Determinants of medication withdrawal strategy in the epilepsy monitoring unit*

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SUMMARY

Background. Video-EEG (VEEG) monitoring is a vital diagnostic tool, but there are no guidelines for withdrawal of antiepileptic drugs (AEDs).

Aim. The main objectives of this study were to understand the different withdrawal strategies used in the EMU, how strategies are chosen, and the efficacy and safety of different withdrawal strategies in producing seizures.

Materials and methods. We retrospectively analyzed 95 consecutive patients and measured time to first seizure, incidence of status epilepticus, and need for rescue medications.

Results. We found that AED withdrawal strategies can be divided into four categories based on level of aggressiveness. The main factors which impacted choice of strategy was number of AEDs on admission and frequency of pre-admission seizures. Abrupt cessation of medications was correlated with longer time to first seizure compared to other methods (hazard ratio (HR) 0.36, 95% confidence interval (CI) 0.20–0.65, p = 0.0007). Patients remaining on medications had shorter time to first seizure (HR 2.98, 95% CI 1.22–7.24, p = 0.016). Withdrawal technique was not correlated with need for rescue medications (OR 5.0, 95% CI 0.77–43, p = 0.20). No patients had status epilepticus in the study.

Conclusions. Pre-admission seizure frequency and number of AEDs are the main factors which drive choice of withdrawal strategy on the epilepsy monitoring unit (EMU). Counterintuitively, least aggressive strategy is associated with highest risk of seizures. Results of this analysis suggest that disease factors, not choice of withdrawal strategy, determine seizure frequency on the EMU.

Key words: epilepsy monitoring unit epilepsy • antiepileptic drugs • medication weaning • focal epilepsy • seizure • medication withdrawal

BACKGROUND

Video-EEG monitoring is a vital diagnostic tool in epilepsy. It is the gold standard in distinguishing epilepsy from non-epileptic seizures and is also used in presurgical evaluation of drug-resistant epilepsy. Questions remain regarding the optimal management of patients during VEEG admission. Previous work on duration of monitoring found that 3–5 days is average (Nordli, 2006; Hupalo et al., 2016). In patients with frequent events the majority had a typical event within two days (Cox et al., 2017). Monitoring can be used in patients with infrequent events, and tapering antiepileptic drugs (AEDs) has a beneficial effect on seizure frequency in this population (Al Kasab et al., 2016).

* This project was unfunded.

Table 1. Demographics

Gender	**Male 47 (49.5%)**	**Female 48 (50.5%)**
Type of epilepsy	Temporal 49 (51.6%)	Extra-temporal 46 (48.4%)
Length of stay	Mean 3.57 days	Range 3–16 days
Age	Mean 43.3 years	Range 21–85 years
Weaning strategy	Remain on medications	n = 6
	Cutting doses	n = 12
	Stop one by one	n = 57
	Abrupt cessation	n = 20

Table 2. Factors associated with time to first seizure: abrupt cessation of medications was used as a reference, this was compared to other withdrawal methods

Time to first seizure	**Hazard ratio (95%CI)**	**p-value**
Years of seizures	0.99 (0.98–1.01)	0.42
Seizure frequency	1.00 (0.99–1.00)	0.38
Abrupt cessation	1.0 (reference)	
Cut doses	1.67 (0.74–3.77)	0.22
Stop one-by-one	2.79 (1.53–5.09)	0.00084
Remain on medications	7.01 (2.46–20)	0.00027

There is little consensus regarding the best AED withdrawal regimen during VEEG. A recent survey of epilepsy monitoring units (EMUs) revealed 80% of centers do not have a protocol for medication taper, and withdrawal is generally done on a case by case basis (Buelow et al., 2009). Guld et al. (2017) compared slow and fast AED taper and found higher incidence of rescue therapy and increased risk of generalized seizures with rapid taper. Kumar and colleagues (2018) also found increased need for rescue therapies with taper but no increased risk of generalized seizures. Several other studies have also suggested that AED withdrawal is safe and effective but may lead to increased risk of acute repetitive seizures (Gennaro et al., 2012; Henning et al., 2014; Yen et al., 2001; Rose et al., 2003; Rizvi et al., 2014).

AIM

The main objectives of this study were to understand the different withdrawal strategies used in the EMU, how various strategies are chosen, and the efficacy and safety of different withdrawal strategies in producing seizures.

MATERIALS AND METHODS

We performed a retrospective observational study of adult patients with a diagnosis of focal epilepsy undergoing scalp or intracranial monitoring at Dartmouth Hitchcock Medical Center from 2015 to 2016. Lack of epileptic seizures during admission or length of stay greater than 29 days were exclusion criteria. Variables recorded were age, gender, AEDs, self-reported outpatient seizure frequency, use of rescue medications during admission, withdrawal method, occurrence of status epilepticus, number of days in the monitoring unit, and duration of epilepsy. The data was analyzed using cox regression plots, hazard ratios and T tables.

One limitation of our methods was our inability to capture the nature and severity of patient's epilepsy. The use of Kaplan-Meier plots and multivariable Cox regression models attempted to capture the variables associated with time to first seizure and need for rescue medications but could not capture the efficacy of the monitoring itself with respect to whether all seizure types were seen and the severity of those seizures.

RESULTS

The demographics of our population are illustrated in Table 1. All patients had focal epilepsy with temporal and extra temporal localization approximately equal.

Based on time and number of medications stopped, we found that withdrawal methods can be separated into four categories: remaining on AEDs (least aggressive), cutting doses of AEDs gradually, stopping medications one-by-one, and abrupt cessation of all medications (most aggressive). The most common weaning strategy was stopping medications one by one (n = 57), with other strategies used less frequently (Table 1).

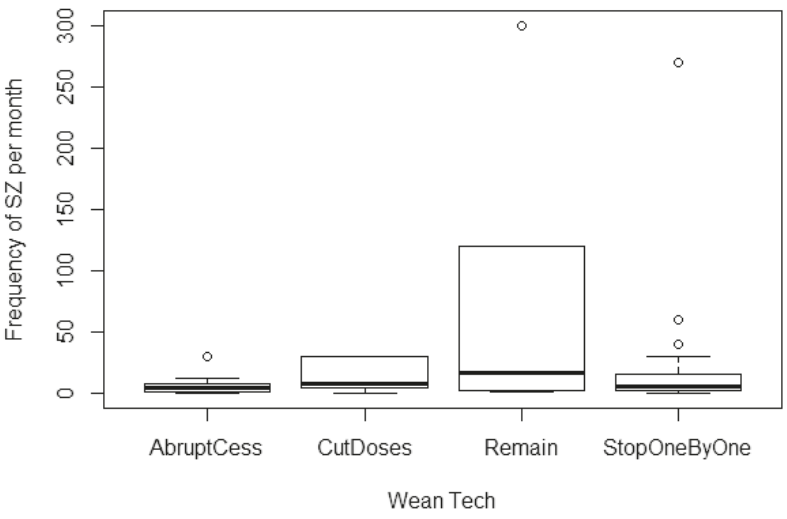

Figure 1. Remaining on medications was significantly associated with higher frequency of seizures per month compared to other groups (p = 0.00036).

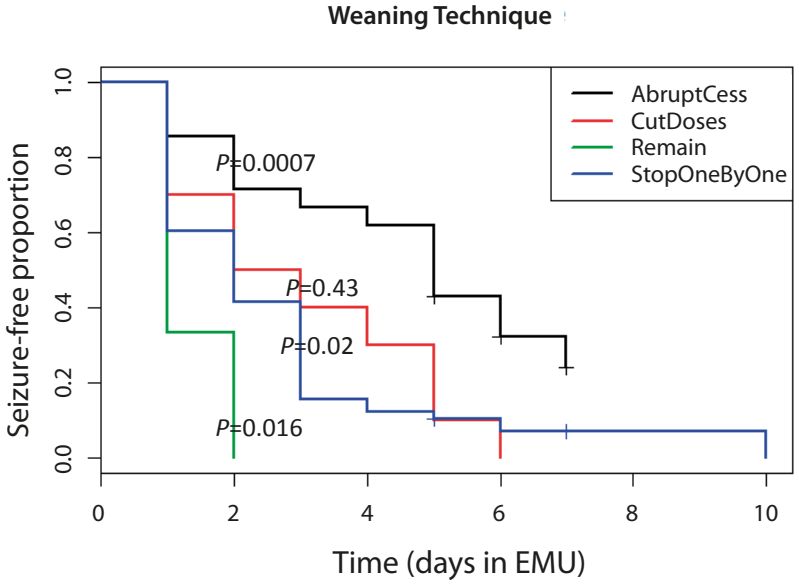

Figure 2. Time to first seizure by weaning technique: Cox regression used to calculate p-values comparing the seizure free proportion for weaning method to the others with adjustment for years of seizures and frequency of seizures per month.

Factors associated with choice of weaning strategy are shown in Table 2. The main factors associated with choice of weaning strategy were number of AEDs at the time of admission (p = 0.0044) and frequency of seizures per month (p = 0.00036) (Figure 1). Self-reported frequency of seizures was not associated with time to first seizure. Years of seizures and frequency of seizures were not associated with the need for rescue medications.

Figure 2 shows time to first seizure for each weaning strategy using a cox-regression analysis adjusted for length of epilepsy and outpatient seizure frequency. Pa-

tients with abrupt cessation of medications had longer time to first seizure compared to other methods (hazard ratio (HR) 0.36, 95% confidence interval (CI) 0.20–0.65, p = 0.0007). Patients with one-by-one stopping strategy had shorter time to first seizure compared to other groups (HR 1.73, 95% CI 1.09–2.75, p = 0.02). Patients remaining on medications also had shorter time to first seizure (HR 2.98, 95% CI 1.22–7.24, p = 0.016). There was no difference between cutting doses or stopping one-by-one (p = 0.43).

There were no episodes of status epilepticus in the study. Weaning technique was not associated with need for rescue medications (OR 5.0, 95% CI 0.77–43, p = 0.20). There was a significant correlation with number of outpatient seizure medications and need for rescue medicines (p = 0.045 when comparing 1 AED vs 2–3 AEDs).

DISCUSSION

Previous work has shown that VEEG with medication taper yields diagnosis in 75–88% of epilepsy and nonepileptic seizures (Moien-Afshari et al., 2009; Lobello et al., 2006). Physicians responsible for patients in the EMU are therefore tasked with deciding on an appropriate medication taper plan. This plan must balance the need for induction of seizures with the necessity to maximize safety and minimize the risk of status epilepticus or injury. For this purpose, AED taper plans of various aggressiveness have been developed.

At our institution we use four distinct taper plans which range from keeping patients on medications to abrupt discontinuation. These varying strategies attempt to maximize benefit of reduced time to first seizure and minimize risk of acute repetitive seizures and status epilepticus. We found that the key drivers of withdrawal strategy are the number of seizures per month and the number of AEDs taken in the outpatient setting. Patients with a higher number of seizures per month were more likely to have a conservative medication taper.

Disease factors, not withdrawal strategy influence time to first seizure in the EMU. Our findings are contrary to previous studies which showed a correlation between rapid AED titration and increased seizure frequency in the EMU (Al Kasab et al., 2016), and are more consistent with the previous finding that AED taper rates do not affect daily seizure frequency in EMU (Henning et al., 2014).

Our work also confirms previous reports which demonstrated that tapering medications in the EMU is safe. First, we found that the risk of status epilepticus is very low, confirming previous studies (Rose et al., 2003). Second, we found that patients with medication discontinuation do not have higher risk of acute repetitive seizures or seizure clusters, applying the need for rescue medications as a surrogate for this. A recent randomized controlled trial compared rapid versus slow medication weaning in pediatric and adult patients with drug resistant epilepsy. Time to first seizure and seizure clusters were increased in the rapid taper group (Kumar et al., 2018). Our contrasting results may be accounted for by different patient populations.

The limitations of our study are that it is nonrandomized and retrospective. Because of this, the results should not be taken to suggest that choice of specific weaning strategy has no influence on seizure frequency or safety in the EMU. Evidence from this study supports the idea that weaning approach should be tailored to the individual patient. Another limitation is that we included only patients with focal epilepsy, so findings may not be generalizable to patients with nonepileptic events or generalized epilepsies. Most groups were well powered but the group which remained on medications only had 6 participants so conclusions may be limited by that sample size. Last, previous work has shown that patient self-reporting of seizures may be unreliable, especially for focal epilepsy (Blum et al., 1996).

CONCLUSIONS

Disease factors determine medication withdrawal strategy in the EMU and influence time to first seizure. Clinicians should tailor their weaning approach to the individual patient. Medication taper is safe with low risk for status epilepticus and acute repetitive seizures. These findings should be confirmed with a large, prospective study in adult patients with focal epilepsy.

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