**Continuous EEG for nontraumatic aneurysmal subarachnoid hemorrhage**

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening disease that affects close to 30,000 individuals per year in the United States (Zacharia et al., 2010), an equivalent of 5 to 20 per 100,000 person years (de Rooij et al., 2007). aSAH is a major cause of mortality and morbidity – although aSAH constitutes only around 5% of all strokes, it contributes to almost 30% of potential life lost (Johnston et al., 1998). aSAH is associated with long hospital stays, substantial financial costs and a decrease in health-related quality of life (Taylor et al., 1997; Meyer et al., 2010). At least a quarter of people with aSAH suffer mortality; and of the patients that do survive, as many as half can have permanent neurological deficits (Connolly et al., 2012). Complications associated with aSAH are numerous (Jan van Gijn et al., 2007), and can occur even after the aneurysm has been secured with the help of clipping or coiling procedures. Cerebral complications of aSAH are hydrocephalus, rebleeding and delayed cerebral ischemia (DCI); systemic complications include fever, ionic imbalances, hypertension, hypotension and cardiac failure, whereas long-term complications are epilepsy, anosmia, cognitive and psychosocial deficits (Raper et al., 2013).

Delayed cerebral ischemia (DCI) is a serious complication of aSAH, and can occur in as many as 30% of patients that survive the initial hemorrhage (Roos et al., 2000). DCI typically occurs 4-10 days after the initial aSAH event, and can lead to cerebral infraction – a major cause of unfavorable outcome in patients with aSAH (Macdonald, 2014; Vergouwen et al., 2011; Rosengart et al., 2007; Crowley et al., 2011). Diagnosis of DCI is made by exclusion i.e. once rebleeding and hydrocephalus have been excluded, DCI is defined as new focal/global neurological deficit which may be accompanied by cerebral infarction (Kondziella et al., 2014).

DCI is thought to be potentially preventable (Hijdra et al., 1987), but it is important to understand the mechanisms underlying DCI to be able to prevent it in subjects with aSAH. One of the mechanisms underlying DCI is vasospasm - a complex phenomenon that ultimately results to constriction of blood vessels and hypoperfusion of the brain. Additional mechanisms are cortical spreading depression, disruption of the blood-brain barrier and release of ferrous haemoglobin by the subarachnoid clot which leads to delayed, (but poorly understood) effects on nitric oxide (NO), smooth muscle contraction, inflammation and endothelin-1 (Macdonald, 2014; Budohoski et al., 2014; Pluta et al., 2009). The current thought is that the early brain injury (EBI) caused by the aneurysm leads to alterations in intracranial pressure and decreased cerebral blood flow, which ultimately lead to disruption of the blood-brain barrier and sets into play inflammation and oxidative cascades (Lin et al., 2014; Fujii et al., 2013).

Current modalities for detection of DCI include transcranial Doppler, angiography, computed tomography (CT), cerebral microdialysis and magnetic resonance (MR) techniques (Macdonald, 2014; Schulz et al., 2000). All these techniques are associated with issues of low selectivity and sensitivity and the presence of artifacts; hence, a new technique to detect vasospasm would be of great utility. Diagnosis of DCI is challenging because the presence of radiological and clinical symptoms alone is not the best predictor of DCI (Dabus and Nogueira, 2013). Only half of the individuals with vasospasm go on to develop DCI; one reason could be the case is that only very severe vasospasm leads to DCI (Fisher et al., 1980). DCI can be asymptomatic – for example, cerebral infarcts were observed in people who had not been diagnosed with DCI before (Schmidt et al., 2008). There are other cases where individuals with aSAH are shown to have clinical worsening due to DCI, but they have no vasospasm that can be detected radiologically (Dhar et al., 2012). The presentation of vasospasm after DCI is variable (Frontera et al., 2009; Brown et al., 2013), and reversing vasospasm does not necessarily decrease the incidence of DCI (Budohoski et al., 2014). In addition, diagnosis of DCI remains difficult in people who may be sedated and ventilated (Diringer et al., 2011). Even cerebral infarction which has a stronger connection to poor outcome after aSAH has its problems - almost a quarter of cerebral infarction events go undetected, as they are clinically silent (Schmidt et al., 2008). Hence, there is considerable discrepancy between clinical/ radiological diagnosis and final outcome. There are issues with current tools to detect vasospasm as well: vasospasm in peripheral sites can be more serious than vasospasm limited to basal vessels, but existing transcranial Doppler method (TCD) is not able to detect this (Okada et al., 1999).

Continuous EEG (cEEG) is routinely used in the critically ill population (Shah et al., 2006; Sutter et al., 2013), and is an increasingly useful tool for monitoring ischemia (Friedman et al., 2009). cEEG provides good temporal resolution which is necessary for monitoring patients with aSAH. cEEG is also uniquely suited for monitoring distal vasospasm and early tissue changes that may be undetectable by other modalities – for example, alpha delta ratio (ADR) has been shown to provide a sensitive tool for detecting DCI (Claassen et al., 2004). Quantitative EEG (qEEG) can provide additional useful diagnostic information (Rathakrishnan et al., 2011; Stuart et al., 2010; Claassen et al., 2005). Although the use of qEEG has been suggested and reviewed (Kondziella et al. 2014), it is not yet known whether aggressive treatment of DCI as detected by qEEG is feasible, and if it would improve clinical care. The triple-H therapy of hypertension, hypervolemia, and hemodilution has been historically used and widely accepted to manage vasospasm in aSAH, but evidence for its clinical utility has not yet been validated (Lee et al., 2006). **We propose that cEEG can potentially be a tool to detect vasospasm sooner than the existing modalities enabling faster diagnosis, care and treatment. Hence, we propose cEEG as an alternative to current diagnostic modalities for vasospasm**.

1. Early diagnosis
2. Does cEEG monitoring lead to an earlier detection of DCI compared to other modalities?
3. Can cEEG predict DCI prior to clinical neurological deterioration?
4. Can cEEG and QEEG provide diagnostic advantage for aSAH patients with clinical worsening due to early brain injury and distal vasospasm as opposed to proximal vasospasm?
5. Can cEEG predict the rate of evolution of DCI?
6. Clinical Outcomes
7. Does aggressive treatment of EEG patterns suggestive of DCI improve clinical outcome in aSAH?
8. Does aggressive treatment of EEG patterns lead to serious side effects?
9. What clinical variables play a role in predicting outcomes?
10. Proposal for prospective randomized trial - Does early or late AED administration affect clinical outcome?
11. What is the feasibility of performing cEEG monitoring in the Neuro ICU as compared to currently existing diagnostic tools?
12. Are cEEG changes specific and reproducible enough to predict and serve as a marker for vasospasm/DCI?

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