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Frequency of non-convulsive seizures and non-convulsive status epilepticus in subarachnoid haemorrhage patients in need of controlled ventilation and sedation

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Running head: seizures in subarachnoid haemorrhage patients

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Abstract

Background: Non-convulsive seizures (NCSZ) can be more prevalent than previously recognized among comatose neuro-intensive care patients. The aim of this study was to evaluate the frequency of NCSZ and non-convulsive status epilepticus (NCSE) in sedated and ventilated subarachnoid haemorrhage (SAH) patients.

Methods: Retrospective study at a university hospital neuro-intensive care unit, from January 2008 until June 2010. Patients were treated according to a local protocol, and were initially sedated with midazolam or propofol or combinations of these sedative agents. Thiopental was added for treatment of intracranial hypertension. No wake-up tests were performed. Using NicoletOne® equipment (VIASYS Healthcare Inc., U.S.A.), continuous EEG recordings based on four electrodes and a reference electrode was inspected at full length both in a two electrode bipolar and a four channel referential montage.

Results: Approximately 5500 hours of continuous EEG were registered in 28 SAH patients (33% of the patients eligible for inclusion). The median Glasgow Coma scale was 8 (range 3-14) and the median Hunt & Hess score was 4 (range 1-4). During EEG registration no clinical seizures were observed. In none of the patients inter ictal epileptiform activity was seen. EEG seizures were recorded only in 2/28 (7%) patients. One of the patients experienced four minutes of a NCSZ and one had a five hours episode of a NCSE.

Conclusion: Continuous EEG monitoring is important in detecting non-convulsive seizures in sedated patients. Continuous sedation, without wake-up tests, was associated with a low frequency of subclinical seizures in SAH patients in need of controlled ventilation.

Key words: Epilepsy, seizures, non-convulsive seizures, continuous electroencephalogram, subarachnoid haemorrhage

Introduction

Even if it is still not a method used in daily clinical routine, continuous EEG (cEEG) has over the last decades earned an increased interest in the neuro-intensive care setting [1-4]. The cEEG can serve as a method to detect events, which may give rise to secondary brain injury such as cerebral vasospasm, ischemia and subclinical epileptic seizures [5-10]. Clinical seizures have been reported to occur in 8-43 %, and subclinical EEG seizures have been reported in 3-36 % of patients treated at neuro-intensive care units [11-15]. Clinical seizures are common in patients suffering from subarachnoid haemorrhage (SAH). The seizures can occur at the onset of the bleeding or during the acute treatment period [16-18]. Early clinical seizures have often been associated with re-bleeding, and as the frequency of re-bleeding have declined in recent years, due to more aggressive treatment and early surgical intervention, the number of clinical seizures overall among SAH patients have decreased. The reported incidence of clinical seizures is in the range of 0.2-27%, with the higher incidence in poor grade patients [13, 19, 20-23]. A study on the occurrence of non-convulsive seizures (NCSZ) in poor grade SAH patients reported seizures in 18% of the patients [14]. Other studies have reported non-convulsive status epilepticus (NCSE) in 3 – 31% of SAH patients [1, 11, 15]. Detection of epileptic seizures is of importance since secondary brain injury is correlated to epileptic seizures [16, 24-26].

We studied the occurrence of subclinical electroencephalographic seizures in patients with severe traumatic brain injury and found, in contrast with other publications, no EEG seizures [6, 27, 28].

The aim of this study was to investigate the frequency, type and length of clinical and electroencephalographic subclinical seizures in sedated SAH patients in need of controlled ventilation, treated at an intensive care unit (ICU).

Methods

Patients

All patients, from 15 years of age, treated for SAH from a verified intracranial aneurysm, referred to Umeå University hospital during the period from January 2008 to June 2010, and in need of prolonged (≥ 48 hours) controlled ventilation and sedation were eligible for inclusion in this study. The university hospital has a vast referring district, covering half of Sweden, which gives long transportation times. Patients with minor neurological deficits can therefore be intubated and sedated due to long transportation time only. These patients will stay sedated and ventilated until the aneurysms are secured and are thereafter extubated. The inclusion for the patients in need of prolonged ventilation was consecutive and based on the availability of EEG monitoring equipment only.

Scoring

Patients were scored before sedation and intubation. For assessment of the level of consciousness the Glasgow Coma Score (GCS) was used [29]. The clinical neurological status due to the SAH was further scored according to the Hunt and Hess scale (H&H) and the World Federation of Neurological Surgeons Scale (WFNS) [30, 31]. The first CT scan was examined and assessed according to the Fisher classification [32].

Treatment

The patients were treated in accordance with a local protocol. They were all mechanically ventilated and sedated to a level where they could cooperate with the ventilator and were able to cough. At no stage the sedation was aimed at an EEG with burst suppression pattern. Initially, usually a continuous infusion of propofol was used and if in need of a longer period of sedation, a change to midazolam in continuous infusion was made. Thiopental was used for treatment of intracranial hypertension, aiming at a continuous delta activity on the EEG. Fentanyl was given in continuous infusion for analgesia in addition to all sedative agents. Muscle relaxants were not routinely used. The cerebral aneurysms were treated either by endovascular coiling or surgical clipping. The treatment was performed as early as possible, usually within 24 hours after admittance. Expansive haematomas were surgically removed. All patients were normoventilated (PaCO_2 around 5 kPa), with a target $\text{PaO}_2 > 12$ kPa. Normally neither mannitol nor hyperventilation was used. Prophylactic treatment with anti-epileptic drugs (AED) was not included in the protocol. Treatment with continuous infusion of nimodipine (Nimotop®, Bayer) 0.2 mg/mL 1.0–15 mL/hour intravenously was used for prevention of cerebral vasospasm, if not contraindicated by the actual blood pressure. Cerebral perfusion pressure (CPP) was normally kept ≥ 70 mmHg. Triple H-therapy was not used, but normovolemia was aggressively maintained by infusions of albumin, packed red blood cells and saline [33]. If in need of cardiovascular support dobutamine was primarily used. For vasopressor support, norepinephrine or phenylephrine was added.

ICU Monitoring

Intracranial pressure (ICP) was monitored in all patients, either using an intraparenchymal pressure measuring device (Codman MicroSensor™, Johnson & Johnson Professional Inc., U.S.A.) or a ventriculostomy. The Codman MicroSensor™ was calibrated according to the manufacturer's instructions. For the ventriculostomy the external meatus was used as zero reference level. Arterial blood pressure was invasively continuously monitored with the zero reference set at heart level. Mean arterial blood pressure (MAP), ICP and CPP were digitally assessed and displayed bedside, together with other physiological parameters, such as oxygen saturation and heart rate. Physiological data were continuously digitally stored; using the Marquette Solar System (GE Healthcare, U.S.A.), while data concerning drugs and fluids administered to the patient was digitally stored using the Picis system (Picis Inc., U.S.A.). Neurologically the patient's pupils size and reaction was monitored. No wake-up tests were performed.

EEG monitoring

Continuous monitoring of digital EEG was performed with the NicoletOne® equipment (VIASYS Healthcare Inc., U.S.A.). To document and better evaluate the appearance of the EEG background activity at the start of the monitoring, a routine 16-lead surface electrode EEG recording was performed prior to the cEEG, with electrodes positioned according to the international 10-20 system. The cEEG was recorded with five subcutaneous needle electrodes, positioned at positions F3, F4, P3, P4 (active), and Cz (reference) and hence the cEEG was based on a 4 electrodes and 1 reference electrode set-up. All recordings in all patients were inspected at full length, both in a two electrode bipolar and a four channel referential montage. Montage calculations were performed on-line and the bedside EEG was displayed as a continuously scrolling two-channel display of F3/P3 and F4/P4. The channels were displayed without notch filtering, to allow the supervising staff to notice poor electrode connection and increased impedance at the active electrodes. Six hour continuous EEG

activity was locally stored on file, after which it was transferred to a central secured server, while simultaneously the next six hours of recording was started. Attending nurses were trained to continuously enter electronic text comments into the recorded curve, not only concerning suspected epileptic seizures but also about patient care and change in medication, as well as technical comments concerning electrodes and recording details.

Qualitative evaluations of the recorded cEEG files were done continuously offline within 12 hours after the storing of each individual file. At the evaluation, the cEEG was inspected both as original signal in a two channel bipolar montage (F3/P3 and F4/P4; amplification 100 μ V; time base 30 mm/s) and as trend curves (display 2 hours/screen; semi logarithmic plots of relative band-power and rectified amplitudes; filtering (-10 dB) at high-pass 3 Hz and low-pass 22 Hz). All EEG recordings were evaluated by a specialist in clinical neurophysiology, with more than ten years of EEG reading experience.

In order to be accounted for as a seizure sequence, the patient's cEEG record should present one or more of the following features:

1. Uni- or bilateral rhythmic activity distinguishable from the background activity, and with or without high frequency components, eventually occurring with a crescendo-shaped appearance and short time for cessation/abolition, and eventually preceded by a sudden and temporary drop in EEG amplitude.
2. Pseudo-rhythmic spikes or spike-wave activity.
3. Repetitive 'broad sharp' complexes.

In cases of uncertainty or ambiguity the EEG signals were additionally displayed in 4-channel bipolar and/or referential montages (F3/P3, F4/P4, F3/F4, P3/P4; and F3-REF, P3-REF, F4-REF, P4-REF, respectively).

Statistics

Results are reported as mean $\pm$ standard deviation, or in case of non-parametric variables median (range).

Ethics

The Regional Ethical Review Board in Umeå, Sweden (Dr 2012-21-31M) approved the study. The protocol adheres to the principles of World Medical Association Declaration of Helsinki.

Results

During the study period, 108/164 SAH patients, were in need of controlled ventilation, and treated at the intensive care unit. In 22/108 patients, continuous EEG was never considered, since these 22 patients were only sedated and ventilated while waiting for treatment with surgery/coiling. Of the 86 patients where cEEG was considered, EEG monitoring equipment was available for 28/86 (33%) patients during the study period. 28 patients, 21 females and 7 males, with a mean age of 53 ± 11 years and a median age of 54 (15-62) years, were thus included in the study. All patients had SAH on their primary CT-scan. Fisher, GCS, H&H, WFNS score, localisation and treatment of the aneurysm are given in Table 1. None of the patients had pre-existing epilepsy or was treated with any kind of AED prior to the SAH. Paramedics reported that 17/28 (61%) of the patients had suspected clinical seizures at the onset of the SAH.

During the study period, totally 5468 hours ($\approx$ 228 days) of cEEG were recorded. The median recording time was 190 (68 – 475) hours per patient, mean 202.5 ± 90.0 hours ($\approx$ 8.5

days). The different sedative drugs given to the patients each day with cEEG during the study period are shown in Table 2. Nine patients were without any sedative drugs for a total 408 hours, 7.5% of all registered time. The cEEG monitoring was started at median 42 (16–77) hours, mean 41.4 ± 16.2 hours after arrival in the ICU and covered in mean 61% of the total time at the ICU. During this recording time no clinical seizures were observed nor were any inter ictal epileptiform activity detected on the cEEG.

In one patient, a 50-year-old woman with an initial H&H of 4, one single NCSZ of four minutes duration, was observed on the 8th day after admission. The patient was at the onset of the NCSZ sedated with continuous infusion of midazolam 15mg/hour, fentanyl 0.075 mg/hour, and thiopental 250 mg/hour.

In a second patient, a 46-year-old woman with an initial H&H of 4, an ongoing NCSE was seen on the third day after admission. The day before, on which she had no cEEG registration, she received fosphenytoin on suspicion of non-convulsive seizures (short ICP elevations without any other explanation). In this patient, a nearly five hour's period of NCSE was registered, during which three to five NCSZ episodes were seen per twenty minutes. At the start of the NCSE the administered sedation was; midazolam 3 mg/hour, fentanyl 0.1 mg/hour and thiopental 150 mg/hour. The sedation was gradually increased during the ongoing NCSE and reached at the end of the period; midazolam 4.5 mg/hour, fentanyl 0.1mg/hour, propofol 140 mg/hour, and thiopental 750 mg/hour.

In sum, we recorded epileptic seizure activity in 2/28 (7.1%) patients during approximately 5/5468 (0.09%) registered hours of cEEG monitoring.

Discussion

In almost 5500 hours of cEEG monitoring, in 28 SAH patients without pre-existing epilepsy or AED treatment, only about five hours (0.09%) of seizure activity were observed in two of the patients. One of the patients had a short NCSZ and the other patient experienced a NCSE. During these episodes no clinical seizures were observed.

Although the existence of seizures in neuro-intensive care patients is of importance, we have only found three reports on the occurrence of electroencephalographic NCSE or NCSZ in patients with SAH; Claassen et al (2004), Dennis et al (2002) and Little et al (2007) [1, 11, 15]. These three studies are reporting frequencies of NCSE in the range of 3 -31% [1, 11, 15]. In all of these three studies, cEEG was initiated on suspicion of subclinical seizures. In our study, all SAH patients in need of controlled ventilation were consecutively included and monitored, if EEG monitoring equipment was available and all of the cEEG registered was saved and analysed. The frequency reported by Claassen and Dennis et al is higher than in our study, but the same as in the study by Little et al [1, 11, 15]. But, in the study by Little et al, only three minutes of every 30 minutes period of cEEG was saved for retrospective analysis, which indicates that the actual frequency of NCSE could have been higher [15].

The only authors, except for our study, that are reporting on NCSZ in SAH patients are Claassen et al, who report a NCSZ frequency of 18% [1]. This frequency is higher than the frequency reported in our study, but Claassen et al only included patients with suspected seizures, unexplained deterioration and patients in persistent coma, which could indicate that the patients in the study by Claassen et al were more critically ill. In none of the three studies (Claassen, Dennis and Little) the routines used for sedation, if any, are reported. Neither is it described whether the patients were under controlled ventilation or not, nor if wake up tests were used. This lack of information makes it difficult to evaluate the eventual effect of continuous sedation used in our study [1, 11, 15].

We do not use wake-up test for clinical evaluation of the patients, as we believe that withdrawal of sedatives in combination with various actions for awakening add undesired stress to the patient, which may result in increased ICP and may provoke seizures [34, 35]. The surveillance of our patients is instead based on monitoring of the ICP and other physiological parameters, together with clinical evaluation of pupil size and reactions, frequent CT-scans and transcranial doppler investigations.

In our study, seizures were described in the early period after the SAH in 17/28 (61%) patients. This number of reported early seizures is high compared with the literature, but the reliability of the reporting of seizures outside the hospital by paramedics could be questioned [17, 18].

The use of prophylactic AED differs between studies and makes comparison difficult [1, 11, 15, 21, 36]. Although neither SAH guidelines by the Stroke Council, American Heart Association (STROKEAHA), nor the statement of the Neurocritical Care Society, recommend AED prophylaxis, it is still common and routinely used by approximately 40% of the neurosurgeons in the United States and by 8% of neurosurgeons in Germany [37-40]. AED is not without risk and has been linked to worse outcome in SAH patients. In a study with SAH patients, seizures were observed in 15% and adverse events of AED were observed in 23.4% of the patients [41].

The recommendation from the recently published consensus statement from the Neurocritical Care Society was that AED could be used to treat identified NCSZ on cEEG, but there was no consensus on whether infusions with midazolam or thiopental, administered in this study, could be used if treatment with AED proved to be ineffective [38]. However, the antiepileptic properties of the sedative agents used in this study, could have contributed to a reduction of epileptic seizures.

All the patients in our study received nimodipine as continuous intravenous infusion, for the prevention of cerebral vasospasm. Nimodipine, a Ca^{2+} blocker, has been shown to reduce seizures in animals [42-44]. It has also been discussed as a putative additive drug in therapy resistant epilepsy [45, 46]. Even though nimodipine is not recognized as an add-on therapy for refractory epilepsy, there are theoretical and animal experimental data suggesting that the substance may influence the occurrence of seizures [47].

In contrast to the reports on the occurrence of subclinical seizures in head trauma, which have mostly been reported to occur relatively early after trauma, the majority of the reports on subclinical seizures in SAH patients report a later onset of seizures [17, 23, 28]. In our study the median starting time for cEEG registration was 42 hours after admittance, which is well within the range reported by other authors [1, 11, 15, 17].

During our study period, no clinical seizures were observed. Other studies report a frequency between 1-12.5% of clinical seizures [13, 22, 23, 41]. The low incidence of seizures in our study could be due to that all patients were continuously sedated with midazolam, propofol or thiopental, alone or in combinations, all drugs with antiepileptic properties. It is notable that the two patients with EEG seizures in our study both had high doses of thiopental when seizures were registered.

In most studies 20 electrodes are used for detection of seizures [1, 2, 6, 11, 15]. We used five electrodes for the cEEG monitoring, in accordance with two other reports [48, 49]. Given the possibility for digital off-line recombination of electrode montages, a fewer number of electrodes was presumed to allow a sufficient quality of monitoring. The advantage of few electrodes is a simplified daily care of the patients, especially for repeated CT-scans and surgical procedures. Further, all patients had an ICP measuring device, and in several cases also a ventricular drainage, which makes multiple electrode positioning more difficult.

The use of five electrodes was thus considered as a sufficient clinical compromise, adequate to detect occurrence of subclinical seizures in patients with SAH. This paper, though not including a high number of patients studied, is the first paper that in a consecutive and prospective way has monitored a well-defined patient population i.e. patients with aneurysmal SAH in need of sedation and controlled ventilation. It is also the first study to clearly demonstrate in which way the patients have been treated during their cEEG monitoring. Further it is the first study to investigate the occurrence of subclinical seizures and status epilepticus, without setting inclusion criteria for monitoring.

Even though we registered a low frequency of NCSZ or NCSE, we believe that our results underline the need for cEEG as an additional monitoring in sedated SAH patients. In order to identify the few patients who experience subclinical seizures, cEEG gives the possibility to early intervention and treatment of these episodes and thereby hopefully lowers the risk of secondary brain injuries due to seizure activity.

Further prospective studies have to be undertaken, to better define the true frequency of subclinical seizures in this group of patients.

Conclusion

The result of this study supports the use of cEEG in the monitoring of sedated SAH patients, even if the patients are sedated subclinical seizures can still occur.

Our data also indicate that continuous sedation in SAH patients, in need of controlled ventilation, is associated with a low frequency of clinical and subclinical seizures.

Disclosure:

The author's reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Table 1. Scoring characteristics of the study population

GCS ¹ median (range)	8 (3-14)
H&H ² median (range)	4 (1-4)
WFNS ³ median (range)	4 (2-5)
Fisher ⁴ median (range)	4 (3-4)
Localisation of the aneurysm n (%)	
ACA/ACoA ⁵	9/28 (32)
ICA ⁶	4/28 (14)
PCoA ⁷	4/28 (14)
MCA ⁸	9/28 (32)
BA ⁹	2/28 (7)
Treatment n (%)	
Endovascular coil	13/28 (46)
Surgical clip	15/28 (54)

¹Glasgow coma scale. Obtained before sedation and intubation at the primary hospital.

²Hunt & Hess score: Obtained before sedation and intubation at the primary hospital; 1 asymptomatic/minimal headache, slight nuchal rigidity; 2 moderate/severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy; 3 drowsiness, confusion or mild focal deficit; 4 stupor, moderate to severe hemiparesis; 5 deep coma, moribund appearance

³World Federation of Neurosurgical Surgeons Scale: Obtained before sedation and intubation at the primary hospital. The scale including five grades based on GCS acknowledge the present of neurological motor deficit were grade I is GCS 15 with no motor deficit; II GCS 14-15 no motor deficit, grade III; GCS 13-14 with motor deficit; grade IV; GCS 7-12 with or without any motor deficit and grade V is GCS 3-6 with or without any motor deficit

⁴Fisher grade: Classifies the appearance of blood on the primary CT scan. 1: No haemorrhage evident; 2: SAH <1mm thick; 3: SAH >1mm thick; 4 SAH of any thickness with intra-ventricular or parenchymal haemorrhage

⁵ACA= Anterior Cerebral Artery, ACoA = Anterior Communicating Artery

⁶ICA = Internal Carotid Artery

⁷PCoA = Posterior Communication Artery

⁸MCA = Middle Cerebral Artery

⁹BA = Basal Artery aneurysm

n= numbers

Table 2. Administered drugs during continues EEG monitoring

Day with cEEG ¹	Number of patients with cEEG monitoring	Midazolam ²	Propofol ³	Thiopental ⁴	No sedation ⁵
1	28	27	3	8	
2	26	26	3	12	
3	26	26	2	11	
4	26	26	4	10	
5	25	23	6	8	
6	23	20	9	6	
7	22	17	11	4	1
8	17	8	10	4	2
9	14	7	7	2	4
10	9	4	5	1	2
11	7	3	3	1	2
12	6	3	3		1
13	4	2	1		2
14	2	2	2		
15	2	1	1		1
16	2	1	1		1
17	2	1	1		1
18	1		1		
19	1		1		
20	1				1

¹Day 1 represents the first day each patient was monitored with continuous EEG (cEEG). Day 2-20 represents the following days with cEEG. The patients had different numbers of days with EEG monitoring.

²Number of patients receiving midazolam in continuous infusion

³Number of patients receiving propofol in continuous infusion

⁴Number of patients receiving thiopental in continuous infusion

⁵Numbers of patients without any sedative drug during EEG registration

One patient can receive more than one drug at the same day.

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