Journal of Clinical Neuroscience xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Incidence of delayed seizures, delayed cerebral ischemia and poor outcome with the use of levetiracetam *versus* phenytoin after aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Article history:
Received 12 February 2014
Accepted 16 March 2014
Available online xxxx

Keywords:
Anticonvulsants
Brain ischemia
Intracranial vasospasm
Levetiracetam
Phenytoin
Seizures
Subarachnoid hemorrhage

ABSTRACT

Current guidelines recommend against the use of phenytoin following aneurysmal subarachnoid hemorrhage (aSAH) but consider other anticonvulsants, such as levetiracetam, acceptable. Our objective was to evaluate the risk of poor functional outcomes, delayed cerebral ischemia (DCI) and delayed seizures in aSAH patients treated with levetiracetam *versus* phenytoin. Medical records of patients with aSAH admitted between 2005–2012 receiving anticonvulsant prophylaxis with phenytoin or levetiracetam for >72 hours were reviewed. The primary outcome measure was poor functional outcome, defined as modified Rankin Scale (mRS) score >3 at first recorded follow-up. Secondary outcomes measures included DCI and the incidence of delayed seizures. The association between the use of levetiracetam and phenytoin and the outcomes of interest was studied using logistic regression. Medical records of 564 aSAH patients were reviewed and 259 included in the analysis after application of inclusion/exclusion criteria. Phenytoin was used exclusively in 43 (17%), levetiracetam exclusively in 132 (51%) while 84 (32%) patients were switched from phenytoin to levetiracetam. Six (2%) patients had delayed seizures, 94 (36%) developed DCI and 63 (24%) had mRS score >3 at follow-up. On multivariate analysis, only modified Fisher grade and seizure before anticonvulsant administration were associated with DCI while age, Hunt-Hess grade and presence of intraparenchymal hematoma were associated with mRS score >3. Choice of anticonvulsant was not associated with any of the outcomes of interest. There was no difference in the rate of delayed seizures, DCI or poor functional outcome in patients receiving phenytoin *versus* levetiracetam after aSAH. The high rate of crossover from phenytoin suggests that levetiracetam may be better tolerated.

1. Background

Anticonvulsant prophylaxis is widely used following aneurysmal subarachnoid hemorrhage (aSAH). Retrospective studies report the rate of seizures after aSAH to be between 1–18% [1–6]. The incidence of delayed or in-hospital seizures may be even lower, 4–8%, when anticonvulsant prophylaxis is used [4–6]. It is not known whether the choice of anticonvulsant used for prophylaxis has an impact on the subsequent risk of seizures or poor outcomes after aSAH. A retrospective study of patients with aSAH found that phenytoin burden may be associated with poor cognitive outcome at 3 months [7]. Current guidelines from the Neurocritical Care Society (NCS) therefore specifically recommend against the routine use of phenytoin for prophylaxis [2], while the American Heart Association guidelines state that the use of anticonvulsants is reasonable, without specifically recommending against or for any particular anticonvulsant [1]. Unlike the case with phenytoin, the NCS guidelines do not specifically recommend against the use of other anticonvulsants, and state that alternate anticonvulsants may be considered for prophylaxis for a duration of 3–7 days from ictus [2,3]. While levetiracetam is a popular alternative to phenytoin, the relative value of alternate anticonvulsants such as levetiracetam has not been systematically addressed, and it is not clear that their routine use is associated with better outcomes compared to the use of phenytoin in this specific setting. One study suggests that the short term use of levetiracetam may be

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http://dx.doi.org/10.1016/j.jocn.2014.03.009
0967-5868/

associated with an increase in the rate of late seizures compared to a longer duration of prophylaxis with phenytoin [8]. To our knowledge the specific risk of delayed cerebral ischemia (DCI) with levetiracetam *versus* that with phenytoin has also not been systematically evaluated – a relevant question in view of the association between phenytoin burden, fever and poor outcomes [7,9,10]. It is also possible that a less efficacious anticonvulsant may increase the risk of DCI through the mechanism of delayed seizures and increased metabolic demand, as has been previously described [11]. One animal study has demonstrated a decreased risk of poor neurological outcomes as well as vasospasm associated with the use of levetiracetam after aSAH [12]. To our knowledge there is no study in the literature directly comparing the risk of delayed seizures, DCI and poor outcomes associated with the use of levetiracetam *versus* phenytoin in patients with aSAH.

We aimed to compare the rate of poor functional outcomes, delayed seizures and DCI in patients treated with phenytoin *versus* levetiracetam following aSAH.

2. Methods

Approval for this study was obtained from the University of Michigan's Institutional Review Board (HUM00050017). The medical records of patients with an aSAH admitted between January 2005 and February 2012 were reviewed. Patients with aSAH receiving phenytoin or levetiracetam for at least 72 hours following admission were included. Patients with non-aneurysmal etiology, age <18 years, non-availability of CT scan within 24 hours of onset, modified Fisher grade 0–1, those who died within 72 hours and patients with a pre-existing seizure disorder were excluded.

2.1. Outcomes of interest

The primary outcome of interest was poor functional outcome at first recorded follow-up. Follow-up was assessed between 6 weeks and 6 months from discharge or at date of last contact following discharge. The modified Rankin Scale (mRS) [13] score was used to assess functional outcome at follow-up, based on specific documentation at the time of Rehabilitation, Neurosurgery and Neurology clinic visits. Poor neurological outcome was defined as mRS score >3. The secondary outcomes of interest were the incidence of seizures following initiation of anticonvulsant prophylaxis (delayed seizures) and the occurrence of DCI. Both clinically apparent as well as non-convulsive seizures detected only on electroencephalography (EEG) were included when determining the incidence of delayed seizures. Continuous EEG monitoring (cEEG) was not routinely performed, however, and was requested only at the discretion of the treating physician. DCI was defined as the composite of symptomatic vasospasm and/or delayed infarction on imaging [14]. Symptomatic vasospasm was defined as a change in neurological status during days 3–14 consisting of neurological worsening lasting $\geqslant$2 hours. Neurological worsening was defined as modified Glasgow Coma Scale score decline by 2 or more points, an increase by 2 or more points on the abbreviated National Institutes of Health Stroke Scale, or a new focal neurological deficit or new hypodensity on head CT scan with clinical signs. Symptoms must not have been explained by hydrocephalus, surgical trauma, new hemorrhage, recognized seizure, fever, sedation, hypoxia, infection, or metabolic abnormality, and must have been thought to be due to symptomatic vasospasm by the treating team, including the attending neurointensivist and neurosurgeon. Delayed infarction was documented on head CT scan between day 3 and 6 weeks from ictus and could not be procedure related.

2.2. Variables of interest

The primary variables of interest were the use of phenytoin or levetiracetam for at least 72 hours within the first week after aSAH. Seventy-two hours was considered the threshold for "significant" use of phenytoin and other anticonvulsants since some authors as well as the current guidelines from the NCS recommend that anticonvulsant use following aSAH be confined to a 3–7 day period [2,15]. All changes from one anticonvulsant to another were recorded, along with the reason for the change if documented in the medical record.

All seizures that occurred in the risk period for delayed cerebral ischemia (up to 21 days from admission), including those observed in the pre-hospital setting and emergency room prior to anticonvulsant initiation, as well any seizures occurring following initiation of anticonvulsant therapy (delayed seizures), were recorded and analyzed as variables in association with the outcomes of DCI and poor functional outcome. We analyzed the occurrence of seizures in these two different clinical settings (i.e, seizures occurring pre and post-initiation of anticonvulsant) as separate variables in association with the outcomes of interest since the pathophysiology, prognostic significance and implications for treatment are potentially very different for seizures occurring at the time of ictus *versus* those occurring at a later time despite the use of anticonvulsant prophylaxis. Other variables analyzed for association with delayed cerebral ischemia and poor functional outcome were age, race, sex, smoking history, history of hypertension, Hunt and Hess grade [16], modified Fisher grade [17], presence of intracerebral hematoma, aneurysm location, aneurysm size and the use of clipping *versus* coiling.

2.3. Management protocol

Every effort was made to secure the aneurysm with microsurgical clipping or endovascular coiling within 24 hours of admission. All patients were admitted to the neuro-intensive care unit for monitoring. External ventricular drainage was performed for hydrocephalus. Anticonvulsants were started on admission for all patients, continued for the duration of the inpatient admission and tapered off within 30 days following discharge, unless the patient had suffered a seizure and required ongoing anticonvulsant use. Choice of anticonvulsant was at the discretion of the attending neurosurgeon or neurointensivist. Phenytoin was typically initiated with a 20 mg/kg intravenous load and then continued at a dose of 4–6 mg/kg/day. Phenytoin levels were not routinely measured on a daily basis and were ordered intermittently at the discretion of the treating physician. Aggressive supplementation to maintain "therapeutic" levels was not routinely performed and the phenytoin burden could not therefore be reliably estimated. Levetiracetam was typically initiated at 250–500 mg twice daily and further dose adjustments were at the discretion of the treating physician. cEEG monitoring was ordered at the discretion of the treating physician. Nimodipine was used in all patients for 21 days if hemodynamically tolerated. A magnesium infusion (fixed dose of 0.5 g/hour) was used in all patients for 14 days. The infusion was not titrated to target levels and serum levels were measured inconsistently. The goal of fluid management was euvolemia using normal saline in all patients. Patients with otherwise unexplained acute neurological deterioration were given a bolus of crystalloid or colloid and had their blood pressure augmented by 20–30% using vasopressors. Augmentation of cardiac index was variably performed. Angiographic imaging with either digital subtraction angiography or CT angiography was performed as soon as possible in all patients with neurological deterioration following a non-contrast head CT scan, regardless of response to hemodynamic augmentation.

Please cite this article in press as: Karamchandani RR et al. Incidence of delayed seizures, delayed cerebral ischemia and poor outcome with the use of levetiracetam *versus* phenytoin after aneurysmal subarachnoid hemorrhage. J Clin Neurosci (2014), http://dx.doi.org/10.1016/j.jocn.2014.03.009