Original article

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Clinical predictors of adverse events during continuous video-EEG monitoring in an epilepsy unit

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ABSTRACT – *Aims*. Patients admitted to epilepsy monitoring units (EMUs) for diagnostic and presurgical evaluation have an increased risk of seizure-related injury, particularly in the many cases in which medication is withdrawn. The purpose of this study was to assess the prevalence of adverse events (AEs) in this setting and to analyse associated clinical factors and costs.

Methods. We evaluated consecutive patients admitted to an EMU at a tertiary care hospital over a 10-year period based on a descriptive, longitudinal study. We analysed the occurrence of AEs (traumatic injury, psychiatric complications, status epilepticus, cardiorespiratory disturbances, and death), investigated potential risk factors using univariate and multivariate logistic regression analysis, and compared admission costs between patients with and without AEs.

Results. In total, 411 EMU admissions were studied corresponding to 352 patients (55% women; mean [SD] age: 41.7 [12.1] years). Twenty-five patients (6%) experienced an AE. The most common event was traumatic injury (n=9), followed by status epilepticus (n=8), psychiatric complications (n=7), and cardiorespiratory disturbances (n=1). On comparing patients with and without AEs, we observed that the former were more likely to experience generalized seizures (OR: 7.81; 95% CI: 3.51-12.23; $p<0.001$) or have more seizures overall during admission (OR: 3.2; 95% CI: 1.42-6.8; $p=0.002$). Patients with AEs also had longer EMU stays (6.91 [2.64] vs 5.08 [1.1]; $p=0.004$), longer hospital stays (8.45 [3.6] vs 5.18 [1.2]; $p<0.001$), and higher costs (€7277.71 [€2743.9] vs €5175.7 [€1182.5]; $p<0.001$).

Conclusion. Patients with generalized seizures and more seizures during admission were at greater risk of AEs, which were associated with higher admission costs.

Key words: adverse events, safety, costs, epilepsy, epilepsy monitoring unit

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Patients with epilepsy havent an increased risk of seizure-related injuries and even death (Buck *et al*., 1997; Lawn, 2004; Deekollu, 2005). Continuous video electroencephalography (VEEG) monitoring provides a potential means of improving diagnosis and treatment and protecting against injuries in this setting. The specific indications for admission for continuous VEEG monitoring are based on determining whether spells are epileptic seizures, identifying seizure types in individuals with known epilepsy, localizing the seizure focus for presurgical evaluation, performing ictal single-photon emission computed tomography, monitoring seizure frequency, adjusting medications to control seizures, and differentiating between seizures and adverse drug-related effects (Shih *et al*., 2018). In such cases, antiepileptic drug (AED) treatment often needs to be tapered or withdrawn and additional provocative measures are sometimes needed to exacerbate seizure frequency and severity. Such measures are potentially harmful for patients, even in the controlled setting of an epilepsy monitoring unit (EMU).

There have been some brief reports of adverse events (AEs) associated with VEEG monitoring (Noe *et al*., 2009; Dobesberger *et al*., 2011; Arrington *et al*., 2013; Ley *et al*., 2014), the most common being seizure-related injuries, status epilepticus, postictal psychosis, cardiorespiratory disturbances, and death (Shafer *et al*., 2011). Little, however, has been published on the clinical factors associated with the probability of these effects (Dobesberger *et al*., 2011) or on the associated costs, making it difficult to provide recommendations that could improve clinical practice. Although Shafer *et al*. (2012) published a series of consensus-based recommendations for ensuring patient safety in EMUs, these were based on expert opinion and therefore rank low in the hierarchy of evidence.

The purpose of this study was to add to the limited body of knowledge in this area by assessing the prevalence and type of AEs in patients admitted to the EMU at our hospital and to analyse associated clinical factors and costs.

Materials and methods

Patients admitted for continuous VEEG monitoring at the EMU at Hospital Germans Trias i Pujol, a public tertiary care hospital in Barcelona, Spain, were consecutively recruited between November 2007 and February 2019. Candidates for inclusion were patients admitted for evaluation of recurrent spells or for presurgical evaluation, and patients with a final diagnosis of focal or generalized epilepsy. Patients with both epilepsy and psychogenic non-epileptic seizures were included, but only epileptic seizures were used in the analysis. Paediatric patients and patients with exclusively psychogenic non-epileptic events were excluded. Patients admitted to the EMU on several occasions were treated as different patients in order to analyse the occurrence of AEs and demographic and clinical data corresponding to each admission.

Continuous VEEG monitoring was indicated by a team of epilepsy specialists and was generally performed over five days, although the duration varied according to individual needs. At the time of admission, the attending physician recorded the patient's personal history, performed a physical examination, and completed a blood test. All patients underwent a brain magnetic resonance imaging scan according to the EMU's epilepsy protocol and also had to undergo a neuropsychological study. Electrodes were placed according to the international 10-20 system by staff trained in epilepsy. Patients were assessed by continuous VEEG monitoring in protected, adapted beds for 24 hours a day over five days. During this time, they were monitored by specialized staff and all seizures and AEs were recorded.

Although the study was retrospective, the variables were recorded prospectively and systematically according to a protocol established prior to admission to the EMU. The following variables were collected for all patients: demographic information (age, sex) and clinical variables, including duration of epilepsy (defined as time from onset of habitual seizures), previous history of psychiatric illness, monthly seizure frequency before admission (calculated as the mean number of seizures experienced during the four weeks prior to admission) and at six and 12 months, reason for referral, number of seizures during admission to the EMU, main seizure type during admission classified as generalized seizure, focal seizure evolving to a bilateral convulsive seizure, focal seizure with impairment of consciousness, focal seizures without impairment of consciousness with observable motor components, and focal seizure without impairment of consciousness with sensory or autonomic manifestations (Berg *et al*., 2010). Additional variables analysed were type of seizure onset for the main seizure observed during admission, length of EMU and hospital stay (days), number and type of AEDs, and quality of life measured by the QOLIE-10 before admission and at six and 12 months.

During admission, antiepileptic drugs were tapered on a case-by-case basis by the treating physician according to previous seizure frequency, drug half-life, risk of seizures due to treatment withdrawal, and history of status epilepticus or serial seizures.

For ascertaining and defining the adverse events, we relied on the work by Shafer *et al*. (Shafer *et al*., 2011) who designed a questionnaire to identify the extent of adverse events in EMUs. The authors reported, as the more frequent adverse events: falls, status

epilepticus, and postictal psychosis. Although infrequent, cardiorespiratory disturbances and death were also described.

Based on these results, we assessed the incidence of traumatic injury (falls with or without injuries or fractures), interictal and postictal psychosis, status epilepticus, cardiorespiratory disturbances, and death. Convulsive status epilepticus was defined as a convulsive seizure lasting longer than five minutes or failure to regain consciousness between two consecutive convulsive seizures (Lowenstein, 1999). Non-convulsive status epilepticus was defined as continuous seizure activity without major motor signs, lasting longer than 30 minutes.

To analyse the cost increase associated with the occurrence of AEs in the EMU, we compared admission costs between patients with and without events. The daily admission costs considered were €1,004 for the EMU, €652 for a hospital ward, and €1,500 for the intensive care unit. Additional tests required for patients who experienced an AE were priced at €12 per X-ray and €2,320 per pacemaker placement.

Statistical analysis

To analyse the clinical factors associated with the occurrence of AEs, all variables were compared statistically between patients with and without AEs. Descriptive statistics (mean [SD] and frequency tables) were used to analyse the main variables. The Chi-square test was used to compare categorical variables and the *t* test to compare continuous variables. Multiple regression analysis with stepwise entry was used to assess the independent effects of each variable. To analyse the number of seizures related to a greater likelihood of AEs, we calculated the area under a receiver-operating characteristic (ROC) curve, which estimated the probability of a model assigning a higher risk of AEs. Youden's index was calculated to identify the cut-off point that optimized sensitivity and specificity for the prediction of outcomes. Data were collected and analysed using SPSS version 20.0. In all cases, statistical significance was established at p=0.05. The protocol was approved by the hospital's ethics committee and all participants gave their written informed consent.

Results

Patients

We analysed 411 EMU admissions corresponding to 352 patients; 306 patients (87%) were admitted once, 37 (10.5%) twice, six (1.7%) three times (1.7%), two four times, and one five times. Ninety percent of the patients were admitted for evaluation of recurrent spells or presurgical evaluation and the remaining 10% were admitted for differential diagnosis. The mean (SD) age of the group was 41.7 (12.1) years and 226 of the patients (55%) were women. The mean duration of epilepsy was 17.9 (14.5) years. Epileptic seizures were recorded in 92% of patients (378/411) during continuous VEEG monitoring. The seizure types were focal seizure with impairment of consciousness in 208 patients (55%), focal seizure evolving to a bilateral convulsive seizure in 95 patients (25.1%), focal seizure without impairment of consciousness with sensory or autonomic manifestations in 38 patients (10%), generalized seizure in 22 patients (5.8%), and focal seizures without impairment of consciousness with observable motor components in 11 patients (3%). The most common type of onset for the main seizure during admission was temporal seizure onset, observed in 47.8% of patients (181/378). The prevalence of other onset types was 28.5% for extratemporal onset (108 patients), 9.5% for generalized onset (36 patients), 7.4% for multifocal onset (28 patients), and 6.6% for non-localizing onset (25 patients).

The pre-admission diagnosis was revised in 24% of patients (98/411). The changes were epilepsy to non-epilepsy in 12% of patients (49/411), temporal to extratemporal epilepsy in 7% (29/411), and epilepsy to a different type of diagnosis such as syncope or sleep disorder in 5% (20/411).

The AED regimen was modified at discharge in 30% of patients (123/411). A new drug was added or the dose of an existing drug increased in 14.6% of patients (60/411), existing doses were decreased in 8.4% (35/411), and AED treatment was started in 3.1% (12/411) and withdrawn in 2.6% (10/411).

Sixty-nine patients (16.8%) underwent epilepsy surgery (vagus nerve stimulator implantation in 37 cases [9%] and resective surgery in 32 [7.8%]).

There was a significant reduction in the mean number of seizures per month during follow-up (18 [35.7] seizures a month before admission vs 8.41 [16.9] at six months and 6.89 [21.3] at 12 months, $p<0.0001$).Mean quality of life scores measured using the QOLIE10 were 55.48 (20.4) before admission, 62.4 (20.1) at six months, and 64.8 (18.5) at 12 months (p=0.001).

Adverse events

Twenty-five patients (6%) experienced AEs during admission to the EMU (*table 1*). Nine patients (2.2%) were injured: seven experienced a fall with minor injuries (bruises, abrasions, lacerations), one dislocated and fractured his shoulder during a convulsive seizure, and one fell and sprained his foot. Both of these patients required an X-ray. Eight patients

Table 1. Adverse events during admission to the epilepsy monitoring unit.

Adverse event: no	386 (94%)
Adverse event: yes	25 (6%)
Traumatic injury	9 (2.2%)
Status epilepticus	8 (2%)
Psychiatric complications	7 (1.7%)
Cardiorespiratory disturbances	1 (0.2%)
Sudden unexpected death	0% (0)

(2%) experienced status epilepticus (convulsive in six cases and non-convulsive in two). One of the patients with convulsive status epilepticus required treatment with third-line agents and was admitted to the intensive care unit for three days. Psychiatric complications were observed in seven patients (1.7%). There were four cases of postictal psychosis (two visual and auditory hallucinations, one mystical experience, and one pregnancy delirium) and three cases of agitation with self- and hetero-aggressiveness after a convulsive seizure. None of the patients required hospitalization in the psychiatric unit, although four required antipsychotic treatment. Cardiorespiratory disturbances were recorded for one patient (0.2%) with tonic-clonic seizures who required pacemaker implantation due to extreme bradycardia. There were no cases of sudden unexpected death.

Factors associated with AEs

Table 2 shows the factors significantly associated with the occurrence of AEs during admission. We observed a greater likelihood of AEs in patients with generalized seizures or focal seizures evolving to a bilateral convulsive seizure (OR: 7.81; 95% CI: 3.51-12.23; $p<0.001$) and with more seizures during admission (OR: 3.2; 95% CI: 1.42-6.8; $p=0.002$). There was a greater likelihood of AEs in patients with more than four generalized seizures or focal seizures evolving to a bilateral convulsive seizure with an area under the curve (AUC) of 0.89 (sensitivity [0.92] and specificity [0.85]). No other risk or protective factors were observed. We also found no association between specific AEs and clinical factors (traumatic injury, status epilepticus, and psychiatric events).

Patients who experienced AEs spent longer in the EMU (6.91 [2.64] days vs 5.08 [1.1] days; $p=0.004$) and in hospital (8.45 [3.6] days vs 5.18 [1.2] days; $p< 0.001$) than those without AEs. On analysing AEs associated with longer hospital stays, we found that patients with psychiatric AEs had a significantly longer stay (9.1 [2.8] days) than those who experienced status epilepticus (7.9 [3.9] days; $p=0.01$) or injury (5.21 [1.2] days; $p=0.02$). The difference in length of hospital stay between patients with injuries and patients without AEs was not significant.

The mean cost of admission based on the variables analysed was higher for patients with AEs than for those without (€7,277.71 [€2,743.9] vs €5,175.7 [€1,182.5]; $p<0.001$) and higher for patients with status epilepticus than for patients with psychiatric complications (€8,102.4 [€3,012.6] vs €6,268.5 [€1,071.2]; $p=0.02$). Again, no significant differences were observed between patients who experienced a traumatic injury and patients without an event.

Discussion

The results of this study support previous findings demonstrating the utility of continuous VEEG monitoring (Sauro *et al*., 2014; Bilakota and Sinha, 2016; Shih *et al*., 2018). In our series, patients who underwent this procedure experienced improved quality of life and a significant reduction in mean seizure frequency at six and 12 months after discharge.

This study also adds to the body of knowledge on the prevalence of AEs during continuous VEEG monitoring in EMUs. Our findings for a large series of patients support the safety of this procedure, as the overall rate of AEs was only 6% and there were no serious events or deaths. There have, however, been anecdotal reports of near-death experiences during VEEG monitoring (Tavee and Morris, 2008). The adverse rate of 6% observed in our series is similar to rates reported by Dobesberg *et al*. (9%) and Ley *et al*. (7.9%), but much lower than the 23% described by Noe *et al*., however, this is probably because seizure clusters were included in the definition of AEs in the latter study. The most common AEs in our series were traumatic injury (2.2%) -supporting previous reports (Shafer *et al*., 2011)-, status epilepticus (2%), and psychiatric complications (1%). Ley *et al*. and Dobesberg *et al*. reported similar rates of status epilepticus to that reported by us. Noe *et al*. observed a lower rate, of 0.67%, but probably because they defined status epilepticus as seizure activity lasting longer than 30 minutes, as opposed to five minutes in our case. None of the patients with status epilepticus in the studies of Ley *et al*., Dobesberg *et al*., and Noe *et al*. required endotracheal intubation or anaesthetic care. In our series, one of the eight patients with this condition required sedation and endotracheal intubation for three days in the intensive care unit.Very few studies have examined the link between clinical factors and AEs in EMU settings. Like Ley *et al*., we found no clinical predictors of classes of AEs or specific AEs. Dobesberger *et al*., by contrast, found that duration of epilepsy was significantly associated with the overall occurrence of AEs,

Table 2. Factors associated with adverse events.

	Adverse events *n*=25 (6%)	**No adverse events *n*=386 (94%)**	***p***
Age, mean years (SD)	42.25 (16.7)	39.74 (13.4)	0.59
Female sex, %	57.1%	54.2%	0.76
Duration of epilepsy, mean years (SD)	17.9 (15.7)	18 (14.5)	0.69
Previous history of psychiatric illness, %	59%	55%	0.15
Monthly seizures prior to admission, mean no. (SD)	26.43 (39.8)	17.43 (35.36)	0.25
Seizures during hospitalization, mean no. (SD)	7.2 (3.4)	2.8 (2.5)	0.002
Main seizure type (generalized seizure or focal seizure evolving to a bilateral convulsive seizure), %	53.6%	17.6%	<0.001
Main seizure onset (frontal), %	15.8%	10.9%	0.71
Length of stay in EMU, mean days (SD)	6.91 (1.64)	5.08 (1.1)	0.004
Length of hospital stay, mean days (SD)	8.45 (3.6)	5.18 (1.2)	<0.001
No. of antiepileptic drugs before admission, mean no. (SD)	2.61 (1.28)	2.32 (1.15)	0.31
Quality of life (QOLIE10), mean score (SD)	56.78 (22.4)	60.4 (19.1)	0.67
Cost of admission, mean (SD)	€7277.71 (€2743.9)	€5175.7 (€1182.5)	<0.001

psychiatric comorbidity increased the risk of psychiatric complications, and a history of status epilepticus increased the risk of status epilepticus during EMU admission.

According to our univariate analysis, patients with severe epilepsy who experienced generalized seizures during admission and more seizures overall during their time in the EMU were more likely to experience an AE. Noe *et al*. also observed a greater frequency of AEs in patients with tonic-clonic seizures. Unlike Noe *et al*., we observed longer admission times in patients with AEs.

One novel aspect of our study is that we investigated whether specific types of AEs resulted in increased admission costs. While traumatic injury was not associated with either longer hospital stays or higher costs, patients who experienced status epilepticus had longer hospital stays and incurred higher costs than patients without AEs and patients with psychiatric complications. Patients who experienced psychiatric complications had longer hospital stays but incurred lower costs than those with status epilepticus because they did not need intensive care treatment.

Another novel aspect is that we provide the number of generalized seizures related to a greater likelihood of AEs. According to our results, when patients have at least four generalized seizures, restarting antiepileptic drugs might be recommended.

Our study has some limitations. First, for our cost analysis we only calculated admission costs and the costs of additional tests required. Despite the lack of a detailed cost analysis, however, ours is the first study to provide preliminary insight into the additional costs associated with the occurrence of AEs during continuous VEEG monitoring.

Considering that patients with generalized tonic-clonic seizures and more seizures during their time in the EMU had a higher prevalence of AEs, precautions against seizures during admission (Labiner *et al*., 2010) should be considered as a means of preventing events that are likely to increase length of stay and costs. □

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Is admission for continuous VEEG monitoring useful?

(2) Is admission for continuous VEEG monitoring safe?

(3) Are there predictors of adverse events related to admission for continuous VEEG monitoring?

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".