Timing of seizure occurrence and response of medical staff in video-EEG monitoring for drug-resistant epilepsy

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Abstract

Purpose: The purpose of this study was to determine the optimal duration of long-term video-EEG monitoring (VEEG) in patients with epilepsy. The response time of medical staff to seizures was also evaluated from the viewpoint of safety of the monitoring.

Methods: We estimated the optimal duration of VEEG from the seizure onset pattern. We retrospectively investigated all VEEG sessions performed in our department during the period between June 2005 and July 2016. Sessions with no seizures and with only non-epileptic seizures were excluded. Using 91 sessions from 69 patients, information on the onset time and response time of medical staff to seizures was collected.

Results: The median duration from the start of VEEG to the first seizure was 2 days. Seventy-seven percent of first seizures occurred within 3 days of VEEG. The median duration from the first seizure to the third seizure was 2 days. Eighty percent of third seizures occurred within 3 days of the first seizure. There was no significant diurnal distribution of seizure occurrence. Medical staff did not respond to 20% of generalized seizures and 69% of focal seizures. The overlooking of generalized seizures occurred mainly during the hours of 1-2 pm and 8-9 pm but there was no significant diurnal pattern in overlooking generalized and focal seizures.

Conclusion: Based on these findings, we suggest that VEEG can be terminated when no seizure occurs within 4 days after onset. In our VEEG protocol, in which all antiepileptic drugs were discontinued before the start of a session, there was no diurnal pattern of seizure occurrence. This is the first study investigating the diurnal pattern of overlooking seizures by medical staff during VEEG. Since there was no diurnal pattern to the overlooking, medical staff should pay equal, 24-hour attention to patients on VEEG.
Introduction

Video-EEG (VEEG) monitoring is recommended as the gold standard for diagnosis of epilepsy, classification of seizures/epilepsy, and pre-surgical evaluation [1–7]. The optimal duration of VEEG monitoring has not been determined but it was found to be between 3 to 6 days in most reported studies to capture more than one seizure [1, 8–10]. The optimal protocol for VEEG monitoring, including the duration of monitoring and time of discontinuation of anti-epileptic drugs (AEDs), also has not been determined. Furthermore, occurrence of seizures, particularly generalized seizures, during VEEG monitoring may cause major adverse events including physical injuries and even death from seizures [3, 7, 9, 11–15]. Medical staff plays important roles in preventing these events during VEEG monitoring [11]. Our study aimed to determine the optimal duration of VEEG monitoring in patients with epilepsy by retrospectively analyzing the timing and pattern of seizure occurrence during VEEG monitoring. From the viewpoint of safety of the monitoring, the responses of medical staff to seizures were also evaluated.

Methods

Patients and VEEG data

The data for this study were obtained from a database of digital EEG and movie files during VEEG monitoring in the Department of Neurosurgery at Jichi Medical University. A list of patients who underwent VEEG during the period starting from June 2005 was constructed by the authors (E.W., K.O., H.Y.), which included patients’ names, ID numbers, and presence or absence of important events (prominent epileptiform discharges, seizures and suspected seizures) during VEEG sessions. The corresponding digital data of VEEG for 2 h which included each event were available for review. Not all digital data throughout each session were available because of the limited capacity of hard disks. VEEG monitoring was performed in patients with drug-resistant epilepsy to determine indication for surgical treatment and/or to localize epileptic focus in presurgical workup. Three patients who had generalized epilepsy were excluded from this study.

The list included 120 sessions obtained from 115 patients during a period of more than 10 years between June 2005 and July 2016. All the corresponding digital data for each event were reviewed by one of the authors (A.D.) in terms of whether the event was a true epileptic seizure based upon EEG and clinical symptoms. In the case of true epileptic seizures, they were classified into focal or generalized seizures. The starting and ending times for each seizure were determined. Sessions with only psychogenic non-epileptic seizures (N = 8) and sessions without any seizures (N = 21) were excluded. Twenty-five seizures were excluded because the corresponding 2-h digital EEG file or movie file was missing. Consequently, 91 sessions with 650 true epileptic seizures obtained from 69 patients were analyzed in the present study. Four patients had two scalp EEG sessions and one patient had three scalp EEG sessions. Eighteen patients had one intracranial EEG session and two patients had two intracranial EEG sessions. All patients who underwent intracranial EEG sessions had preceding scalp EEG sessions.
VEEG monitoring

A single monitoring room equipped with a 128-channel EEG system and a video camera (Nihon Kohden® 1100, Tokyo, Japan) was used. A mobile toilet was placed in the room. Patients had their meals in the room. On the first day, scalp EEG was prepared using the international 10-20 system. Sphenoidal electrodes were used when needed (N = 38). For intracranial studies, subdural electrodes and/or depth electrodes were used as indicated. Patients were instructed to push a nurse-call button or an EEG-marked button when they had seizures. There was no accompanying person during monitoring except visitors. A video feed was streamed for 24 h in the nurses’ station, but it was not continuously monitored by an assigned observer.

In principle, all AEDs were discontinued on the day before the start of VEEG monitoring, all of which were resumed immediately after termination of VEEG. However, in 14 sessions, some AEDs were continued because the patients had daily seizures even under AEDs, and these patients were excluded from the study of the timing of seizures. Recorded VEEG data were checked twice a day by the authors (K.O., H.Y. and A.D.). Important events were marked in the digital data and were listed up. There were no strict criteria for terminating the session, but in principle VEEG was continued until more than 5 seizures were captured or otherwise for 1 week. There were no strict criteria for resuming AEDs either, but in principle pre-monitoring AEDs were resumed when three seizures were captured for analysis.

Data acquisition and analysis

For the study on the timing of seizures, we used 571 seizures in 77 sessions from 58 patients, after excluding 14 sessions in which AEDs were not discontinued before the start of VEEG sessions. The starting time of every seizure was obtained and expressed as the 24-hour clock time of a given day. The time of each day was defined as from 00:00 to 24:00, and not as the time elapsed from the start of the session. For a given session, the number of seizures per hour of each day was counted. The number of days from the start of a session to the first seizure and the number of days from the first seizure to the third seizure were determined for each session. Then we counted the number of sessions during which the first seizure occurred on each day. Similarly, we counted the number of sessions during which the third seizure occurred on each day from the day of the first seizure. Because 11 patients experienced only one or two seizures during monitoring sessions, the latter analysis was done using 66 sessions from patients who had three or more seizures.

To test the hypothesis that patients with a higher seizure frequency had the first seizure earlier, we analyzed the association between seizure frequency and the day of the first seizure. The seizure frequency of each session was calculated by dividing the total number of seizures during the session by the number of days of session. Similarly, we tested the hypothesis that patients with a higher seizure frequency had the third seizure after a shorter duration from the first seizure.

To study the diurnal distribution of seizure occurrence, we used the above-mentioned data on the total number of seizures per hour.
of each day in all 91 sessions. We used two methods to evaluate the diurnal distribution. First, we adopted a method that was used in a previous study [16]. The 24-h day was divided into four bins. The summated numbers of seizures in all 91 sessions in the four bins were compared. Since the effects of inter-patient differences in seizure frequency and session length cannot be avoided in this method, we compared the diurnal rates of seizure occurrence in each patient. For each patient, we summated the number of seizures in all sessions for each hour of the day, and determined the rate of seizure occurrence in the given bins of that day.

Whether any nurse and/or doctor appeared in the movie during seizure was also checked. When they were observed on the video, the seizure was regarded as response positive. Response negative was defined as when neither a nurse nor a doctor appeared in the movie from the start to finish of a seizure. The diurnal distribution of response to seizures was evaluated. For each time bin, the summated numbers of response-positive seizures and response-negative seizures were determined using all session data. The null hypothesis was that the numbers are equally distributed in all time bins.

Statistical analysis

Student’s t-test was used for the comparison of seizure frequency between the patient groups in which patients had the first seizure before and after a given day, and between the patient groups in which patients had the third seizure before and after a given number of days following the first seizure. Repeated ANOVA was used for the comparison of seizure occurrence during four time bins in 24 h. The Wilcoxon sign rank test was used for comparison of seizure occurrence during two bins in 24 h. IBM® SPSS® 20 was used for the above-mentioned statistical tests.

Results

Patients, VEEG sessions and seizures

We retrospectively analyzed all VEEG sessions in our department for an approximately 10-year period. There were 91 sessions obtained from 69 patients. The median age of the patients was 31 years (range, 8 to 63 years). Thirty-nine of 69 were males. The median duration of VEEG sessions was 5 days (range, 1 to 13 days). Six hundred and fifty seizures were captured in 91 sessions of the 69 patients. One hundred and seventy-three were generalized seizures and 477 were focal seizures. The median number of all seizures in a session was 6 (range, 1 to 38). The median numbers of generalized and focal seizures were 1 (range, 0 to 22) and 4 (range, 0 to 23), respectively.

Timing of seizure occurrence

Figure 1A demonstrates the day of occurrence of the first seizure. The peak number of first seizures was observed on the second day and the number gradually decreased thereafter. The median days from the start of VEEG to the first seizure was 2 (range, 1 to 10). Seventy-seven percent of seizures had occurred by the third day. Figure 1B demonstrates the day of occurrence of the third seizure after the first seizure. The peak number of the third seizure was again observed on the second day and the number decreased abruptly thereafter. The median number of days from the first seizure to the third seizure was
Eighty percent of seizures had occurred by the third day after the first seizure.

To provide an overview of the association between the timing of the first seizure and seizure frequency in a given session, all sessions are plotted in Fig. 2A. The first seizure tended to occur earlier in sessions with higher seizure frequencies. To confirm this tendency, we compared the seizure frequency between sessions with the first seizure occurring before the second or third day than in sessions with the first seizure occurring after those days.

A similar analysis was performed for the day of occurrence of the third seizure (Fig. 2B). We found that seizure frequency was significantly higher in sessions with the third seizure occurring before the second or third day after the first seizure than in sessions with the third seizure occurring after those days.

**Figure 1.** Times of occurrence of the first seizure and the third seizure. A. Day of occurrence of the first seizure. Line graph shows the cumulative percentage of first seizures on each day of monitoring. Bar graph shows the number of first seizures that occurred on each day of monitoring. B. Day of occurrence of the third seizures. Line graph shows the cumulative percentage of third seizures on each day after the first seizure. Bar graph shows the number of third seizures that occurred on each day after the first seizure.

**Figure 2.** Association between seizure frequency and timing of the first seizure (A) and third seizure (B). All sessions were plotted using the days of the first and third seizures (X axis) and mean seizure frequencies per day (Y axis).
Diurnal pattern of seizure occurrence

While there were two peaks; between 6 am and 7 am and between 6 pm and 7 pm, in the occurrence of focal seizures, there was no apparent peak in the occurrence of generalized seizures (Fig. 3). Reflecting the peaks in focal seizures, the total number of seizures demonstrated two peaks in the same hours. Although seizure occurrence was apparently higher from midnight to early morning than during daytime, we did not detect a statistically significant diurnal pattern of the occurrence of total seizures, generalized seizures or focal seizures.

Response of medical staff

Twenty percent of 173 generalized seizures and 69% of 477 focal seizures were overlooked by medical staff. Figure 4A demonstrates the diurnal distribution of total and overlooked generalized seizures. Figure 4B demonstrates the diurnal distribution of the rate of overlooking generalized seizures. While there were apparently peaks between 1 pm and 2 pm and between 8 pm and 9 pm, the rate varied prominently during a 24-h period. We did not detect a significant diurnal pattern in overlooking of generalized sei-
The lack of diurnal pattern in over-looking was clearer for focal seizures (Fig. 5A, B). Again, we did not detect a significant diurnal pattern in overlooking of focal seizures. Another significant finding was that the overlooking rates were much higher for focal seizures than generalized seizures over 24 h.

Discussion

The optimal duration of VEEG monitoring has not been determined but most studies reported between 3 and 6 days to capture more than one seizure [1, 9, 10]. Capturing one seizure may be enough to rule out non-epileptic seizures or to make a diagnosis of epilepsy, but is not regarded sufficient for presurgical evaluation. Many researchers have recommended that at least three seizures are required to properly locate the epileptic region [8, 9, 14, 17, 18]. Therefore, we investigated the times of occurrence of the first seizure and third seizure. The occurrence of the first seizure declined steeply after 5 days. Seventy-seven percent of first seizures occurred by the third day. Eighty percent of third seizures occurred by the third day after the first seizure. Eighty percent of third seizures occurred by the fifth day of VEEG monitoring. Knowledge of these patterns of occurrence is useful to avoid meaningless continuation of VEEG and to save medical resources.

VEEG has been regarded as the gold standard for diagnosis and classification of epilepsy and presurgical evaluation. Therefore, nearly all previous retrospective studies on the usefulness or optimal duration of VEEG monitoring included a variety of patients with various purposes for performing VEEG [8, 10]. However, inclusion of diverse patients with various purposes of VEEG may increase the variability of the time of seizure occurrence. Alving and Beniczky [8] reported that the duration of successful VEEG monitoring was significantly longer in the presurgical group (mean: 3.5 days) than in the diagnostic and classification groups (2.4 and 2.3 days, respectively). More recently, Hupalo et al. [10] reported that VEEG should last at least 72 h in patients with refractory epilepsy, while most of the cases with psychogenic non-epileptic seizures could be diagnosed after 48 h. A non-uniform regimen of AED dose reduction or discontinuation during VEEG monitoring in previous studies also may have resulted in greater variability of the time of seizure occurrence [10, 19]. Our study was unique and strong in that the patient cohort was considerably uniform because VEEG was performed solely for presurgical evaluation in patients with drug-resistant partial epilepsy, and AED was discontinued in all patients one day before the start of VEEG.

To taper or withdraw AEDs before VEEG monitoring facilitates recording of seizures sooner or in larger numbers [10, 20]. Our findings on the association between the time of occurrence and the frequency of seizures support this finding. In one study in which 60% of patients had AEDs reduced by half but none discontinued AEDs totally, only 15% of epileptic seizures occurred within the first 24 h of long-term VEEG monitoring (53% and 32% on the second and third day, respectively) [10]. In contrast, in our study, seizure occurrence was higher from the beginning of monitoring, considering that we started VEEG in the afternoon of the first day.
and that the first day represented less than 24 h.

Importantly, tapering or withdrawal of AEDs has been believed to be potentially dangerous, as it carries a 3% risk of status epilepticus or cluster seizures [4, 13, 21, 22]. Therefore, most epilepsy centers gradually taper or partially discontinue AEDs [10, 19]. There were no previous studies in which all AEDs were discontinued before the VEEG admission. Interestingly, we and a number of other authors observed no complications related to discontinuation or dose reduction of AEDs [2, 9, 10, 18, 19, 21–25]. However, it is too early to conclude that we can discontinue all AEDs from our single series of VEEG monitoring. It is highly probable that frequency of seizure and risk of status epilepticus are dependent on pre-VEEG seizure frequency, semiology of each patient, and medication regimen. There is also the concern that discontinuing all AEDs may increase the epileptic activity of various brain regions too extensively, making it difficult to properly localize the true epileptic focus to be surgically treated.

While seizure prevalence associated with the wake-sleep cycle has been studied extensively, studies on the diurnal pattern of seizure occurrence are limited. Hofstra et al. [16, 26] reported that more seizures were observed from 11:00 to 17:00, and fewer seizures from 23:00 to 05:00. They suggested that certain types of seizures have a strong tendency to occur in a truly diurnal pattern. However, they tested the diurnal pattern only by comparing the total number of seizures from all patients for a 5-year period in four bins of 24 h. We did not detect any significant diurnal pattern by using more extensive testing applied to a more homogeneous patient group. Therefore, at least in partial epilepsy, it is unlikely that seizure occurrence has a clear diurnal pattern.

Our study is the first to examine the diurnal pattern of overlooking seizures by medical staff. In our center, there are three meal times in a day; 7:30 for breakfast, 11:30 for lunch and 18:30 for dinner. Nurses are busiest at those times. Interestingly, the peaks of overlooking seizures did not coincide with those busiest hours. It is noteworthy that 20% of generalized seizures and 69% of focal seizures were overlooked by medical staff. Spanaki et al. [24] reported that focal seizures had a tendency to be missed by medical staff during VEEG sessions due to difficulties in visual detection. Improvement in detection measures for generalized and focal seizures may improve the safety of VEEG and save medical resources by avoiding futilely lengthy VEEG.

References


