was 4.8/month).

In our cohort of DRE patients the drugs were reduced after the patient was admitted to the wards for the evaluation and work up for epilepsy surgery. The patients were connected to VEEG and seizure type and EEG correlates were studied. Drug tapering was done in this setting. Seizure type and epilepsy syndrome could be better characterized by the treating neurologist thus AEDs tailored for the specific seizure type were continued and the AEDs which were having minimal or no effect were tapered off.

The other reason could be due to the reduction in number of AEDs, the pharmacokinetic and pharmacodynamic drug interactions were minimized. Thus, the drug levels achieved were better and probably resulted in a better seizure control. A decrease in the number of drugs also leads to better compliance; a reduced cost and also may result in a decrease in seizure frequency.

It is well established that seizure frequency can show fluctuations in a patient of DRE as part of the natural course of the DRE. With an average duration of epilepsy for 7.21 years, it is unlikely that a spontaneous remission in seizure frequency could explain the magnitude of improvement seen in our cohort of DRE patients.

There is growing evidence indicating that AEDs may worsen pre-existing seizures by increasing their frequency or inducing a new type of seizure. Carbamazepine, oxcarbazepine, and phenytoin can aggravate absence and myoclonic seizures; to a lesser extent, atonic seizures; and, more rarely, tonic seizures. Absence and myoclonic seizures are triggered by all of the GABAergic drugs. Severe myoclonic epilepsy of infancy seems to be predictably aggravated by lamotrigine. There are reports in the literature reporting precipitation of status epilepticus due to AEDs [11]. By decreasing the number of AEDs the risk of paradoxical increase in the seizure frequency is relatively reduced.

The proportion of patients with an increase in seizure frequency was approximately 18% in our study. This is similar to what Schmidt reported in prospective studies of 36 patients with intractable complex partial seizures where two-drug treatment regimen was converted to a single-drug therapy [2]. In a long-term population-based study of 144 patients followed up for 37.0 years since their first seizure before the age of 16 years, a worsening of seizure frequency was seen in 14% of patients [12].

Our study is probably the largest study, which has seen the effect of reducing the number of AEDs in DRE patients during their stay in neurology ward and the impact on seizure frequency in the subsequent months. The strength of our study is the large number of patients and the prospective design of our study. It is the largest published study looking into the effect of decreasing polypharmacy in patients of DRE in a prospective manner.

5. Conclusion

Our study proves that it is not worthwhile to give more than three AEDs in patients with DRE. Seizures can be controlled better and adverse reactions can be reduced with a less number of drugs. However, sometimes just changing combinations and dose adjustments could reduce the number of side effects and improve seizure control.

Conflict of interest statement

None declared.

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